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AN OVERVIEW ON IRRITABLE BOWEL SYNDROME DIAGNOSIS AND MANAGEMENT IN PRIMARY HEALTH CARE CENTERS

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ABSTRACT.

Background: Irritable bowel syndrome is the most prevalent gastrointestinal disease characterized by recurrent abdominal pain or discomfort associated and relieved by defecation. Irritable Bowel Syndrome (IBS) is the most common functional gastrointestinal disorder where no obvious structural or biochemical etiology can be found. It is two times more prevalent in women than in men. Objective: In this study, we aim at giving an overview of IBS and the pathophysiology, predisposing factors, and management options. Methodology: We searched the PubMed database looking for relevant articles. Three mesh terms "Irritable Bowel Syndrome," "Pathophysiology", and "Management" were used. Conclusion: Irritable Bowel Syndrome (IBS) is a multifactorial disease in which one or multiple factors might be involved. It is classified according to the stool pattern to IBS with constipation, diarrhea, mixed, or unclassified. Management should involve and target various pathways, including the predominant symptoms and the believed predisposing factors, such as psychosocial factors, diet modifications, or enhance gut microbiota.

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Introduction

Overview and Diagnosis

Irritable Bowel Syndrome (IBS) is the most prevalent gastrointestinal condition worldwide, with a prevalence of 10%-20% [1, 2]. It is defined as a presence of abdominal pain or discomfort associated with impaired bowel habits, bloating, or distension in the absence of other organic gastrointestinal (GI) diseases [1-3]. Symptoms can vary from mild to severely debilitating, and 1.5 to 2 times more common in women than men [1, 2]. Although there is no reported mortality related to IBS, this condition may decrease life quality in many people with severe disabilities; therefore, seeking medical advice has been significantly increased [3, 4]. Diagnosis of IBS is mainly clinically by addressing the typical symptoms, and investigations are generally used to rule out other similar GI disorders such as Inflammatory Bowel Disease (IBD) or coeliac disease [4]. Due to the absence of specific laboratory tests, markers, or radiological studies that can establish IBS diagnosis, multiple diagnostic criteria have been published to diagnose IBS [5]. The Rome consensus criteria were established in 1989 for diagnosis guidance, and the most recent Rome IV criteria were published in May 2016 (**Table 1**) [5].

Over the past decades, IBS has not been linked to an underlying structural or biochemical basis, and treatment of IBS is usually focused on the predominant symptom that the patient experiences [4]. Consequently, treatment is inadequately effective, and the background of the condition has been unchanged by most therapeutic interventions [4]. Irritable Bowel Syndrome (IBS)can be associated with multi-comorbidities, including somatic pain syndrome (fibromyalgia, chronic fatigue

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syndrome, and chronic pelvic pain), other GI disorders (gastroesophageal reflux disease, non-cardiac chest pain, and dyspepsia), and psychological symptoms (depression, anxiety, & somatization) [1, 6].

Table 1. Rome IV Diagnostic Criteria for IBS

A Recurrent Abdominal Pain for at Least 1 Day per Week in the Past 3 Months, Associated with 2 or More of the Following:
1. Related to Bowel Movements
2. Associated with Altered Stool Frequency
3. Associated with Change in Stool Form

Classification and Clinical Features

Classification of IBS was made clinically according to the stool pattern into IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed pattern IBS (IBS-M), or unclassified IBS (IBS-U) (**Table 2** shows a detailed classification of IBS) [2-6]. Women are more likely to complain of IBS with constipation and men more commonly have IBS with diarrhea [1]. Most patients with IBS have a chronic relapsing pattern in which symptoms may change over time, with a worsening rate of 2%-18%, stable disease in 30%-50%, and improvement in 12%-38% [1, 6]. Although abdominal pain is the most common reported symptom, IBS can present with a wide range of GI symptoms, and it varies from person to person [2, 5]. Patients with IBS may complain of bloating, a sense of incomplete evacuation, urgency, straining, diarrhea, and constipation [5].

Abdominal pain due to IBS is crampy or colicky with variable location and intensity [5]. The pain is typically related to bowel motion, with pain relief after defecation in some patients, and pain worsening during defecation for others [5]. Moreover, specific meals and emotional stress aggravate abdominal pain and bloating in some patients [2, 5]. Patients with IBS-D experience frequent soft stool with soft blobs, fluffy pieces, or watery stool [5]. Bowel motions occur during the day and usually associated with meals [5]. Almost half of the patients with IBS report stools with mucus discharge [5]. Patients with IBS-C usually report hard stool with periodic bowel motions and incomplete evacuation or tenesmus [5]. Certain alarm features must notify the physician that the diagnosis is possibly organic rather than functional [2]. These alarm features include weight loss, nocturnal awakening due to other GI symptoms, bloody stool, family history of GI cancer or IBD, abnormal laboratory testing, recently used antibiotics, and fever (**Table 3**) [2,5].

