REVIEW

Antibiotics, gut microbiota, and irritable bowel syndrome: What are the relations?

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Abstract

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder in which recurrent abdominal pain is associated with defecation or a change in bowel habits (constipation, diarrhea, or both), and it is often accompanied by symptoms of abdominal bloating and distension. IBS is an important health care issue because it negatively affects the quality of life of patients and places a considerable financial burden on health care systems. Despite extensive research, the etiology and underlying pathophysiology of IBS remain incompletely understood. Proposed mechanisms involved in its pathogenesis include increased intestinal permeability, changes in the immune system, visceral hypersensitivity, impaired gut motility, and emotional disorders. Recently, accumulating evidence has highlighted the important role of the gut microbiota in the development of IBS. Microbial dysbiosis within the gut is thought to contribute to all aspects of its multifactorial pathogenesis. The last few decades have also seen an increasing interest in the impact of antibiotics on the gut microbiota. Moreover, antibiotics have been suggested to play a role in the development of IBS. Extensive research has established that antibacterial therapy induces remarkable shifts in the bacterial community composition that are quite similar to those observed in IBS. This suggestion is further supported by data from cohort and case-control studies, indicating that antibiotic treatment is associated with an increased risk of IBS. This paper summarizes the main findings on this issue and contributes to a deeper

understanding of the link between antibiotic use and the development of IBS.

Core Tip: Irritable bowel syndrome (IBS) is among the most common gastrointestinal disorders; however, its etiology and underlying pathophysiology have yet to be fully elucidated. The present review focuses on the existing evidence on the pathogenic role of the gut microbiota in the development of IBS. Moreover, it provides a comprehensive review on the magnitude of changes in the gut microbiota in response to antibiotics. The paper contributes to a deeper understanding of the link between antibiotic use and the development of IBS.

INTRODUCTION

Recent advances in culture-independent techniques have greatly expanded our understanding of the human gut microbiota and its functionalities. 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.

The gut microbiota is established early in life, remains relatively stable thereafter, and is subject to shaping by environmental and host factors (*e.g.,* age, diet, lifestyle, and medications)[1,2]. With regard to the environment, antibiotics have been reported to play a particularly important role in the modulation of the gut microbial community. However, most studies in this area were undertaken 30 to 40 years ago and relied on culture-based techniques. Global antibiotic use has grown 66% since 2000 and continues to grow at a high rate[3,4]. This fact, along with rapid technological advancements for culture-independent analysis, has reinforced the need to take a fresh look at antibiotic-induced changes in the human gut microbiota and clinical consequences of antibiotic intervention. Several studies have reported that antibiotic treatment is associated with an increased risk of irritable bowel syndrome (IBS) [5-8].

IBS is a common gastrointestinal disorder affecting 10%–15% of the population in Europe and North America[9]. This condition negatively affects the quality of life of patients and imposes a significant socioeconomic burden[10]. Over the past few decades, the gut microbiota has emerged as a potential factor that contributes to the pathophysiology of IBS[11,12]. Microbial dysbiosis within the gut has been implicated in intestinal barrier dysfunction, visceral hypersensitivity, impaired gastrointestinal motility, and altered immune response[13-17]. Moreover, various studies have consistently shown the efficacy of microbiota-directed therapies, including prebiotics, probiotics, nonabsorbable antibiotics, dietary changes, and fecal microbial transplantation, in alleviating IBS symptoms[18].

In this paper, we provide a brief overview of the human gut microbiota and its impact on host homeostasis. We highlight what is currently known regarding the role of gut bacteria in the pathophysiology of IBS. Furthermore, we provide an overview of the most up-to-date literature about the impact of antibiotics on gut microbiota composition and discuss a possible link between antibiotic use and the development of IBS. Finally, we identify knowledge gaps and uncertainties that must be filled to orient future research in this area.

GUT MICROBIOTA AND ITS ROLE IN HOST HOMEOSTASIS

The human gut microbiota is a community of microorganisms that inhabit the gastrointestinal tract and is composed of approximately 10^{14} bacterial cells[19,20]. In healthy adults, more than 90% of gut bacteria belong to four dominant phyla, namely, *Firmicutes, Bacteroidetes, Actinobacteria,* and *Proteobacteria,* whereas other phyla are far less abundant[21,22].

Currently, the gut microbiota is considered an indispensable "organ" within the body with distinct metabolic and immune functions (Table 1). Most of its effects are mediated through metabolites.

