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Risk Associated with Antibiotic in Irritable Bowel Syndrome (Ibs), Role of Microbiota and Future Aspects

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ABSTRACT
Irritable bowel syndrome (IBS) is functional gastrointestinal (GI) disorder that characterized by abdominal pain in relation to disturbed bowel habits. It is a substantial burden on both patient health – related quality of life and healthcare cost. Although various path physiologic mechanisms have been formulated including visceral hypersensitivity, altered bowel motility, gut- brain dysregulations but it is believed that gut microbiome plays an important role in the genesis of symptoms. The composition and diversity of the gut micro biota can be modified by use of antibiotics, as they have the capacity to diminish the levels of advantageous bacteria while allowing the proliferation of detrimental bacteria. It is well known that micro biome takes a crucial role in development of IBS, but antibiotics itself is a potential risk factors for IBS has not been clarified yet. However, lack of highly predictive diagnostics biomarkers and the complexity and the heterogeneity of IBS patients make management difficult and unsatisfactory in most of the cases, thereby reducing patient health- related quality of life and increasing the sanitary burden. So, this review would help us to understand the risk factors associated with antibiotics in developing IBS, the role of gut micro biome and the other potential future approaches which are useful for the diagnosis, prevention and treatment of irritable bowel syndrome.

Keywords: Irritable bowel syndrome (IBS), Gut microbiota, Antibiotic risk

INTRODUCTION

Irritable bowel syndrome (IBS) is a prevalent disorder that displays a significant global impact on the gut-brain interaction. The occurrence of IBS exhibits variation across different countries, with higher rates observed in East Asian nations such as Japan and South Korea, in contrast to China [1]. The pathophysiology of IBS is intricate and encompasses various factors, including genetics, diet, and the gut microbiome, which may exhibit varying degrees of significance among nations [1]. The diagnosis of

IBS is founded on symptom clusters as defined by the Rome criteria, although the most recent Rome IV criteria have faced criticism for their lack of sensitivity, particularly among Asian patients. Research on IBS has also concentrated on the role of the gut-brain axis and the microbiome, resulting in an increase in scholarly publications in recent years [5]. Overall, IBS represents a condition of global significance that necessitates further investigation to comprehend its regional disparities and establish efficacious interventions [1,2].

Irritable bowel syndrome (IBS) is influenced by a myriad of risk factors. The development of IBS is associated with a variety of lifestyle factors such as smoking, body mass index (BMI), sleep duration, diet, physical activity, and alcohol consumption [3,4]. Mental disorders, namely anxiety and depression, as well as poor sleep quality, exhibit a significant association with an augmented risk of IBS [3,4,5].

It is also believed that IBS creates a interaction between the brain and gut which is characterized by abdominal pain and irregular bowel movements. Additionally, it is associated with substantial psychological coexisting conditions [6,7]. Although various path physiologic mechanisms have been formulated including visceral hypersensitivity, altered bowel motility, gut- brain dysregulations but it is believed that gut microbiome plays an important role in the genesis of symptoms. The composition and diversity of the gut micro biota can be modified by use of antibiotics, as they have the capacity to diminish the levels of advantageous bacteria while allowing the proliferation of detrimental bacteria. It is becoming increasingly recognized that gut bacteria play a pivotal role in host homeostasis and are involved in the progression and development of numerous human diseases [9,10]. Moreover, various studies have consistently shown the efficacy of microbiota-directed therapies, including prebiotics, probiotics, nonabsorbable antibiotics, dietary changes, and faecal microbial transplantation, in alleviating IBS symptoms [36,37]. So, this review would help us to understand the risk factors associated with antibiotics in developing IBS, the role of gut micro biome and the other potential future approaches which are useful for the diagnosis, prevention and treatment of irritable bowel syndrome

ROLE OF GUT MICROBIOTA IN HOST HOMEOSTASSIS

There are approximately 1014 no of bacterial cells that are inhabitant in the gastrointestinal tract of human gut [8,9]. More than 90% of the gut bacteria are belong to phyla, namely firmicutes, actinobacteria and proteobacteria. They are the predominant bacteria in a healthy adult [10,11].