Table 2. IBS Classification According to Bowel Habits.

IBS Subtype	Manifestation
IBS-C	Constipation Predominance: >25% Hard Stools and <25% Loose Stool
IBS-D	Diarrhea Predominance: >25% Loose Stool and <25% Hard Stool
IBS-M	Mixed Stool Habits: >25% Loose Stool and >25% Hard Stool
IBS-U	Unclassified: <25% Loose Stool and <25% Hard Stool

Discussion

Pathophysiology:

Irritable Bowel Syndrome (IBS) is the most common functional GI disorder (FGD) [3]. FGDs are defined as disorders manifested by recurrent and persistent GI symptoms that are not caused by a structural or biochemical basis [3]. The exact pathophysiology of IBS is not well understood [1]. However, it is thought to be potentially related to multifactorial factors, including genetics, gut immune system dysfunction, alteration of gut microbiota and bowel motility, intestinal permeability, diet intolerance, and psychosocial or functional brain alterations [1-3]. The intestinal mucosa of some patients with IBS showed activation of the innate and adaptive immune system [1]. An increase in small and large intestine permeability with visceral and thermal hypersensitivity has been reported in IBS-D patients [1, 6]. The fecal microbiota is significantly impaired in IBS patients, reflecting the impact of genetic factors, stress, infection, and drugs or antibiotics use [1]. The relation between functional brain disorders and impaired gut microbiota that exacerbate IBS will be explained further below.

Post Infectious Irritable Bowel Syndrome IBS-PI:

In some cases, IBS might be developed after GI infection (postinfectious IBS, IBS-PI), described by two or more of the following: fever, vomiting, diarrhea, or positive stool culture [6]. Symptoms of IBS-PI are similar to IBS-D, but typically follows a GI infection [7]. IBS-D presentation can mimic several diarrheal conditions, including parasitic infections such as giardiasis, fructose and bile acid malabsorption, small intestinal bacterial overgrowth, inflammatory bowel disease, celiac disease, and microscopic colitis [8]. IBS-PI has been increasingly linked to the evidence of immune activation post GI infection [9]. About 1/10 patients with IBS report that their IBS symptoms started with an infectious illness [9]. Prospective studies have concluded that 3%-36% of enteric infections lead to persistently new IBS symptoms [9]. The IBS-PI duration and intensity are generally related to the infecting organism [9]. In viral GI, symptoms are generally short-term, while bacterial, protozoal, and helminth enteritis are associated with prolonged IBS-PI [9].

Predisposing factors for IBS-PI include prolonged infection, toxicity produced by certain bacterial strains, smoking, mucosal degree of inflammation, female gender, depression, recent antibiotics use, and preceded adverse events within three months [9]. Age more than 60 years considered protectant against IBS-PI [9]. The mechanism of IBS-PI remains unclear but could be related to residual inflammation or persistent changes in mucosal immunocytes, enterochromaffin, cytokines and mast cell activation, enteric nerves, gastrointestinal microbiota alteration, and gut-brain impaired interaction [7, 9]. These findings suggest that activation of the immune system may play a significant role in the pathogenesis of IBS [9]. It is crucial to rule out persistent GI infection before diagnosing IBS-PI [7]. Although the prognosis is commonly acceptable, some patients may develop persistent symptoms and progress to IBD [7],

Table 3. Red Flags Symptoms

• Age >50 Years
• Nocturnal Awakening Symptoms, Particularly Diarrhea
• Blood in Stools
• Fever
• Weight Loss
• Recent Antibiotics Use
• Abnormal Laboratory Findings: Anemia, Raised Inflammatory Markers
• Family History of Inflammatory Bowel Disease or GI Cancer

The Gut Microbiota:

The human body composed of trillions of microbes inhabiting the gastrointestinal tract, and it covers more than 200m square of mucosal surface [10]. The microbes are ten times higher in number than our body cells [10]. The mucosal surface separates and protects our tissues from the microorganisms by the immune system, of which a significant part of the body's immunological defense is located within the GI system [10]. Generally, our microbiota remains stable over a long period, and with age increase, the microbiota becomes more pro-inflammatory, which might be linked to many adverse health events [10]. In patients with IBS, a significant functional modification of the microbiota in the colon leads to a change in microbiota diversity, immunology, the integrity of the gut barrier, and gut-brain signaling [10]. A recent meta-analysis confirmed the association between probiotics in IBS and showed that its impact in IBS is highly considerable [11]. The exact role of microbiota diversity in IBS is unclear [5]. Small bacterial intestinal overgrowth (SIBO) is found to be prevalent in IBS, and whether SIBO is the etiology of IBS remains questionable [7, 9]. Studies have shown that in patients with IBS-D, the mucosal microbiota increases in Bacteroides and Clostridia, and reduction in Bifidobacteria [5, 9]. The fecal composition of Bifidobacteria is indirectly related to the pain score in IBS [5]. A meta-analysis suggested microbiota's role in IBS after concluding the efficacy of probiotics in IBS symptoms, especially in abdominal pain and bloating [5]. Additionally, a mixture of probiotics has been associated with slow colonic transit in IBS-D patients, implying that gut microbiota's diversity may play a role in IBS symptoms [5]. Therefore, it can be concluded that microbiota plays a major role in IBS symptoms; still, it cannot be the only explanation, and the relation between SIBO and IBS remains uncertain [9]. Further studies are needed to understand the association between IBS and gut microbiota.

The Gut-Brain Axis:

Clinical studies have shown that psychological stress has a major impact on IBS, although whether these factors directly impair the GI function remains an area of debate [9, 10]. Also, it is suggested that GI dysfunction can change the central process [9]. There is good evidence that IBS is associated with childhood or adulthood abuse, although whether it directly causal to IBS remains in dispute [9]. Furthermore, the relation between mental health conditions such as anxiety or depression and IBS has been reported [12]. This association led some physicians to categorize IBS as a psychiatric illness [12]. The central nervous system regulates various body functions such as secretion, motility, and blood flow [9], and the gut signals are involved in regulating reflexes [9, 10]. Psychological stress can significantly alter gut sensitivity, motility, secretion, permeability, and mucosal immune activation [10]. These alterations are influenced by CNS, peripheral neurons, and GI microbiota [10]. Therefore, stress-induced gut-brain axis stimulation which can cause IBS symptoms to flare-up [10]. IBS is considered a stress-sensitive disorder, and IBS management must address the psychological part [10]. Over the last years, the gut-brain axis concept has been more understood and clarified [10]. Current evidence showed that the gut-brain axis is involved in the microbiota to brain signaling by various mechanisms, including endocrine and neurocrine pathways [10]. Consequently, the brain can alter the diversity of the microbiota and cognitive behaviors through the autonomic nervous system [10].

The severity of IBS and psychological illness is common, and the prevalence of at least one psychiatric illness typically ranges from 40% to 60% and has been reported as high as 80% [13]. Moreover, the severity of IBS symptoms is directly related to comorbid psychiatric disease, particularly anxiety and depression [13]. A review reported that an increase in stressor score highly corresponds to the progression from non-IBS patients to IBS patients [13]. Further, major life traumas such as separation of a close relationship, marital separation, a family member left home, or a serious girl/boyfriend relationship break-up were reported frequently 38 weeks before the onset of IBS symptoms [13]. Additionally, many studies have concluded that Early Adverse Life Events (EALs) are directly associated with IBS prevalence [13]. Early Adverse Life

Events (EALs) refer to traumatic exposures during childhood, such as maladjusted relationships, death or severe disease of a parent, and physical, sexual, or emotional abuse [13]. Meanwhile, the evidence of IBS severity and psychological stress is an area of controversy [13]. Surdea-Blaga et al., in his review, have concluded that stressful life accidents can worsen abdominal pain and distention in up to one-third of IBS patients [13]. Oppositely, Blanchard et al. showed that the relation between IBS symptoms and stress was reciprocal, not causal [13]. In another cross-sectional study conducted with 153 patients with various IBS subtypes, Farzaneh et al. found no significant difference in the psychological factors in IBS patients [13].

Management:

Taken into account the multiple factors involved in the pathophysiology of IBS, treatment should be classified and targeted the follows Diet modification, Normalization of gut microbiota, normalization of mucosal inflammation, normalization of intestinal motility, normalization of colonic bile acid overload, and correct brain-gut axis dysfunction and its regulatory pathways [14].

