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REVIEW

Irritable bowel syndrome: A clinical review

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Abstract

Irritable bowel syndrome (IBS) remains a clinical challenge in the 21st century. It's the most commonly diagnosed gastrointestinal condition and also the most common reason for referral to gastroenterology clinics. Its can affect up to one in five people at some point in their lives, and has a significantly impact of life quality and health care utilization. The prevalence varies according to country and criteria used to define IBS. Various mechanisms and theories have been proposed about its etiology, but the biopsychosocial model is the most currently accepted for IBS. The complex of symptoms would be the result of the interaction between psychological, behavioral, psychosocial and environmental factors. The diagnosis of IBS is not confirmed by a specific test or structural abnormality. It is made using criteria based on clinical symptoms such as Rome criteria, unless the symptoms are thought to be atypical. Today the Rome Criteria Ⅲ is the current gold-standard for the diagnoses of IBS. Secure positive evidence of IBS by means of specific disease marker is currently not possible and cannot be currently recommended for routine diagnosis. There is still no clinical evidence to recommend the use of biomarkers in blood to diagnose IBS. However, a number of different changes in IBS patients were demonstrated in recent years, some of which can be used in the future as a diagnostic support. IBS has no definitive treatment but could be controlled by non-pharmacologic management eliminating of some exacerbating factors such certain drugs, stressor conditions and changes in dietary habits.The traditional pharmacologic management of IBS has been symptom based and several drugs have been used. However, the cornerstone of its therapy is a solid patient physician relationship. This review will provide a summary of pathophysiology, diagnostic criteria and current and emerging therapies for IBS.

Key words: Irritable bowel syndrome; Clinical review; Pathogenesis; Diagnostic; Treatment; Biopsychosocial model

Core tip: Irritable bowel syndrome (IBS) remains a clinical challenge in the 21st century. Various mechanisms and theories have been proposed about its etiology, but the biopsychosocial model is the most currently accepted. Today the Rome Criteria are the current gold-standard for the diagnoses of IBS. Traditional management of IBS has been symptom based and several drugs have been used. However, the cornerstone of its therapy is a solid patient physician relationship. This review will provide a summary of pathophysiology, diagnostic criteria and current and emerging therapies for IBS.

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INTRODUCTION

The functional gastrointestinal disorders (FGIDs) are a heterogeneous group of chronic conditions that are considered important to public health because they are remarkably common, can be disabling, and induce a major

social and economic burden. Irritable bowel syndrome (IBS) is the most prevalent FGID noted in the general population worldwide and also the most common reason for referral to gastroenterology clinics[1-4]. Even though it was described to 150 years ago, IBS remains a clinical challenge in the 21st century[5,6]. Its can affect up to one in five people at some point in their lives, and has a significantly impact of life quality and health care utilization[7,8]. The prevalence varies according to country and criteria used to define IBS[9-21]. Various mechanisms and theories have been proposed about its etiology, but the biopsychosocial model is the most currently accepted for IBS[22]. The complex of symptoms would be the result of the interaction between psychological, behavioral, psychosocial and environmental factors[23-27]. The diagnosis of IBS is not confirmed by a specific test or structural abnormality. It is made using criteria based on clinical symptoms such as Rome criteria, unless the symptoms are thought to be atypical. There is still no clinical evidence to recommend the use of biomarkers in blood to diagnose IBS. Today the Rome Criteria are the current gold-standard for the diagnoses of IBS[26,28,29]. There is no definitive treatment for IBS and the traditional management has been symptom based but recent developments in the understanding of complex interaction between the gut, immune system and nerve system have led to an expanded arsenal of therapeutic options for relief of both bowel movement-related symptoms and pain[30-34]. However, a strong doctor-patient relationship is the key for effective treatment of patients and realistic expectations.

This review will provide a summary of pathophysiology, diagnostic criteria and current and emerging therapies for IBS[35-39].

PATHOGENESIS

In despite its high prevalence, the pathophysiology of IBS is not yet completely understood and seems to be multifactorial[22-25]. Various mechanisms [gastrointestinal (GI) dismotility[40,41] visceral hypersensitivity[42,43] intestinal mucosa activation[44-48], Increased intestinal permeability[49-54], have been proposed about the IBS pathophysiology. Studies suggest interplay between luminal factors (*e.g.*, foods and bacteria residing in the intestine], the epithelial barrier, and the mucosal immune system[48]. However, the biopsychosocial model[22,25,26,36] is the most currently theory accepted for IBS. The complex of symptoms would be the result of the interaction between psychological, behavioral, psychosocial and environmental factors Since fifty years ago, several theories have proposed regarding the etiology of IBS of which the most important are as follows.

