Wójcik Magdalena, Dąbrowska Justyna, Szarpak Julita, Bator Damian, Nieścior Hubert, Milanowska Joanna. Irritable bowel syndrome - risk factors, pathogenesis and treatment options. Journal of Education, Health and Sport. 2020;10(9):161-171. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2020.10.09.018
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.09.018
https://zenodo.org/record/4017970

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 10.08.2020. Revised: 15.08.2020. Accepted: 07.09.2020.

Irritable bowel syndrome - risk factors, pathogenesis and treatment options

Magdalena Wójcik[1*], Justyna Dąbrowska[1], Julita Szarpak[1], Damian Bator[1], Hubert Nieścior[1], Joanna Milanowska[2]

(1) Student Science Club at the Department of Applied Psychology, Medical University of Lublin

(2) Department of Applied Psychology, Medical University of Lublin

* E-mail address: Magdalena.wojcik967@gmail.com

ORCID ID:

Magdalena Wójcik https://orcid.org/0000-0002-0999-6284

Justyna Dąbrowska https://orcid.org/0000-0002-1356-6965

Julita Szarpak https://orcid.org/0000-0002-5091-0235

Damian Bator https://orcid.org/0000-0002-8464-932X

Hubert Nieścior https://orcid.org/0000-0002-4709-4396

Joanna Milanowska https://orcid.org/0000-0001-9741-1583

ABSTRACT

Introduction: Irritable bowel syndrome (IBS) is a chronic common gastrointestinal disorder. It contributes to the burden of patients and society due to direct medical costs, lost productivity and also affects the quality of life. The etiology of irritable bowel syndrome is not fully understood which makes it difficult to treat patients more effectively.

The aim of the study: The purpose of this systemic review was to collect and analyse current data of risk factors, pathogenesis and treatment options of irritable bowel syndrome.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed and Google Scholar database was carried out using the following keywords: irritable bowel syndrome, gut microbiota, treatment

Description of the state of knowledge: Altered gastrointestinal motility, visceral hypersensitivity, post infectious reactivity, brain-gut interactions, alteration in fecal microflora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation are considered to contribute to the onset of IBS. The biopsychosocial model of illness and disease aims to help understand better the bi-directional relationship between mind and body. Patients suffering from IBS use pharmaceutical treatment but also complementary and alternative medicine. Probiotic and fecal microbiota transplantation are gut microbiota oriented treatment options.

Summary: The pathophysiology of IBS is not clear . Alterations in bidirectional brain-gut microbiota interactions are believed to be involved in the pathogenesis of well-known brain-gut disorders such as IBS. Human microbiome research continues to expand, although it still requires more study.

Key words: irritable bowel syndrome, gut microbiota, treatment

1. Introduction

Irritable bowel syndrome (IBS) is a chronic common gastrointestinal disorder. Abdominal discomfort/pain is the main symptom and is associated with altered bowel habits and abdominal bloating/distension [1]. IBS affects around 5%-20% of individuals worldwide [2]. The prevalence varies according to country and criteria used to define IBS [3].Irritable bowel syndrome is responsible of reduced quality of life, also patients suffering from IBS may more often be unable to work [4]. Four subtypes of IBS can be distinguished: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), mixed-diarrhea-and-constipation IBS (IBS-M) and unclassified IBS [1]. Trying to understand the pathogenesis of irritable bowel syndrome many targets are considered such as altered gastrointestinal motility, visceral hypersensitivity, post infectious reactivity, brain-gut interactions, alteration in fecal microflora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation [5]. However, other somatic comorbidities such as pain syndromes, overactive bladder and migraine often coexist with IBS as long as psychiatric conditions (like depression and anxiety) and visceral sensitivity [6]. Irritable bowel syndrome was described to 150 years ago and yet still remains a clinical challenge [3].