Gut microbiota has been considered as an indispensable organ in the body because of their various metabolic and immune functions and most of them are mediated by different metabolites [Table 1]

Table 1: Examples of different gut microbiota and their functions

Gut microbiota	Functions
Clostridium and Lactobacillus	Metabolism of bile salts, lipids, carbohydrates and different amino acids
Bacteroides and Prevotella	Synthesis of vit k2, regulation of appetite, maintenance of intestinal epithelial integrity
Bifidobacterium and Corynebacterium	Protection against enteric pathogens

PATHOPHYSIOLOGY OF IBS:

EPIGENETIC INVOLVEMENT OF IBS: The gene most likely linked to irritable bowel syndrome (IBS), specifically IBS with constipation (IBS-C), is the gene responsible for encoding tumour necrosis

factor superfamily 15 (TNFSF15). Additional genes that have been examined in relation to IBS comprise the gene for the serotonin transporter protein (SLC6A4) and genes implicated in immune activation, bile acid synthesis, neuropeptide activity, and intestinal secretion [12,13]. Nonetheless, it is crucial to acknowledge that the correlation between these genes and IBS is still under investigation and verification. Gene polymorphism and DNA methylation another contributing factors to IBS involvement of Epigenetics. Other influencers are described below [Figure1]

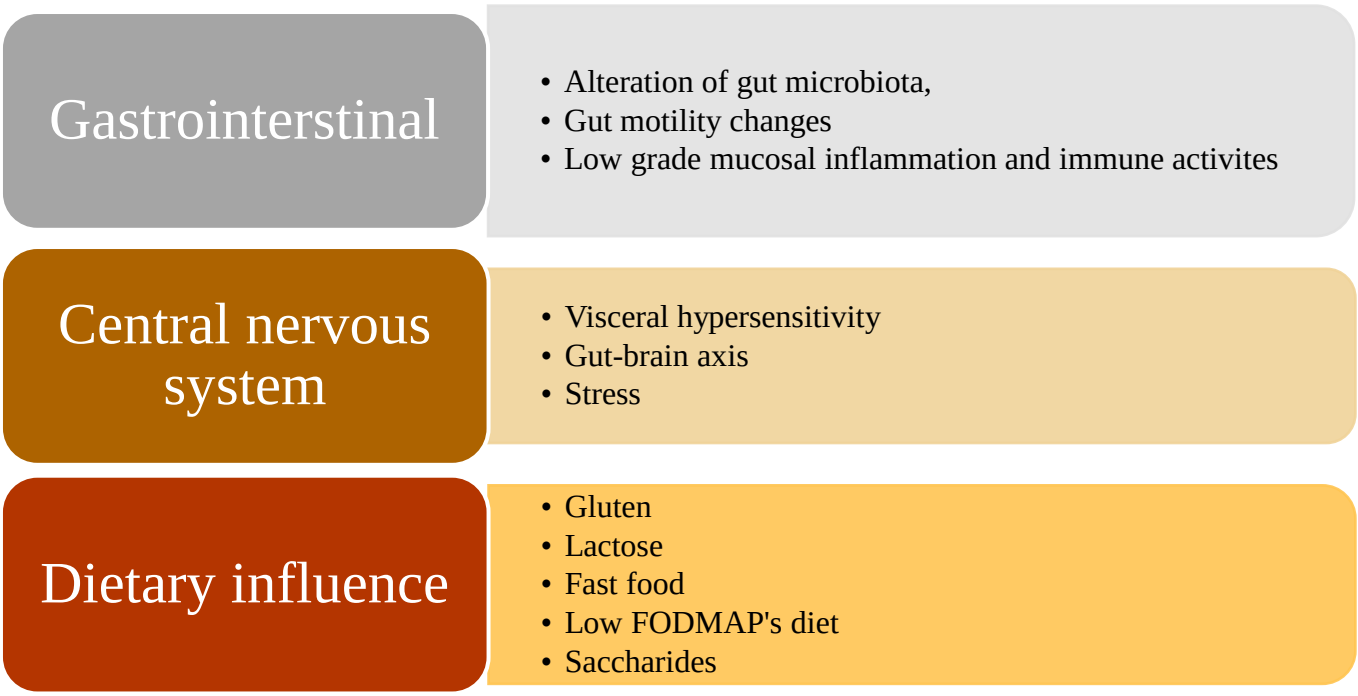

FIGURE 1: PATHOPHYSIOLOGY OF IBS

IBS –ITS COMPLICATION AND IMPACT ON GLOBAL HEALTH

Inflammatory bowel disease (IBD) is associated with cardiovascular complications. IBD patients have increased risk of atherosclerosis, thrombosis [13], and cardiovascular events. Study analyzed impact of IBD on outcomes in patients with intestinal perforation that results in IBD patients associated with increased mortality, hospital stay, and charges. Presence of sepsis and acute kidney injury further worsen outcomes. Chronic inflammation plays a role in atherogenesis, thrombosis, and myocarditis. Thromboprophylaxis is recommended in hospitalized IBD patients with active disease. The state of the intestinal microbiota and endotoxemia play a key role in the development and progression of inflammatory bowel diseases (IBD). Trimethylamine N-oxide is a factor in the early development of atherosclerosis in patients with IBD. Trimethylamine N-oxide (TMAO) has been identified as a factor in the early development of atherosclerosis in patients with inflammatory bowel diseases (IBD) [5,6,12,13]. The presence of TMAO in patients with IBD suggests a potential link between intestinal permeability, the gut microbiota, and cardiovascular complications. TMAO is produced by gut bacteria from dietary nutrients, such as choline and carnitine, and has been associated with increased cardiovascular risk. The exact mechanisms by which TMAO contributes to the development of atherosclerosis in patients with IBD are not fully understood and require further investigation. However, the presence of TMAO highlights the importance of considering the role of the intestinal microbiota and endotoxemia in the