Evidences and not evidences of GI motility disorders in IBS

IBS is a complex disorder that is associated with altered GI motility, secretion and sensation[55,56]. In some patients with IBS motor abnormalities of the GI are detectable, *e.g.*, increased frequency and irregularity of luminal contractions, prolonged transit time in constipation-predominant IBS and an exaggerated motor response to cholecystokinin and meal ingestion in diarrhea-predominant IBS. Despite this no predominant pattern of motor activity has emerged as a marker for IBS[57-60] and the relevance of these motor function alterations to symptoms has yet to be established. However, pharmacological stimulation of gut motility in IBS patients appears to reduce gas retention and improve symptoms. These data suggest that a motility disorder could be associated with this complaint in some patients[61,62]. Role of serotonin in the pathophysiology of IBS. Serotonin (5-HT) plays a critical role in the regulation of GI motility, secretion and sensation. It is an important signaling molecule in the gut targeting enterocytes, smooth muscles and enteric neurons. Most of the body serotonin is present in enterochromaffin cells. Serotonin activates both intrinsic and extrinsic primary afferent neurons to, respectively initiate peristaltic and secretory reflexes and to transmit information to the central nervous system. Serotonin activates both intrinsic and extrinsic primary afferent neurons to, respectively initiate peristaltic and secretory reflexes and to transmit information to the central nervous system. It is inactivated by the serotonin reuptake transporter (SERT) in the enterocytes or neurons[22,24,30,32]. There are lines of evidence that FGIDs, as IBS, are associated with defective enteric serotonergic signaling. Altered serotonin signaling could lead to intestinal and extra intestinal symptoms in IBS. These results support the concept that diarrhea-predominant (IBS-D) IBS is characterized by reduced 5-HT reuptake, whereas impaired release may be a feature of constipation predominant IBS (IBS-C). However, exogenous serotonin application evokes so many responses that it is difficult to determine which is physiologically relevant. Therapeutic agents targeting altered serotonin signaling may provide new effective treatment for patients with IBS[62-65].

Evidences and not evidences of visceral hypersensitivity in IBS

Visceral hypersensitivity is considered to be one of the main factors that cause symptoms in IBS patients and increased sensation in response to stimuli is a frequent finding in IBS patients[42,43,65-68]. This selective hypersensitization results from stimulation of various receptors in the gut wall of visceral afferent nerves in the gut[69-71], triggered by bowel distention or bloating, as a possible explanation for IBS symptoms[72-77]. Rectal distension in patients with IBS also increased cerebral cortical activity more than in controls. The increased sensitivity of the colon could be influenced by a psychological tendency to report pain and urgency, rather than increased neurosensory sensitivity[78]. About half of patients with IBS (mainly those with constipation) have a measurable increase in abdominal girth associated with bloating (sensation of abdominal fullness), although this may not be related to the volume of intestinal gas[72,74,79]. In addition, other

factors may contribute to visceral hyperalgesia, such as specific GI mediators (serotonin, linins), or increases in spinal cord excitability due to activation of an N-methyl-D-aspartate (NMDA) receptor[80]. In addition, IBS patients show an increased secretion in the duodenum and jejunum. Larsson *et al*[81] proposed that the enhanced secretion may reflect disturbed enteric network behavior in some patients with IBS.

Evidences and not evidences of intestinal barrier disorders in IBS

Some authors reported an increase in permeability of the intestinal mucosa and disruption of tight junctions in sub-groups of patients with IBS often triggered by some factors[45-50]. The possible mechanisms underlying these changes could be associated with the interaction between mucosa permeability, visceral hypersensitivity and inflammation mucous[48-54,82,83]. Studies suggest that an interaction between luminal factors (for example, food and bacteria that reside in the gut), the epithelial barrier and mucosal immune system could result in pain through the inflammatory stimulation of afferent nerves[45-48,51,82,83]. Some factors were described as triggers for intestinal permeability alterations. They are stress, food, bile, infection and dysbioses[48,49].

Role of stress: The association between IBS and psychological factors, especially anxiety and stress, has been described for many years[22-25,36]. In rats chronically stressed the consequently increased corticosterone release leads to intestinal inflammation with consequent mucosal barrier dysfunction[84-88]. However, the direct association between intestinal barrier dysfunction and stress in patients with IBS still needs confirmation.