2. Epidemiology and risk factors

Prevalence estimates for irritable bowel syndrome vary greatly internationally, both within and between countries [7]. Although IBS is not associated with increased mortality rates, it still contributes to the burden of patients and society due to direct medical costs, lost

productivity, and reduced health-related quality of life [8]. Irritable bowel syndrome has an insidious onset, partially due to the symptoms that are commonly experienced within the population, This can lead to discrepancy between incidence of the first occurrence of symptoms and the first diagnosis of IBS [7]. IBS is considered a functional disorder. Those of functional disorders that do not have a specific biomarkers tend to be underdiagnosed in the primary care setting [9]. IBS has a pooled global prevalence of 11.2%. Most European countries, the United States and China report the prevalence rate of 5–10%. However, date from most African and many Asian countries are unavailable which may be due to the inability to differentiate between infectious diarrhoea and IBS in tropical countries [6]. However, female predominance in IBS was not observed in newly developed Asian economies. It has been proposed that factors like westernization of the diet and increased psychosocial stress due to the evolution of Asian economies may contribute to the rise to a more uniform worldwide prevalence of IBS [10].

Traditionally, irritable bowel syndrome was known as a condition of visceral hypersensitivity manifested as abdominal discomfort or pain and gastrointestinal motor disturbances which manifested as diarrhea or constipation. It has been suggested that mixed or alternating IBS may be secondary to psychological disturbances [11]. The biopsychosocial model of illness and disease aims to help understand better the bi-directional relationship between mind and body. Irritable bowel syndrome results from dysregulation of central and enteric nervous system interactions. Patients suffering from IBS often mostly complain about "abdominal" symptoms. However, it is important to recognize stress factor [12].

The study by Bradford et al. (2011) shows the association between early adverse life events and IBS. Early adverse life events are traumatic experiences during childhood that include physical, sexual, or emotional abuse but also discordant relationships with primary caretaker, or the loss of a parent. According to the study, comparing to healthy control group, many types of early adverse life events are more prevalent in IBS, especially among women. Moreover, they were linked to a greater prevalence of psychological and somatic symptoms [13]. Family history is a known risk factor/predictor of irritable bowel syndrome. IBS aggregates strongly in families [14]. Van Tilburg et al. (2015) examined familial aggregation of irritable bowel syndrome *via* parental reinforcement/modeling of symptoms, coping, psychological distress, and exposure to stress. Results of the study showed that multiple factors influence the reporting of children's gastrointestinal and non-gastrointestinal symptoms. Familial aggregation may be explained by many psychosocial similarities between the mother and child such as the mother's modeling of IBS symptoms, shared psychological distress, and shared family stress [15]. Kalantar et al. (2003) showed that occurring familial aggregation of IBS supports a genetic or intrafamilial environment component. Although, this may be also in part due to familial aggregation of somatisation [16]. The study of irritable bowel syndrome in twins by Bengtson et al. (2006) showed that restricted fetal growth significantly affected susceptibility to IBS later in life. Birth weight less than 1500 g influenced age at onset of symptoms. It was also noticed that genetic contribution appeared to be important for IBS among females [17].

The aetiology of irritable bowel syndrome is still unclear. However, many factors have been suggested including genetics, visceral hypersensitivity, disordered gastrointestinal motility, abnormalities of the brain–gut axis, and alterations in the gut microbiome [18]. Additionally, lifestyle factors such as diet [19], alcohol consumption [20] and physical activity [21] have been linked to IBS.

3. Symptoms and pathogenesis

Irritable bowel syndrome is present when all three of the following are fulfilled:

- The patient has chronic symptoms, i.e. lasting longer than 3 months (e.g., abdominal pain, bloating), that are ascribed by both patient and physician to the gut and that are usually accompanied by altered bowel habit.
- The symptoms are the reason why the patient has consulted the physician for help and/or is worried, and are so strong that the patient's quality of life is significantly impaired by them.
- It is a precondition that no changes are present which are characteristic of other diseases that are likely to be the cause of the symptoms (strong consensus) [22].

Most likely is that many factors contribute to the etiology of IBS. Those factors are psychosocial stressors, gut flora alterations along with abnormal gastrointestinal motility and secretion and altered visceral perception [23].

Visceral hypersensitivity and altered intestinal motility are supposed to be the reason for IBS symptoms of chronic abdominal pain and an altered bowel habit. Visceral hypersensitivity, or an increased perception of stimuli originating from the viscera is a hallmark feature of IBS and involve both hyperalgesia, meaning an increased response to a normally painful stimulus and allodynia which means a painful response to a normally innocuous stimulus [24]. Many factors are thought to influence visceral hypersensitivity. These are factors such as acute physical or psychological stress, cognition, or adverse experience during early life. Moreover, visceral perceptron can be influanced by some pharmacological manipulations with amitriptyline. Corticotropin-releasing hormone (CRH) and its receptors may modulate visceral pain hypersensitivity, but also serotonin (5-HT) can modulate visceral perception [25]. In the study by Ludidi et al. (2014) groups of IBS patients with visceral hypersensitivity and IBS patients without visceral hypersensitivity were compared. The result showed that IBS patients with visceral hypersensitivity are significantly younger and report significantly increased intensity of GI symptoms [26].