pathogenesis of cardiovascular complications in individuals with IBD. The Rome IV criteria are used to diagnose patients with IBS. Gut microbiota, SIBO, visceral hypersensitivity, disruption of gut-brain axis, psychosocial distress, altered GI motility as potential risk factors.IBS is associated with psychosocial comorbidities impacting quality of life. Thrombotic complications are 3 times higher in patients with inflammatory bowel disease (IBD) compared to healthy individuals. Chronic inflammation and increased bleeding in the intestinal wall activate the coagulation system, impair fibrinolysis, and increase the risk of thrombotic complications [12,13].

PSYCHOSOCIAL CO-MORBIDITIES ASSOCIATED WITH IBS

Irritable bowel syndrome (IBS) is linked to significant psychosocial comorbidities, which can have a noteworthy impact on the quality of life of patients, the progression of the disease, and the financial costs of healthcare. Anxiety disorders, depressive disorders, and somatic symptom disorder are among the common psychosocial comorbidities associated with IBS. Individuals with IBS often face heightened levels of anxiety and depression in comparison to the general population [5,6,12]. The emergence and aggravation of IBS symptoms can be influenced by psychosocial factors such as stress, trauma, and adverse life events. The existence of psychosocial comorbidities in patients with IBS may influence the outcomes of treatment and the response to therapy.

EXTRAINTESTINAL MENIFESTATION OF IBS

Inflammatory bowel disease (IBD) is a condition characterized by immune dysregulation, resulting in a disorder driven by this immune dysfunction. The disease follows a pattern of relapses and remissions, with flares being marked by the presence of abdominal pain and bloody diarrhoea. The management of IBD typically involves the use of potent immunosuppressive regimens, which are often accompanied by significant toxicities. However, the introduction of biologic therapies has revolutionized the treatment of refractory cases. Surgery also plays a crucial role in the overall treatment plan, particularly for patients who present with acute mechanical complications or those who are at a high risk for colorectal cancer (CRC) and require prophylactic total colectomy. IBD is associated with various complications related to the intestines, including intestinal stricture, fistula formation, small bowel obstruction, toxic megacolon, CRC, and malnutrition. Furthermore, there are numerous extraintestinal manifestations that can affect almost every organ system, such as primary sclerosing cholangitis, ankylosing spondylitis, pyoderma gangrenosum, and uveitis [5,6,12,13]