Role of food and bile: Some patients with IBS report worsening of symptoms after eating and perceive food intolerance to certain foods[89-93]. Multiple factors have been considered to contribute to food sensitivity in patients with IBS. Investigations have centered on food specific antibodies, carbohydrate malabsorption, and gluten sensitivity. Although some IBS patients related relief of symptoms on a gluten-free diet the specific relationship between gluten and increased intestinal permeability in IBS have not yet confirmed[93-96]. We reported that IBS patients have difficulties with food in general and specific foods may not be involved in IBS pathogenesis.

It is reasonable to assume that IBS causes food sensitivity, rather than vice versa[97,98]. Certain bile acids could increase intestinal permeability through the phosphorylation of epidermoid growth factor receptor, which induces occludin desphosphorylation[99] or *via* dysfunction of the enteric neurons[100].

Role of infection-IBS post-infectious: Gastroenteritis is a common trigger for IBS. The IBS symptoms can be triggered by an enteric infection and can persist for weeks, months and years[52,101-104]. Two meta-analyses demonstrated an increased risk of IBS in patients who experienced an episode of acute gastroenteritis. Risk factors for post infectious IBS included young age, prolonged fever, anxiety, and depression. A longer duration of the initial infection has also been associated with increased risk for IBS. One of the largest prospective studies included a total of 2069 individuals who had been exposed to contaminated drinking water after heavy rainfall[105,106]. The cause of the intestinal symptoms after PI-IBS is not yet defined. The likely increase in intestinal permeability during the episode of acute gastroenterite could cause inflammation and intestinal microbiota change, leading to intestinal barrier dysfunction and infection-induced dysbiosis[107,108]. Development of idiopathic malabsorption bile acids and increase in serotonin-containing enteroendocrine cells and T lymphocytes[108-111]. The use of antibiotics for GI or other infections was observed to be a risk factor for developing functional bowel symptoms[112].

Evidences of small intestinal bacterial overgrowth in IBS

Small intestinal bacterial overgrowth (SIBO) is associated with an increased number and/or type of bacteria in the upper GI tract[113]. However, data reporting an association between IBS and SIBO have been conflicting. In support of an association between SIBO and IBS are studies demonstrating abnormal breath hydrogen levels in IBS patients after receiving a test dose of a carbohydrate, as well as improvement in symptoms after eradication of the overgrowth[114,115]. In addition, increased methane production, a gas by product of intestinal bacteria, has been associated with constipation predominant IBS[116,117]. Other studies have failed to support an association between SIBO and IBS The improvement of symptoms with antibiotics described in some patients with IBS may be due to improved intestinal motility or a change in the flora of the colon, rather than SIBO[118-121].

Evidences and not evidences of abnormalities of intestinal flora in IBS

The relationship between stress and microbiota goes back many decades, when Tannack and Savage reported that stressed mice showed dramatic reductions in these populations of lactobacilli[122]. Recent studies demonstrated that the intestinal microbiota can influence the gut-brain communication in health and disease, and consequently altering brain chemistry and behavior. However, it's perhaps premature to extrapolate the current preclinical work to the clinic. The complex ecology of the fecal microflora has led to speculation that changes in its composition could be associated with diseases including IBS. Emerging data suggest that the fecal microbiota in individuals with IBS differ from healthy controls and varies with the predominant symptom[122-124]. However, not all studies have found disturbances in the microbiota composition of IBS patients and his currently unclear whether the alteration that have been reported are primary or secondary in nature. The contribution of altered intestinal composition or function in IBS remains contro-

versial and additional studies are needed to validate these observations[125-129].

Evidences and not evidences of low grade mucosal inflammation and IBS

Increased numbers of lymphocytes have been reported in the colon and small intestine in a subset of patients with IBS[130,131]. These cells release mediators (nitric oxide, histamine and proteases) capable of stimulating the enteric nervous system, leading to abnormal motor and visceral responses within the intestine[132-134]. Studies have demonstrated a correlation between abdominal pain in IBS and the presence of activated mast cells in proximity to colonic nerves[135]. In addition, peripheral blood mononuclear cells of IBS patients produce higher amounts of tumor necrosis factor than healthy controls[136]. Changes in mucosal barrier function and a consequent increase in intestinal permeability could be the basis for the increased inflammation in IBS[45-49]. The interaction between the increased intestinal permeability, low levels of inflammation and hypersensitivity could be the key to the pathophysiology of IBS[48,136-138].