- **Diet Modifications:**

Diet modifications are feasible therapeutic modules that have been quickly and widely assumed by the general consumer market [14]. The mechanism and the criteria of diet modification remain unclear, but around 60% of IBS patients believe that food aggravates their symptoms [14, 15]. Many patients noticed worsening of IBS symptoms related to a specific food, commonly in dairy, fructose, wheat, and caffeine [15]. The dietary modification includes a reduction of caffeine consumption, gluten, and alcohol [15]. Over the past decade, an interesting nutritional approach has been published, including restrict fermentable short-chain carbohydrates, termed fermentable, oligosaccharides, disaccharides0, and polyols (FODMAPs) [15]. This approach has shown promising outcomes in IBS treatment [15]. With the strong evidence of the FODMAPs approach, dietary therapy can no longer be neglected for IBS treatment [15].

- **Symptomatic Treatment:**

This approach has been linked to antispasmodics, bulking agents, laxatives, and antidiarrheal drugs [14]. **Antispasmodics** are medications used to relax the smooth muscles via anticholinergic effect or calcium channel antagonism [16]. Examples of antispasmodic agents, including hyoscyamine, alverine, dicyclomine, pinaverium, scopolamine, and trimebutin [16]. Generally, these agents have been utilized to reduce GI motility symptoms, such as abdominal pain or discomfort [16]. Besides, they have been used in combination with other agents such as acetaminophen, simethicone, and benzodiazepine to reduce GI discomfort [16]. **Bulking agents** are preferably used in IBS-C that increase stool frequency by the natural fiber contents [16]. Other studies showed that fiber supplements do not improve abdominal pain, IBS symptoms score, or overall assessment [16].

Laxatives are usually used for IBS-C treatment due to their efficacy in chronic idiopathic constipation [16]. Examples of these agents include polyethylene glycol and lactulose, working by increasing water into the intestinal lumen to decrease intestinal transit time [16]. Laxatives have approved their efficacy for relieving constipation related to IBS, but no efficacy has been reported for abdominal pain, bloating, or other symptoms compared to placebo [16]. **Antidiarrheal agents**, such as Loperamide, are synthetic opioids that prolong intestinal muscle transit time and inhibit peristalsis [16]. Loperamide has been studied in different IBS subclasses, but it is most effective on IBS-D due to its ability to reduce fecal volume and transit time [16].

- **Gut-Brain Axis Dysfunctional Treatment:**

As mentioned earlier, many neurotransmitters, neural circuits, and integrated brain, spinal, and ganglia structures potentially play a role in producing pain and IBS associated symptoms [14]. Unfortunately, we are unable to specify the level of disturbances that occur in the brain-gut axis [14]. Generally, neuropharmacological medications are uncertainly effective in the brain-gut axis disturbance [14]. Moreover, the psychological approach reports some improvement, although highly dependent on time and operator skills [14]. Physicians must be aware of the notably high placebo response rates (35%-70%) observed in many controlled trials of IBS and other functional-type conditions [14]. **Antidepressant drugs** have a role in IBS symptoms control, such as tricyclic antidepressants (TCA), selective reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI) [14, 16].

These agents are believed to relieve abdominal pain associated with IBS via centrally-mediated antinociceptive pathways [16]. Additionally, these agents may affect the transit time of the GI tract [16]. A recent trial showed that all antidepressants significantly decrease abdominal pain, IBS symptom score, and overall global assessment [16]. **Cognitive-behavioral therapy (CBT)** has effectiveness in relieving IBS symptoms [17]. There was a significant improvement in regards to reducing abdominal pain and the number of diarrheal episodes [17]. CBT can improve the GI symptoms of IBS and symptom-related distress by interaction among psychological (i.e., cognition, emotions, & behavior), social (i.e., support, modeling), and physiological factors [17].

Conclusion

Irritable bowel syndrome is a common gastrointestinal condition characterized by abdominal pain or discomfort associated with watery diarrhea, constipation, or both. The severity of IBS symptoms has been directly linked to the severity of psychological stress. The diagnosis is clinically addressed following the Rome criteria IV, and investigations are generally performed to rule out other gastrointestinal diseases. It is believed that IBS is not related to the organic or structural disease. The pathophysiology is attributed to various factors, including genetic factors, immunological response, gut microbiota, dietary intake, intestinal permeability, and psychological factors. Management is ordinarily targeting the patient predominant symptoms, psychosocial support, dietary modifications, and restore the impaired gut microbiota. Prognosis is generally good, but symptoms can alter the daily patient activities and decrease life quality.

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