COMPOSITION OF GUT MICROBIOTA IN PATIENTS WITH IBS

Various studies have been discussed regarding the altered composition of gut microbiota in patients with IBS, but the studied data are inconsistent and variable. A study by Dior et al;2016 stated that there is increase concentration of *Escherichia coli* and *Bifidobacterium* in stool in patients with IBS which is inconsistent with the study by Gobert et al; 2016, Shukla et al; 2015 and Su et al; 2018[14,15,16] where they showed a increase concentration of *Bifidobacterium* in stool. The discrepancy in these studies could be because of variation in diagnostics methods, study population group (different age group, lifestyle, microbial composition, prior use of probiotics, prebiotics and different antibiotics) and different study design [14,15,16,17]. Majority of the studies showed decreased amount of microbial activity in patients with IBS. [18,19,20,21]. Vast majority of the study also shown fewer faecal bacterium bacteria mainly *F. prausnitzii* which produce butyrate in the gut and increase number of *Enterobacteriacae* family,

mainly *Escherichia coli* and *Enterobacter spp.* [22, 23, 24,]. Moreover, IBS patients were also found to have reduced prevalence of *Bifidobacterium,* which provides a beneficial role to the host [25,26,27]. Although reports were inconsistent, but some of the studies showed increase or decreased numbers of Lactobacillus in patients with IBS and healthy controls [28,29,30]. Overall, there seems to be evidence to indicate that petients with IBS have decreased numbers of bacteria contributing to the maintenance of homeostasis and proper immune response, aw well as increased numbers of microbes with proinflammatory properties.

EFFECTS OF ANTIBIOTICS IN GUT MICROBIOTA AND AS RISK FACTOR FOR IBS: -

Effect on gut microbiota: -

Antibiotics discovery was a huge milestone in the history of medicine, however studies showed that improper use of antibiotics may lead to antibiotic resistance and various risk such as obesity and autoimmune diseases [31, 32, 33, 34]. For the past four decades, there has been increasing interest on effect of antibiotics on gut microbiota and many studies have been conducted till now. Most of the studies were culture-based techniques, but researchers concluded that 80% of the gut microbiota are difficult to culture in routine laboratory methods [35] so there was a shift in culture independent technique such as targeting 16S rRNA gene analysis. It is found that antibiotics has changed a dramatic loss of microbiota diversity and its composition [36, 37, 38, 39].

Various studies have shown their data and it has seen that there is an inconsistent result among the studies. This could be because of their different methodology, study population and variation in antibiotic class, pharmacokinetics, range of action and responds by different gut microbiota [40].

Vancomycin is poorly absorbed when administered orally, resulting in high fecal load. Because of that it significantly alters the composition of the gut microbiota by increasing pathogenic bacteria such as *Klebsiella*, *Escherichia*, *Shigella* and decreasing number of *Bacteroides* [39]. Lipophilic antibiotics such as lincosamides and macrolides are mostly eliminated by biliary excretion and therefore cause profound changes in the intestinal microbiota [40,41]. Changes in the microbial composition were also observed after 12 months use of clindamycin [42]

A study conducted by Haak et al [43] shown that treatment with broad-spectrum antibiotics (ciprofloxacin, vancomycin, and metronidazole) promotes the growth of *Streptococcus* and *Lactobacillus*. Furthermore, the authors found that there was reduced numbers of anaerobes producing SCFAs, such as *Bacteroides*. Another systematic review by Zimmerman et al [44] summarized the data from 129 studies on the effect of antibiotics on the composition of the gut microbiota. The authors concluded that most antibiotics (amoxicillin, amoxicillin/clavulanate, cephalosporins, lipopolyglycopeptides, macrolides, ketolides, clindamycin, tigecycline, quinolones, and fosfomycin) increase the abundance of *Enterobacteriaceae*, mainly *Citrobacter spp*., *Enterobacter* spp., and *Klebsiella spp*. These bacteria contain molecules that directly enhance the inflammatory response of the host and may play a significant role in the alteration of bile acid metabolism [45].

Another negative effect of antibiotic treatment is the loss of colonization resistance. Depletion of beneficial gut commensals, such as *Lachnospiraceae, Ruminococcaceae,* and *Clostridium scindens*, as well as changes in their metabolic activity promote overgrowth of *Clostridium difficile, Enterococcus*, and other pathogens [46, 47].