Evidences and not evidences of genetic contribution in IBS

The pathogenesis of IBS has traditionally been based on the biopsychosocial model that emphasizes that the symptom manifestations of IBS and consulting behavior are influenced at least in part by psychological processes. However, there has been increasing interest in trying to identify potential molecular mechanisms in IBS, and this endeavor has been driven by some evidence that there is a true genetic contribution to IBS[138-140]. IBS does aggregate in families, and the concordance of IBS is twice as great in monozygotic compared with dizygotic twins in most, but not all studies[141-144]. A number of genetic polymorphisms have been associated with IBS but most remain to be independently confirmed, and unknown gene-environment interactions probably remain essential for the disorder to manifest[144-146]. A future direction of investigation includes genome-wide approaches and further delineation of the role of epigenetic factors in IBS. By studying the genetic associations between candidate genes and intermediate phenotypes that are associated with manifestations of the clinical phenotype, one can also evaluate the role of the candidate mechanism in IBS. The intermediate phenotypes most commonly used in IBS are colonic transit, colonic motility and compliance, and sensation thresholds and ratings[147,148].

Evidences and not evidences of brain-gut axis and psychosocial dysfunction in IBS

Psychosocial factors may influence the expression of IBS[149-153]. Though the role of the BGA is not fully understood, there is strong evidence of a crucial involvement of the BGA in the development of IBS and IBS like symptoms[22-24,36]. In patients with IBS the dysregulation of the BGA, a bidirectional and integrated system modified by psychosocial processes and environmental influences, could induce dysmotility or visceral sensitivity. The importance of the knowledge of concepts related brain-gut interactions improves patient physician relationship and identifies what level pharmacological treatment can be beneficial for patients with IBS[154-159].

DIAGNOSIS

Although it is among the most common disorders in gastroenterology and primary care practices IBS continues as a substantial diagnostic challenge[1,3,4,20,22,24,27,160]. Frequently, the IBS diagnosis is missed or delayed. There are several medical conceptions concerning the SII. While a large number of doctors consider that IBS would be a mixture of different organic diseases and others believe IBS does not exist and in your point of view these symptoms are normal and these patients are not medical priority, only a few doctors consider IBS as a functional bowel disease well defined by the byopsychosocial model[22,25,26,36]. This fact is an important obstacle to making IBS diagnosis. However millions of IBS patients around the world are still looking for responses and relief of symptoms. For these reasons is so important to make a diagnosis of IBS. The key issues is to diagnose IBS safely through minimal risks and reasonable costs[9,26,27,29,36,161-164]. To standardize clinical research protocols, was published a definition of consensus for the diagnosis of IBS in 1992 called Rome criteria, which was recently revised in 2005 and named as Rome Ⅲ criteria[28]. The diagnosis must be based on clinical data, using symptoms based on criteria of Rome, unless the symptoms are atypical[165,166]. When the criteria are filled in IBS diagnosis and alarm features are absent, the number of diagnostic tests should be minimal.Reports and guidelines emphasize that IBS is not a diagnosis of exclusion and encourage clinicians to make a positive diagnostic using the Rome Criteria alone[9,26-29,36,167-171].

Definition, clinical manifestations and diagnostic criteria

IBS is the most commonly diagnosed GI condition and also the most common reason for referral to gastroenterology clinics (up to 50% of all offices visits to gastroenterologists). Its can affect up to one in five people at some point in their lives, and has a significantly impact of life quality and health care utilization. The prevalence varies according to country and criteria used to define IBS. IBS is more frequent in women than in men, and its prevalence is less for individuals over 50 years, when compared with those of less than 50 years. Are considered typical clinical manifestations in IBS discomfort or abdominal pain relieved by defecation, associated with a change in stool form[172-176].

Pain

Patients with IBS can present with a variety of symptoms which include both GI and extraintestinal complaints. However, the symptom complex of chronic abdominal pain and altered bowel habits remains the nonspecific pri-

mary characteristic of IBS. It's chronic nature, signs and symptoms which vary periodically from mild to severe have many negative effects on the quality of life for the suffers. Many factors, for example. emotional stress and eating may exacerbate the pain. In contrast defecation usually provides some relief[28,164,168,177-180].

Altered bowel habits

Patients with IBS complain of altered bowel habit, ranging from diarrhea (IBS-D), constipation (IBS-C), or alternating diarrhea and constipation (IBS-M). One half of patients with IBS-D complain of mucus discharge. Large volume diarrhea, bloody stools, nocturnal diarrhea, and greasy stools are not associated with IBS and suggest organic disease. Another sub-group of patients with IBS-D describe an acute viral or bacterial GI before the onset of symptoms compatible with IBS. This clinical entity is called post-infectious IBS. It's important to remember that the most bowel movements are preceded by lower abdominal cramps. 8-Patients with IBS-C may experience a sensation of incomplete evacuation and periods of constipation can last from days to months alternating with diarrhea or normal bowel function[28,164,168,180].