The postinfectious irritable bowel syndrome (PI-IBS) is characterized by the sudden onset of symptoms mentioned in the diagnostic criteria for irritable bowel syndrome that appear after an episode of acute infectious gastroenteritis with by two or more of the following symptoms and findings: diarrhea, vomiting, fever and a positive stool culture result [27]. Pathophysiologic mechanism for PI-BS may be associated with altered motility, increased intestinal permeability, increased numbers of enterochromaffin cells and persistent intestinal inflammation, characterized by increased numbers of T-lymphocytes and mast cells, and increased expression of proinflammatory cytokines. Due to this, it may be possible that an exposure to pathogenic organisms disrupts intestinal barrier function, alters neuromuscular function and triggers chronic inflammation which sustain IBS symptoms [28]. PI-IBS is more prevalent after bacterial than viral infections. Most common bacteria are *Campylobacter*, *Shigella*, *E. coli* and *Salmonella* [29]. It has been suggested that the odds of developing IBS are increased about sixfold after acute gastrointestinal infection and remain significantly increased for up to 3 years. Moreover, there is an association between increasing risk of PI-IBS and younger age [30].

Small intestinal bacterial overgrowth (SIBO) represents the overgrowth of bacterial species that usually predominate in the large bowel in the proximal small intestine. Due to the SIBO, fermentation of dietary carbohydrates results In overproduction of gas and to the generation of symptoms of IBS [31]. The clinical presentation of SIBO can range from mild, non-specific symptoms (such as abdominal pain, bloating, and flatulence) to less common but severe manifestations (such as malabsorption, weight loss, and hypoalbuminemia) [32]. Between 4% and 78% of patients with IBS and 1% and 40% of controls have SIBO [33]. SIBO can be diagnosed either by a small bowel aspirate culture showing $\geq 10^3$ colony-forming units (CFU) per mL of aspirate, or a positive hydrogen lactulose or glucose breath test [34]. Apart from causing increased gas production, bacteria in the intestine may produce toxic by-products after fermentation, which may damage the inner lining of the small intestine and colon. Moreover, they also play an important role in immune activation. Effects of immune mediated cytokines such as altered epithelial secretion, exaggerated nociceptive signaling and abnormal motility may lead to IBS like symptoms [35].

4. Microbiota and the gut–brain axis

There are an estimated 100 trillion bacteria in an adult's body, 80% of which exist in the gut. This complex community take part in maintaining a dynamic metabolic ecological balance [36]. The microbiome is largely defined by two bacterial phylotypes *Bacteroidetes* and *Firmicutes* with *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* phyla present in relatively low abundance [37]. It is well known that the central nervous system (CNS) plays a role in modulation of various gut functions, including motility, secretion, blood flow and gut-associated immune function in response to psychological and physical stressors [38]. Alterations in bidirectional brain-gut microbiota interactions are believed to be involved in the pathogenesis of well-known brain-gut disorders such as irritable bowel syndrome (IBS) and related functional gastrointestinal (GI) disorders [39]. The integrated actions and communication between the microbiota and the autonomous nervous system are central players in the perpetuation of IBS symptoms [40]. Genetics and environmental factors determine the bacterial composition in healthy subjects. However, genetics explains only 5–10% of the bacterial variability between individuals. Environmental factors are diet, the frequency of antibiotic treatment, treatment with certain non-antibiotic drugs, geographical location, surgery, smoking, and depression [41]. In the study by Zhu et al. (2019) fecal samples were collected from IBS patients and healthy controls and then fecal metabolites and microbiota were measured. Results showed IBS patients had a significantly differential metabolite profile as compared to healthy controls. Some clusters of fecal metabolites or microorganisms were significantly correlated with the severity of IBS symptoms, such as the frequency of abdominal pain/discomfort and the number of bowel movements [42]. Central nervous system signals are transmitted to the gut by neuroendocrine neurotransmitters (serotonin, corticotropin-releasing hormone, cholecystokinin, and somatostatin) which are produced in the gut by immune and enterochromaffin cells to alter microbiota behavior [43]. The gut microbiota has provided support to the concept that a disturbed intestinal ecology could promote development and maintenance of symptoms in irritable bowel syndrome [44]. Data suggest that there is a relative abundance of proinflammatory bacterial species including *Enterobacteriaceae*, with a corresponding reduction in *Lactobacillus* and *Bifidobacterium* [45].