Use of anitibiotic and association of developing IBS:

The paper suggests that prior antibiotic use may increase the risk of developing irritable bowel syndrome (IBS) within 12 months. Macrolides and tetracyclines may be associated with a higher rate of IBS development compared to other antibiotic classes. The prolonged utilization of antibiotics has the potential to disturb the equilibrium of the gut microbiota, thereby resulting in the emergence of irritable bowel syndrome (IBS) [48,49,50]. The composition and diversity of the gut microbiota can be modified by antibiotics, as they have the capacity to diminish the levels of advantageous bacteria while allowing the proliferation of detrimental bacteria. This asymmetry within the gut microbiota can lead to an augmentation in intestinal permeability, inflammation, and alterations in gut motility, all of which are closely linked to the manifestation of IBS symptoms. Furthermore, antibiotics can impact the generation of short-chain fatty acids (SCFAs), which hold a pivotal role in upholding gut health. The reduction in SCFA production can further contribute to the development of IBS. It is worth noting that the precise mechanisms through which antibiotics contribute to the onset of IBS may differ depending on the type and duration of antibiotic usage, as well as individual factors [12,13,50 & figure 2]

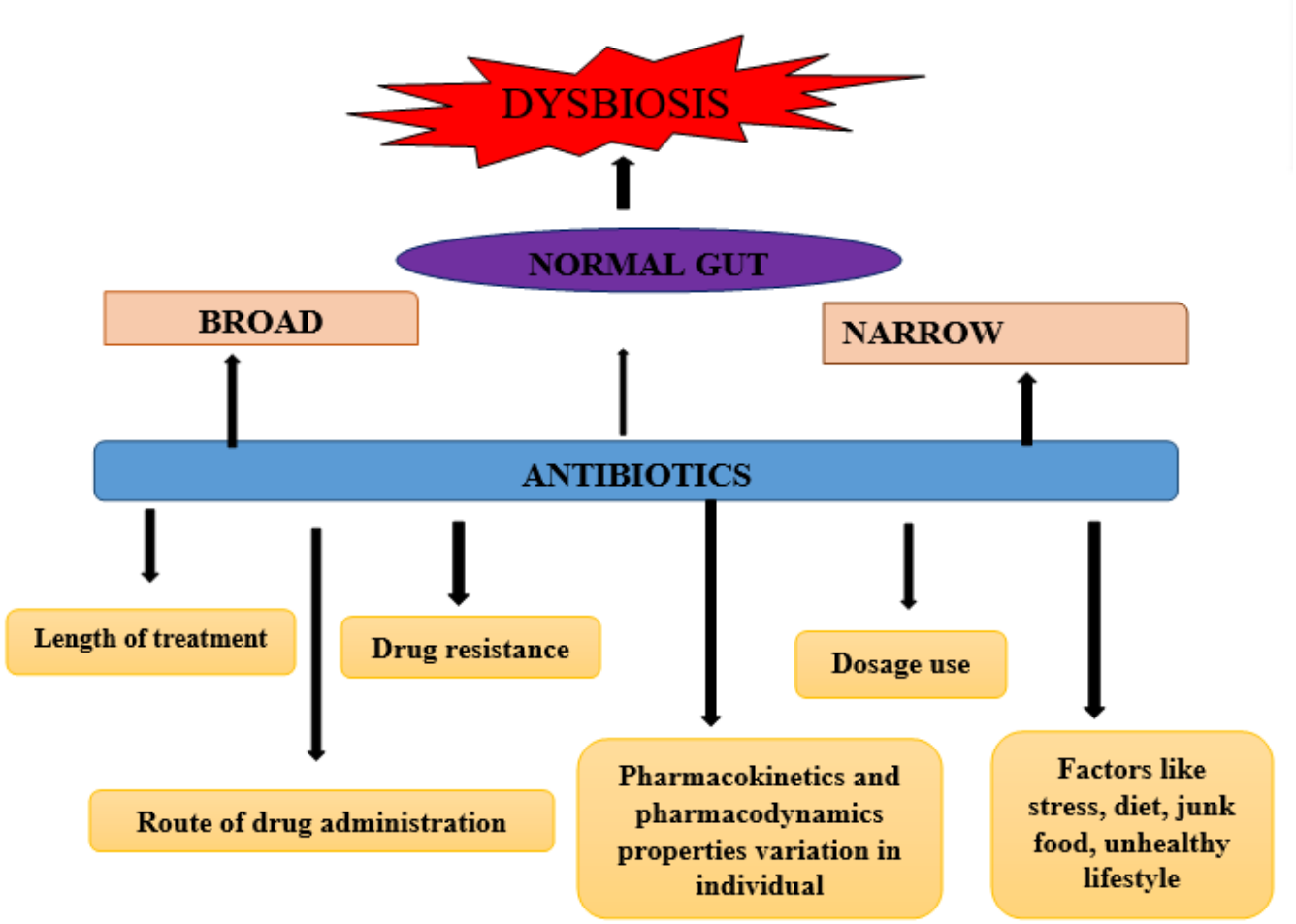

Figure 2: Association Of Antibiotic Use And Its Effect On Occurance Of Irritable Bowel Syndrome

NEWER TREATMENT MODALITIES OF IBS: FUTURE ASPECTS

The management of irritable bowel syndrome (IBS) entails a range of approaches comprising recommendations for lifestyle, medications, and psychological therapies. Medications frequently employed for the purpose of managing IBS include laxatives, antispasmodics, antimotility agents, and

neuromodulators. Furthermore, novel therapeutic alternatives for the treatment of IBS are currently being explored, such as the targeting of specific pathways that are responsible for gastrointestinal functioning [12,13,50]. While Chuna manual therapy (CMT) has demonstrated potential in the treatment of constipation-predominant IBS, further meticulously designed