Other GI symptoms

Bloating or feeling of abdominal distension are very frequent complaints in IBS and may be included in the diagnostic criteria for IBS in the future. Other digestive symptoms as dysphagia, early satiety, intermittent dyspepsia, nausea and non-cardiac chest pain patients with are also often associated with IBS. Comorbidity with other FGIDs is high and can be caused by shared as visceral hypersensitivity pathophysiological mechanisms. Comorbidity with other FGIDs is high and may be caused by shared pathophysiological mechanisms such as visceral hipersensivity[180-185].

Extra-intestinal symptoms

Psychiatric disorders, especially major depression, anxiety, and somatoform disorders occur frequently[158,186,187]. The nonGI nonpschiatric disorders with the best documented association are fibromyalgia, chronic fatigue syndrome, temporal mandibular joint disorder and chronic pelvic pain[188-190]. In addition, IBS is often accompanied by other extra-intestinal symptoms as asthma and cerebral pain symptoms as primary headache[191-193]. The high prevalence of co morbidities in IBS patients has led investigators to develop hypothesis regarding underlying pathophysiologic mechanisms linking these disorders[194,195]. The comorbidities are correlated with enhanced medical help seeking, worse prognosis, and higher rates of anxiety and depression all resulting in a reduced quality of life. The identification of this clinical problem could improve the therapeutic options and the prevention strategies[196-198].

Diagnostic criteria

The concept of utilization of the clinical criteria for IBS diagnosis was formulated at first time for Manning in 1978[199]. Other criteria have also been proposed[200-202]. Today the Rome Criteria Ⅲ are the current gold-standard for the diagnoses of IBS[203]. IBS was defined as recurrent abdominal pain or discomfort associated with altered defecation and IBS patients are grouped into different subtypes based on the predominant stool consistency. Formally, the Rome Ⅲ Criteria require recurrent abdominal pain or discomfort ⩾ 3 d/mo in the last 3 mo associated with ⩾ 2 of the following: 1- improvement with defecation; 2- onset associated with a change in form (appearance) of the stool[203]. Supportive symptoms that are not part of the Rome Ⅲ Criteria include: abnormal stool frequency, abnormal stool form, defecation straining, urgency or a feeling of incomplete bowel movement, passing mucus and bloating[204].

Diagnostic approach

The basic diagnosis should include a careful and thorough medical history. This complaint data should be quantified as precisely as possible (*e.g.*, by symptom diaries). The aim is the most accurate detection of symptom constellation and dynamics, as well as the active queries alarm symptoms. There is evidence that the (patient and doctor alike convincing) exclusion of relevant other causes can contribute for the mutual improved trust and due to also to the success of the treatment[205,206]. The substantial human and economic costs associated with IBS needs to development of efficient diagnostic and management strategies[6,27]. Patients are first identified as having a symptom complex compatible with IBS based upon Rome Ⅲ Criteria. If the patient who have IBS suggestive symptoms, and no alarm symptoms or no family history of IBD or colorectal cancer are present, a limited number of diagnostic studies is required to exclude organic disease in most patients and a considerable number do not require any tests at all. This limited diagnostic approach excludes organic disease in more than 95 percent of patients[201,205,206]. Routine laboratory studies (complete blood count, chemistries) are normal in IBS[22,26,201,207-210]. The rates of prevalence of IBD, colorectal cancer and thyroid disease are different in patients with IBS when compared with the general population. Lactose intolerance seems to be more prevalent in patients with IBS symptoms when compared with controls other carbohydrates such fructose and sucrose can also cause or exacerbate IBS symptoms. However, there is no evidence of cause and effect between lactose intolerance and IBS[211-213]. Stool examination for ova and parasites would be indicated only in patients who live in developing countries or were there recently[214]. There is insufficient evidence to recommend routinely test for SIBO in patients with IBS[26,168,215-222]. The utility of abdominal imaging tests in patients with suspected IBS and no alarm features is scarce. In absence of alarm signals characteristic IBS patients aged less than 50 years need not be submitted to colonoscopy. The image of the colon would not be useful in obtaining colonic imaging that could explain the symptoms of patients with IBS[223].