5. Treatment of Irritable Bowel Syndrome

The older treatment for IBS includes loperamide, antidepressants, such as the tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors, antispasmodics, bulking agents and osmotic laxatives. Newer agents are lubiprostone, linaclotide and rifaximin [46]. Patients suffering from IBS also use complementary and alternative medicine (CAM) alone or in addition to their prescription medicine [47]. Low-FODMAP is a dietary approach consists of restricting foods with highly fermentable oligo-, di-, and monosaccharides, and polyols. It is thought to reduce the absorption of osmotically active short-chain carbohydrates (SCCs) in small intestine [48]. Data shows that FODMAP diet significantly improves general symptoms and quality of life in patients with irritable bowel syndrome [49]. Peppermint oil (PO) (*Mentha Piperita*) is a naturally-occurring carminative herb containing monoterpene compounds that target the pathophysiology of IBS [50]. For centuries peppermint oil has been used for gastrointestinal ailments [51]. Its active ingredient is l-menthol. Peppermint oil is known for many mechanisms of action that makes it an attractive pharmacotherapy for IBS [52]. Peppermint oil was shown to be a safe and effective therapy for pain and global symptoms in adults with IBS [50].

Probiotics are live nonpathogenic microorganisms which are used to treat gastrointestinal and non-gastrointestinal medical conditions. Many of them are part of the normal human gut flora, where they live in a symbiotic relationship [53]. It is not fully known what is the exact mechanisms of probiotics in the human body. Suggested actions include inhibition of pathogenic bacteria overgrowth and prevention of pathogenic invasion of the host, improvement of gut barrier function and receptor interactions and also production or secretion of substances such as short chain fatty acids and neurotransmitters [54]. Probiotics alter the fermentation pattern inside the colon and reducing flatulence due to modifying the intestinal microbiota. Moreover, probiotics stabilize immune dysregulation in IBS which enhance cellular integrity to protect the colon [55]. Fecal microbiota transplantation (FMT) due to modulation of gut microbiota is a potential treatment options for IBS. FMT is a transfer of gastrointestinal microbiota from a healthy donor into the gastrointestinal tract of a patient with dysbiosis [56]. However, some data shows no benefits from FMT [56,57] while another study shows that FMT is an effective treatment and a high-dose transplant and/or repeated FMT increase the response rate and the intensity of the effects of FMT [58].

6. Conclusions

Irritable bowel syndrome is a chronic disorder that contributes to the burden of patients and society due to direct medical costs, lost productivity and also affects the quality of life. The pathogenesis of irritable bowel syndrome is still not fully understood and many factors are thought to contribute to its onset. Not knowing the exact cause makes it difficult to create an effective treatment. The gut microbiota and its dysregulation may contribute to the development and maintenance of symptoms in irritable bowel syndrome. Currently, IBS patient use pharmaceutical treatment but also complementary and alternative medicine. Targeting the gut microbiota is a way for new therapeutic option. Probiotics are thought to have beneficial effect on IBS. However, other gut microbiota oriented treatment which is FMT still requires more study as the data are not consistent.