randomized controlled trials are imperative in order to establish stronger evidence [4]. Moreover, traditional Chinese herbal formulas, including the Chang-Kang-Fang (CKF) formula, in combination with probiotics have also exhibited efficacy in the treatment of IBS-D by means of modulating serotonin levels and enhancing intestinal barrier function [5]. In summary, the treatment of IBS is tailored to the individual patient and strives to alleviate symptoms, enhance quality of life, and target the underlying mechanisms of the disorder [13,50].

Retracted acupuncture and moxibustion in the treatment of adult diarrhoea irritable bowel syndrome: Nonpharmacological intervention

Moxibustion is a traditional Chinese medicine technique that involves burning dried mug wort (Artemisia vulgaris) near specific acupuncture points on the body to stimulate healing and restore balance in the body's energy flow. The burning mug wort can be applied directly to the skin (direct moxibustion) or placed on top of an acupuncture needle (indirect moxibustion). Moxibustion is often used in combination with acupuncture and is believed to help improve blood circulation, relieve pain, and strengthen the immune system [13,50,51].It has been used for various conditions, including digestive disorders, menstrual pain, arthritis, and respiratory conditions. However, the effectiveness of moxibustion for specific conditions is still a subject of debate and further research is needed to understand its mechanisms and efficacy.

pharmacological treatment options include peripheral opioid agonists, bile acid sequestrants, antibiotics, soluble fibers, osmotic agents, prokinetics, antispasmodics, and antidepressants. mentions that drugs with significant evidence of effectiveness include rifaximin-a, eluxadoline, and alosetron, but the last two are having less evidence on randomized control trial. lifestyle and dietary advice, probiotics, low FODMAP diet, antispasmodics, peppermint oil, tricyclic antidepressants, loperamide, laxatives, and psychological therapies. A3AR (Adenosine 3receptor agonist) are effective in relieving visceral hypersensitivity, suggesting a potential therapeutic role against abdominal pain in IBS [51,52].