Alarm features or red flags

In the presence of alarm features or atypical symptoms which are not compatible with IBS, it's important to exclude other causes. The alarm symptoms (*e.g.*, anemia and weight loss) have a high specificity for the presence of inflammatory or malignant diseases. Rectal bleeding, nocturnal or progressive abdominal pain, weight loss, anemia and another laboratory abnormalities such as elevated inflammatory markers, or electrolyte disturbances, a family history of colorectal cancer, IBD or celiac disease are often associated with IBS-like symptoms[216-218]. Faced with a patient with IBS symptoms and alarm signals the colonoscopy should be performed to exclude organic disease[22,26,168,219,224]. We suggest performing screening tests based upon the patient's clinical history in patients with IBS-M, and in IBS with refractory symptoms (change of progression of symptoms or absence in response to general therapeutic measures)[26,225,226]. further evaluation depends upon the predominate symptoms. In IBS C the evaluation is similar to other patients with chronic constipation and in patients with predominant diarrhea is similar to other with chronic diarrhea[26,168,226].

Biomarkers in IBS - the future newer innovative tests for IBS

Secure positive evidence of IBS by means of specific disease marker is currently not possible and cannot be currently recommended for routine diagnosis. However, a number of different changes in IBS patients were demonstrated in recent years, some of which can be used in the future as a diagnostic support. Several non-invasive approaches were investigated for their ability to discriminate IBS from non-IBS disorders. Although a larger number of data are necessary these tests show potential as adjuncts to traditional diagnosis methods in IBS and may reduce unnecessary testing in clinical practice[227-231]. They are examination of stools forms, fecal markers, and serological markers. A blood screening test approved in the United States for the IBS ("Prometheus® IBS diagnostics") tests a constellation from a total of 10 "IBS blood biomarkers" and can thus supposedly secure diagnosis "IBS" in combination with the other clinical parameters[224]. The practical value of this test currently (still) cannot clearly be evaluated, because the published evidence is insufficient. Secure positive evidence of IBS by means of specific "disease marker" is currently not possible and cannot be currently recommended for routine diagnosis.

TREATMENT

General principles in the treatment of IBS

Over the past 2 decades very few agents have achieved regulatory approval for the treatment of IBS. IBS has no definitive treatment but could be controlled by eliminating of some exacerbating factors such certain drugs, stressor conditions and changes in dietary habits. Traditional management of IBS has been symptom based. Because of the abnormalities in bowel states associated with each IBS subtype, it is not likely that one agent would successfully treat all three subtypes. As a result, clinical trials have focused, for the most part, on one IBS subtype[2,25,22,29,32,36,168,229].

NON-PHARMACOLOGIC MANAGEMENT

Fundamental aspects of the doctor patients-interaction as the basis of IBS therapy

Many patients with IBS have bounced around the field of medicine for many years with different diagnoses, due to lack of interest or deep frustration of the doctor in the treatment of IBS. The absence of biological markers for the diagnosis of IBS or even its characterisation as a mental illness. The absence of biological markers for the diagnosis of IBS or even its characterisation as a mental illness could lead to inadequate interpretation. Patients should be informed that the nature of the disease is chronic, benign, and educated on how to deal with and control symptoms of the disease, which vary periodically from mild to severe and have many negative effects on quality of life. Patients should be also informed that their diagnosis is not like being altered, but that it is possible to have a normal life. A detailed medical history and physical examination physician should pay particular attention to their patient's concerns. The treatment goal in patients suffering with IBS is to try eliminating or decreasing the patient's primary symptoms which should be addressed on first encounter with the patient[35].

DIET RECOMMENDATIONS ABOUT DIETARY HABITS

It should be noted that the intake of foods does not cause IBS. However, many IBS patients have non-specific intolerance to foods. The dietary restriction of fermentable carbohydrates popularly termed the low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet has received considerable attention is now accepted as an effective strategy for managing symptoms of IBS. However, limitations still exist with this approach in part due to the fundamental difficulty of placebo control in dietary trials[230]. In essence, IBS patients should avoid foods that trigger an onset of their symptoms, consume a minimum of high fat foods and take part in regular physical activity[168,229,231].

RESPONSES TO PSYCHOLOGICAL FACTORS

In patients with IBS, psychological factors (such as stress factors in career, family, *etc.*) such anxiety and depression, as well as the tendency towards summarization should be evaluated in interdisciplinary collaboration. Trauma and abuse should be considered and carefully be explored. As a result, the treatment success can be positively influ-

enced. The evidence suggests that IBS patients who alternate the intestinal habits more often, are more affected by its symptoms, exhibit a greater tendency towards somatization and have a higher prevalence of psychiatric comorbidities[31,37,232-234].