References

1. El-Salhy M, Ystad SO, Mazzawi T, Gundersen D. Dietary fiber in irritable bowel syndrome (Review). Int J Mol Med. 2017 40(3) 607-613. doi:10.3892/ijmm.2017.3072
2. El-Salhy M. Irritable bowel syndrome: diagnosis and pathogenesis. World J Gastroenterol. 2012 18(37) 5151-5163. doi:10.3748/wjg.v18.i37.5151
3. Soares RL. Irritable bowel syndrome: a clinical review. World J Gastroenterol. 2014 20(34) 12144-12160. doi:10.3748/wjg.v20.i34.12144
4. Wilson S, Roberts L, Roalfe A, Bridge P, Singh S. Prevalence of irritable bowel syndrome: a community survey. Br J Gen Pract. 2004 54(504) 495-502.
5. Occhipinti K, Smith JW. Irritable bowel syndrome: a review and update. Clin Colon Rectal Surg. 2012 25(1) 46-52. doi:10.1055/s-0032-1301759
6. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S et al. Irritable bowel syndrome. Nat Rev Dis Primers. 2016 2 16014. Published 2016 Mar 24. doi:10.1038/nrdp.2016.14
7. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol. 2014 6 71-80. Published 2014 Feb 4. doi:10.2147/CLEP.S40245
8. Weaver KR, Melkus GD, Henderson WA. Irritable Bowel Syndrome. Am J Nurs. 2017 117(6) 48-55. doi:10.1097/01.NAJ.0000520253.57459.01
9. Häuser W, Marschall U, Layer P, Grobe T. The Prevalence, Comorbidity, Management and Costs of Irritable Bowel Syndrome. *Dtsch* Arztebl Int. 2019 116(27-28) 463-470. doi:10.3238/arztebl.2019.0463
10. Gwee KA. Irritable bowel syndrome in developing countries--a disorder of civilization or colonization?. Neurogastroenterol Motil. 2005 17(3) 317-324. doi:10.1111/j.1365-2982.2005.00627.x
11. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. World J Gastroenterol. 2014 20(22) 6759-6773. doi:10.3748/wjg.v20.i22.6759
12. Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. J Neurogastroenterol Motil. 2011 17(2) 131-139. doi:10.5056/jnm.2011.17.2.131
13. Bradford K, Shih W, Videlock EJ, Presson AP, Naliboff BD et al. Association between early adverse life events and irritable bowel syndrome. Clin Gastroenterol Hepatol. 2012 10(4) 385-90.e903. doi:10.1016/j.cgh.2011.12.018
14. Saito YA, Petersen GM, Larson JJ, Atkinson EJ, Fridley BL et al. Familial aggregation of irritable bowel syndrome: a family case-control study. Am J Gastroenterol. 2010 105(4) 833-841. doi:10.1038/ajg.2010.116
15. van Tilburg MA, Levy RL, Walker LS, Von Korff M, Feld LD et al. Psychosocial mechanisms for the transmission of somatic symptoms from parents to children. World J Gastroenterol. 2015 21(18) 5532-5541. doi:10.3748/wjg.v21.i18.5532

16. Kalantar JS, Locke GR 3rd, Zinsmeister AR, Beighley CM, Talley NJ. Familial aggregation of irritable bowel syndrome: a prospective study. Gut. 2003 52(12) 1703-1707. doi:10.1136/gut.52.12.1703
17. Bengtson MB, Rønning T, Vatn MH, Harris JR. Irritable bowel syndrome in twins: genes and environment. Gut. 2006 55(12) 1754-1759. doi:10.1136/gut.2006.097287
18. Black CJ, Ford AC. Rational investigations in irritable bowel syndrome. Frontline Gastroenterol. 2019 11(2) 140-147. Published 2019 Jun 6. doi:10.1136/flgastro-2019-101211
19. Ligaarden SC, Lydersen S, Farup PG. Diet in subjects with irritable bowel syndrome: a cross-sectional study in the general population. BMC Gastroenterol. 2012 12 61. Published 2012 Jun 7. doi:10.1186/1471-230X-12-61
20. Reding KW, Cain KC, Jarrett ME, Eugenio MD, Heitkemper MM. Relationship between patterns of alcohol consumption and gastrointestinal symptoms among patients with irritable bowel syndrome. Am J Gastroenterol. 2013 108(2) 270-276. doi:10.1038/ajg.2012.414
21. Costanian C, Tamim H, Assaad S. Prevalence and factors associated with irritable bowel syndrome among university students in Lebanon: findings from a cross-sectional study. World J Gastroenterol. 2015 21(12) 3628-3635. doi:10.3748/wjg.v21.i12.3628
22. Andresen V, Keller J, Pehl C, Schemann M, Preiss J, Layer P. Irritable bowel syndrome--the main recommendations. Dtsch Arztebl Int. 2011 108(44) 751-760. doi:10.3238/arztebl.2011.0751
23. Karantanos T, Markoutsaki T, Gazouli M, Anagnou NP, Karamanolis DG. Current insights in to the pathophysiology of Irritable Bowel Syndrome. Gut *Pathog*. 2010 2(1) 3. Published 2010 May 13. doi:10.1186/1757-4749-2-3
24. Deiteren A, de Wit A, van der Linden L, De Man JG, Pelckmans PA, De Winter BY. Irritable bowel syndrome and visceral hypersensitivity : risk factors and pathophysiological mechanisms. Acta Gastroenterol Belg. 2016 79(1) 29-38.
25. Kanazawa M, Hongo M, Fukudo S. Visceral hypersensitivity in irritable bowel syndrome. J Gastroenterol Hepatol. 2011 26 Suppl 3 119-121. doi:10.1111/j.1440-1746.2011.06640.x
26. Ludidi S, Mujagic Z, Jonkers D, Keszthelyi D, Hesselink M, et al. Markers for visceral hypersensitivity in patients with irritable bowel syndrome. Neurogastroenterol Motil. 2014 26(8) 1104-1111. doi:10.1111/nmo.12365
27. Iacob T, Ţăţulescu DF, Dumitraşcu DL. Therapy of the postinfectious irritable bowel syndrome: an update. Clujul Med. 2017 90(2) 133-138. doi:10.15386/cjmed-752
28. Thabane M, Marshall JK. Post-infectious irritable bowel syndrome. World J Gastroenterol. 2009 15(29) 3591-3596. doi:10.3748/wjg.15.3591
29. Sadeghi A, Biglari M, Nasseri Moghaddam S. Post-infectious Irritable Bowel Syndrome: A Narrative Review. Middle East J Dig Dis. 2019 11(2) 69-75. doi:10.15171/mejdd.2019.130
30. Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. Aliment Pharmacol Ther. 2007 26(4) 535-544. doi:10.1111/j.1365-2036.2007.03399.x