Role of fodmap diet in IBS:

The FODMAP diet is a dietary approach that imposes restrictions on the consumption of specific carbohydrates referred to as fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. Its objective is to diminish symptoms in individuals with irritable bowel syndrome (IBS) by minimizing the intake of foods that can incite gastrointestinal symptoms. The FODMAP diet is regarded as a secondary therapeutic option for IBS patients who do not respond to initial advice regarding lifestyle and diet [5,6,50]. It entails collaboration with a dietician to identify and eliminate high-FODMAP foods from the diet, followed by a gradual reintroduction to establish individual tolerance levels. The importance of the FODMAP diet in the treatment of IBS lies in its capacity to alleviate symptoms such as bloating, abdominal pain, and alterations in bowel habits. Research investigations have demonstrated that the FODMAP diet can be efficacious in reducing IBS symptoms in a substantial proportion of patients. Nevertheless, it is crucial to acknowledge that the FODMAP diet is not a cure for IBS and may not completely alleviate symptoms. It should be employed as part of a comprehensive management plan

that encompasses additional therapeutic alternatives such as medications and psychological interventions.

Synbiotic maxilac: The future generation IBS treatment

It is a combination of probiotics and prebiotics, which work together to improve the balance of gut microbiota.The probiotics in Maxilac include B*ifidobacteria* and *lactobacilli,* which have been shown to increase in quantity after treatment. Maxilac has been found to reduce the number of harmful bacteria such as hemolytic *E. coli*, *Staphylococcus aureus*, and *Candida* fungi in the gut.In a study involving patients with diarrhea-predominant IBS, Maxilac was found to decrease the frequency of defecation, abdominal pain, and bloating.These positive changes in gut microbiota and clinical symptoms suggest that Maxilac can be an effective and safe part of combination therapy for IBS. Maxilac is a synbiotic drug that combines probiotics and prebiotics [51,52]. The probiotics in Maxilac include *Bifidobacteria* and *Lactobacilli*.These probiotics have been shown to increase in quantity after treatment with Maxilac.Maxilac also contains prebiotics, which are substances that promote the growth of beneficial bacteria in the gut. Probiotics work by colonizing the gut and promoting the growth of beneficial bacteria. They can compete with harmful bacteria for resources and create an environment that is more favorable for their own growth

Role of synbiotics in IBS

Synbiotics, which are a combination of probiotics and prebiotics, have been studied for their potential role in the treatment of irritable bowel syndrome (IBS).Probiotics are live microorganisms that, when consumed in adequate amounts, can provide health benefits by restoring the balance of gut bacteria.Prebiotics are non-digestible fibers that serve as food for beneficial bacteria in the gut, promoting their growth and activity [53,54].The use of synbiotics in the treatment of IBS aims to modulate the gut microbiota, improve gut barrier function, and reduce inflammation, which are all factors believed to contribute to the development and symptoms of IBS.Studies have shown that synbiotic treatment, such as the use of the synbiotic Maxilac®, can lead to positive changes in the gut microbiota, including an increase in beneficial bacteria like *Bifidobacteria* and *Lactobacilli,* and a decrease in potentially harmful bacteria like *E. coli* and *Candida fungi*.In clinical trials, synbiotic treatment has been associated with improvements in IBS symptoms, including a reduction in stool frequency, abdominal pain, and bloating.However, further research is needed to fully understand the optimal composition and dosage of synbiotics, as well as their long-term effects and potential interactions with other treatments for IBS[55].Example includes *Bifidobacteria* and *Fructooligosaccharide* (FOS), *Bifidobacteria* or *Lactobacilli* with FOS or inulins or galactooligosaccharides (GOS), *Lactobacillus rhamnosus* GG and inulins,Polyphenols.

CONCLUSION

It is now clear and consistent evidence from a variety of studies that patients with IBS have altered composition of the gut microbiota and that these alterations are related to the generation of gastrointestinal symptoms. However, studies comparing fecal microbiota in patients with IBS and healthy controls produced variable results. Until now, there is no clear-cut data on microbiome data in relation to IBS. Although many reviewed were found, but there is need of large prospective study in this regard. A thorough Analysis on gut microbiota and its different metabolites should require so that a

novel microbiota-based treatment can be done targeting the pathophysiology of IBS, rather than focusing on symptoms. A few recent studies have addressed the effects of antibiotics on gut microbiota composition, and these effects were found to be quite like those observed in IBS. We suggest that the Rome V criteria could provide a new definition of post antibiotic IBS. As major disruptors of the gut microbiota, antibiotics seem to contribute to all aspects of IBS pathogenesis. However, further research in this area is warranted.

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