COMPLEMENTARY OR ALTERNATIVE FORMS OF TREATMENT

The treatment of IBS, with forms of alternative therapy cannot be recommended on the basis of insufficient evidence. However, in IBS patients who did not respond to conventional treatment, complementary therapy could be effective. More recent studies are related to hypnotherapy[168,235-242].

MEDICATIONS\PHARMACOTHERAPY

Due to the heterogeneity of IBS, there is no standard treatment. The chronic use of drugs should be minimized as much as possible or even avoided. Different time periods may apply for not pharmacotherapy treatment approaches. However a medical therapy attempt without response should be terminated at the latest 3 months and the duration of therapy should be discussed with the patient[30-34,168].

MANAGEMENT OF IBS PAIN

Visceral hypersensitivity is felt to be a major contributing factor in abdominal pain experienced by IBS patients. Managing abdominal pain in IBS has changed very little over the past few decades. The antispasmodics remain a cornerstone of therapy. The antispasmodic are the most prescribed pharmacological agents for IBS, and their effect in reducing abdominal pain would be related to direct action in the contractility of muscle wall. As its use may lead to constipation should be used with caution in patients with IBS. Anxiolitc agents such benzodiazepines are of limited use in IBS. However, they can reduce acute anxiety that may contribute to the symptoms. Their use may be indicated for short-term (less than two weeks)[168,243-245].

ANTIDEPRESSANTS

Antidepressants have analgesic properties. The postulated mechanisms of pain modulation with tricyclic antidepressants (TCAs) and possibly selective serotonin reuptake inhibitors (SSRIs) in IBS are facilitation of endogenous endorphin release, blockade of norepinephrine reuptake leading to enhancement of descending inhibitory pain pathways, and blockade of the pain neuromodulator serotonin[32,168]. Beside imipramine, nortriptilina and desipramine, amitryptline are of the tricycle antidepressant drugs commonly used in the treatment of IBS patients at low doses. TCAs and SSRIS appear to be more effective than placebo in the overall reduction of symptoms associated with IBS. However, the degree of tolerability and safety of use of these patients is not well defined[246-250].

MANAGEMENT OF IBS-C

Dietary modifications and lifestyle should be the initial tools of the treatment of patients with constipation predominant IBS who have mild to moderate symptoms. The consumption of fiber-enriched foods and the increased fluid intake to prevent stool dehydration should be stimulated by the physician in this sub-group of IBS patients. Some improvement has been demonstrated in primary complains. However some patients may experience increased bloating. There is no evidence for the use of laxatives in patients with IBS[168]. In refractory cases polyethylene glycol can be used to improve only the frequency of bowel movements and gaseousness due to colonic metabolism of non-digestible[251,252].

Lubiprostone is a locally acting chloride channel activator that enhances chloride chloride-rich intestinal fluid secretion[32,253]. In a first step it was approved by the Food and Administration (FDA) for use in chronic idiopathic constipation and for women with IBS-C. However, its use is currently only suitable for women with IBS and severe constipation that has been refractory to other forms of treatment. Serious adverse events were similar to placebo. However, the long-term security remains to be established. been refractory to other treatments[168,254-256].

Tegaserode, a first of the agonists of the 5-hydroxityptamine (5-HT4) receptor class of drugs that stimulate the release of neurotransmitters and increase colonic motility, was approved for IBS and constipation but removed from the market in 2007 because of cardiovascular side effects[32,255-258]. It's a 5-HT4 receptor agonist that in clinical trials has been reported to reduce the general symptoms of IBS patients in comparison to attested placebo[259]. The Linaclotide, a guanylate cyclase agonist stimulates intestinal fluid secretion and transit, has been approved by the United States FDA for treatment of IBS with constipation in 2012. Their approval was two randomized controlled trials in phase Ⅲ. The patients initially randomized to placebo had significant improvement in abdominal pain and complete and spontaneous bowel movements. Diarrhea was the most common side effect. However, the long term risks of linaclotide are unknown and therefore its role on the treatment of IBS with constipation remains to be determined[260,261].

MANAGEMENT OF IBS-D

In this group of patients the anti-diarrheal agents are generally effective. There is evidence which suggests that the use of regular low doses of anti-diarrheal agents could be effective in such patients[168]. Among the most commonly used anti of diarrhea agents loperamide is one that has been more studied in patients with diarrhea predominant IBS. Constipation is the major side effect of Loperamide[262,263]. It should not be used in patients with constipation and in patients with IBS diarrhea con-

stipation alternating with diarrhea should be used with caution[168]. In patients with diarrhea predominant IBS reports of stressors (*e.g.*, eating, stressful encounters, travel) that lead to symptoms are frequent. When the predictors of crises are known the physician may start a first line of treatment, using antidiarrhea agents[263]. The use of cholestyramine could be beneficial in patients with IBS-D. However, there are still no definitive evidence for its use in IBS treatment[168].