31. Giamarellos-Bourboulis EJ, Pyleris E, Barbatzas C, Pistiki A, Pimentel M. Small intestinal bacterial overgrowth is associated with irritable bowel syndrome and is independent of proton pump inhibitor usage. *BMC* Gastroenterol. 2016 16(1) 67. Published 2016 Jul 11. doi:10.1186/s12876-016-0484-6
32. Shah SC, Day LW, Somsouk M, Sewell JL. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2013 38(8) 925-934. doi:10.1111/apt.12479
33. Ghoshal UC, Shukla R, Ghoshal U. Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome: A Bridge between Functional Organic Dichotomy. Gut Liver. 2017 11(2) 196-208. doi:10.5009/gnl16126
34. Takakura W, Pimentel M. Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome - An Update. Front Psychiatry. 2020 11 664. Published 2020 Jul 10. doi:10.3389/fpsyt.2020.00664
35. Ghoshal UC, Srivastava D. Irritable bowel syndrome and small intestinal bacterial overgrowth: meaningful association or unnecessary hype. World J Gastroenterol. 2014 20(10) 2482-2491. doi:10.3748/wjg.v20.i10.2482
36. Wang HX, Wang YP. Gut Microbiota-brain Axis. Chin Med J (Engl). 2016 129(19) 2373-2380. doi:10.4103/0366-6999.190667
37. Grenham S, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbe communication in health and disease. Front Physiol. 2011 2 94. Published 2011 Dec 7. doi:10.3389/fphys.2011.00094
38. Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. Nat Rev Gastroenterol Hepatol. 2009 6(5) 306-314. doi:10.1038/nrgastro.2009.35
39. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. J Clin Invest. 2015 125(3) 926-938. doi:10.1172/JCI76304
40. Raskov H, Burcharth J, Pommergaard HC, Rosenberg J. Irritable bowel syndrome, the microbiota and the gut-brain axis. Gut Microbes. 2016 7(5) 365-383. doi:10.1080/19490976.2016.1218585
41. El-Salhy M, Hatlebakk JG, Hausken T. Diet in Irritable Bowel Syndrome (IBS): Interaction with Gut Microbiota and Gut Hormones. Nutrients. 2019 11(8) 1824. Published 2019 Aug 7. doi:10.3390/nu11081824
42. Zhu S, Liu S, Li H, Zhang Z, Zhang Q, et al. Identification of Gut Microbiota and Metabolites Signature in Patients With Irritable Bowel Syndrome. Front Cell Infect Microbiol. 2019 9 346. Published 2019 Oct 18. doi:10.3389/fcimb.2019.00346
43. Hadjivasilis A, Tsioutis C, Michalinos A, Ntourakis D, Christodoulou DK, Agouridis AP. New insights into irritable bowel syndrome: from pathophysiology to treatment. Ann Gastroenterol. 2019 32(6) 554-564. doi:10.20524/aog.2019.0428
44. Distrutti E, Monaldi L, Ricci P, Fiorucci S. Gut microbiota role in irritable bowel syndrome: New therapeutic strategies. World J Gastroenterol. 2016 22(7) 2219-2241. doi:10.3748/wjg.v22.i7.2219
45. Rodiño-Janeiro BK, Vicario M, Alonso-Cotoner C, Pascua-García R, Santos J. A Review of Microbiota and Irritable Bowel Syndrome: Future in Therapies. Adv Ther. 2018 35(3) 289-310. doi:10.1007/s12325-018-0673-5