Alosetron (such as cilansetron, ondasetron and granisetron) is a 5-hydroxitriptamine (serotonin) 3-receptor antagonist. Its modulates visceral afferent activity from GI tract and in IBS patients could act favorably on colonic motility and secretion and afferent neural systems Constipation was reported in approximately one third of patients using alosetron. It was recertified by the FDA (after the withdrawal from the market) with restrictive guidelines and is prescribed under a specific Protocol. Its benefits are more favorable in women with severe IBS and diarrhea that are refractory to conventional therapies[168,264-268].

MANAGEMENT OF IBS WITH CONCOMITANT BLOATING AND THE USE OF ANTIBIOTICS IN IBS

Abdominal bloating, a symptom commonly witnessed in IBS patients, is unfortunately very subjective and often observed in constipation predominant IBS patients. Probable mechanisms of bloating include: psychosocial, weak abdominal muscles, paradoxal relaxation of abdominal muscles and changes in visceral sensitivity. The role of prokinetic agents, simethicone and activated charcoal need to be better assessed with further well-designed studies. Dietary fiber supplementation and no absorbable sugars like lactulose can worse bloating and gaseous food, beans, carbonated beverages can lead to aerophagia symptoms. Some patients with IBS have shown improvement in symptoms of bloating, abdominal pain, or altered bowel habits. when treated with antibiotics[266-268]. The mechanism responsible for the improvement of the symptoms of these patients could be the suppression of gas produced by colonic bacteria or by alteration of colonic flora or by decreasing of the small bacterial overgrowth. It's a question to be answered[269-271]. However, the benefit from the treatment appears to be transient. Currently is not recommended breath testing for intestinal bacterial overgrowth neither. It is not recommended to use antibiotics routinely for all patients with IBS and there are no data available to justify the prolonged use of of nonabsorbable antibiotics in these patients[168]. In patients with moderate to severe IBS without constipation (particularly those with bloating) who failed to respond to all other therapies it's reasonable to try a 2 wk trial (not long term) of a nonabsorbable antibiotic such rifamixin.

PROBIOTICS USE IN IBS PATIENTS-A SHORT-REVIEW

The rationale for the use of probiotics in IBS is its association with infectious diarrhea. It's accepted that IBS-like symptoms are highly prevalent in the months after cure from infectious enteritis. About 7%-30% of patients with infectious diarrhea can develop IBS, in particular associated after travel to tropical countries. Among the possible mechanisms of probiotic therapy is the promotion of the endogenous defense barrier of the gut. These include the normalization of intestinal permeability and increase intestinal microecology changed, as well as improvement of gut immune barrier through the downregulation of a proinflammatory State[272]. The *Bifidobacteria*, *Saccharomyces boulardii* and other combinations of probiotics demonstrate some efficacy in IBS. The *Bifidobacteria* (especially *Bifidobacterium infantis* 35624), *Saccharomyces boulardii* and other combinations of probiotics demonstrate some efficacy in IBS Trials to date remain conflicting and no clear benefit has yet to be established for lactobacilli[273]. However, due to the number of clinical studies available, the role of probiotics in the relief of symptoms of IBS remains uncertain.

CONCLUSION

IBS affects up to one in five people at some point in their lives. However its remains a clinical challenge in the 21st century. The pathogenesis of IBS is likely multifactorial, including disorders the intestinal barrier, motility, secretion, visceral sensitivity and interactions between psycho logic and psychosocial factors. The biopsychosocial model is the most currently accepted for IBS. It's not confirmed by a specific biomarker. Guidelines emphasize that IBS is not a diagnosis of exclusion and encourage clinicians to make a positive diagnostic using the Rome Criteria alone Today the Rome Criteria Ⅲ are the current gold-standard for the diagnoses of IBS.

IBS has no definitive treatment but could be controlled by eliminating of some exacerbating factors such certain drugs, stressor conditions and changes in dietary habits. Traditional management of IBS has been symptom based. Because of the abnormalities in bowel states associated with each IBS subtype, it is not likely that one agent would successfully treat all three subtypes. As a result, clinical trials have focused, for the most part, on one IBS subtype. The modulation of the brain-gut axis is being seen as an attractive target for the development of novel treatments for a wide variety of disorder. However, the cornerstone of its therapy is a solid patient physician relationship. There are no recommendations for preven-

tion for IBS.

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