46. Wall GC, Bryant GA, Bottenberg MM, Maki ED, Miesner AR. Irritable bowel syndrome: a concise review of current treatment concepts. World J Gastroenterol. 2014 20(27) 8796-8806. doi:10.3748/wjg.v20.i27.8796
47. Grundmann O, Yoon SL. Complementary and alternative medicines in irritable bowel syndrome: an integrative view. World J Gastroenterol. 2014 20(2) 346-362. doi:10.3748/wjg.v20.i2.346
48. Altobelli E, Del Negro V, Angeletti PM, Latella G. Low-FODMAP Diet Improves Irritable Bowel Syndrome Symptoms: A Meta-Analysis. Nutrients. 2017 9(9) 940. Published 2017 Aug 26. doi:10.3390/nu9090940
49. Varjú P, Farkas N, Hegyi P, Garami A, Szabó I, et al. Low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet improves symptoms in adults suffering from irritable bowel syndrome (IBS) compared to standard IBS diet: A meta-analysis of clinical studies. PLoS One. 2017 12(8) e0182942. Published 2017 Aug 14. doi:10.1371/journal.pone.0182942
50. Alammar N, Wang L, Saberi B, Nanavati J, Holtmann G, et al. The impact of peppermint oil on the irritable bowel syndrome: a meta-analysis of the pooled clinical data. BMC Complement Altern Med. 2019 19(1) 21. Published 2019 Jan 17. doi:10.1186/s12906-018-2409-0
51. Chumpitazi BP, Kearns GL, Shulman RJ. Review article: the physiological effects and safety of peppermint oil and its efficacy in irritable bowel syndrome and other functional disorders. Aliment Pharmacol Ther. 2018 47(6) 738-752. doi:10.1111/apt.14519
52. Cash BD, Epstein MS, Shah SM. A Novel Delivery System of Peppermint Oil Is an Effective Therapy for Irritable Bowel Syndrome Symptoms. Dig Dis Sci. 2016 61(2) 560-571. doi:10.1007/s10620-015-3858-7
53. Islam SU. Clinical Uses of Probiotics. Medicine (Baltimore). 2016 95(5) e2658. doi:10.1097/MD.0000000000002658
54. Dale HF, Rasmussen SH, Asiller ÖÖ, Lied GA. Probiotics in Irritable Bowel Syndrome: An Up-to-Date Systematic Review. Nutrients. 2019 11(9) 2048. Published 2019 Sep 2. doi:10.3390/nu11092048
55. Didari T, Mozaffari S, Nikfar S, Abdollahi M. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. World J Gastroenterol. 2015 21(10) 3072-3084. doi:10.3748/wjg.v21.i10.3072
56. Myneedu K, Deoker A, Schmulson MJ, Bashashati M. Fecal microbiota transplantation in irritable bowel syndrome: A systematic review and meta-analysis. United European Gastroenterol J. 2019 7(8) 1033-1041. doi:10.1177/2050640619866990
57. Xu D, Chen VL, Steiner CA, Berinstein JA, Eswaran S, et al. Efficacy of Fecal Microbiota Transplantation in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2019 114(7) 1043-1050. doi:10.14309/ajg.0000000000000198
58. El-Salhy M, Hausken T, Hatlebakk JG. Increasing the Dose and/or Repeating Faecal Microbiota Transplantation (FMT) Increases the Response in Patients with Irritable

Bowel Syndrome (IBS). Nutrients. 2019 11(6) 1415. Published 2019 Jun 24. doi:10.3390/nu11061415