Table 1 Gut microbiota functions

Bacterial phylum	Key representatives	Functions
Firmicutes	Members of the genera *Enterococcus, Ruminococcus, Clostridium, Lactobacillus, Faecalibacterium, Roseburia,* and *Eubacterium*	Metabolism of amino acids[23,24], carbohydrates[25], bile acids, and their salts[22]. Lipid metabolism and cholesterol synthesis[25]. Synthesis of vitamins K2, B1, B2, B6, B7, B9, and B12[26]. Maintenance of a proper immune response[28,29] and intestinal epithelial barrier integrity[31,32]. Protection against enteric pathogens[33]
Bacteroidetes	Members of the genera *Bacteroides* and *Prevotella*	Metabolism of amino acids[24], carbohydrates[25,141], bile acids, and their salts[22,142]. Synthesis of vitamin K2[27]. Regulation of appetite[143]. Maintenance of a proper immune response[28-29] and intestinal epithelial barrier integrity[31]. Protection against enteric pathogens[33]
Actinobacteria	Members of the genera *Bifidobacterium* and *Corynebacterium*	Metabolism of bile acids and their salts[22]. Synthesis of vitamins K2, B1, B2, B6, B7, B9, and B12[26]. Protection against enteric pathogens[33]
Proteobacteria	Members of the genera *Desulfovibrio, Escherichia,* and *Shigella*	Metabolism of amino acids[144]

Thus, some of the most important roles of the gut microbiota include metabolism of dietary compounds[23-25], synthesis of vitamins[26,27], regulation of the immune response[28-30], maintenance of intestinal epithelial barrier integrity[25,31,32], and protection against enteric pathogens[33].

MODERN CONCEPT OF IBS: EVOLVING ROLE OF GUT MICROBIOME

Despite extensive research, the etiology and underlying pathophysiology of IBS remain incompletely understood. Proposed mechanisms involved in its pathogenesis include visceral hypersensitivity, impaired gut motility[13,34], increased intestinal permeability[34-36], emotional disorders[11,37], and changes in the immune system[34,37,38].

Over the past decade, there has been an increasing amount of literature on the role of the gut microbiota in the pathogenesis of IBS. The concept of the "microbiota-gut-brain" axis has been proposed [14-17], supporting the crucial role of microbial dysbiosis in the development of IBS symptoms. It is thought that, in genetically predisposed individuals, environmental factors alter the composition of the gut microbiota, leading to disruption of intestinal epithelial barrier integrity[13]. Once the intestinal barrier is breached, bacteria interact with the immune system of the host, provoke a series of immune reactions, and lead to low-grade mucosal inflammation in the gut wall. Collectively, these changes result in sensitivity and motility abnormalities, emotional disorders, and the development of IBS symptoms (abdominal pain, bloating, and alterations in bowel habits)[35]. Interestingly, the gut microbiota not only initiates such a pathological cascade in IBS but also contributes to all aspects of its multifactorial pathogenesis through the release of metabolites[11,12]. These provisions will be discussed below.

Microbiota and motility/sensitivity abnormalities

The enteroendocrine system modulates gut motor and sensory functions through the secretion of neuropeptides and neurotransmitters[39].

Bacterial metabolites are able to stimulate the production of several neuropeptides, including neuropeptide Y, peptide YY, glucagon-like peptide-1 (GLP-1)[40], cholecystokinin, and substance P (Figure 1)[15,41].

For instance, short-chain fatty acids (SCFAs), secondary bile acids, and indole, which are produced by members of the genera *Clostridium, Bacteroides,* and *Ruminococcus*[23,25], stimulate intestinal L-cells to secrete GLP-1[42]. GLP-1 reduces postprandial motility in the upper gastrointestinal tract (antrum, duodenum, and jejunum) and increases colonic transit[43,44]. A study conducted by Li *et al*[45] reported decreased serum GLP-1 levels and reduced mucosal expression of GLP-1 receptors in patients with constipation-predominant IBS (IBS-C). The authors suggested that lower GLP-1 levels lead to the loss of its prokinetic effects in the colon, resulting in constipation and abdominal pain. In a rat model of bowel dysfunction, administration of the GLP-1 receptor agonist exendin-4 alleviated stress-induced defecation and visceral pain sensitivity[46,47]. Clinical interventions in patients with IBS demonstrated that the synthetic GLP-1 analog ROSE-010 reduced abdominal pain and increased colonic transit[45,48]. The underlying molecular mechanisms responsible for the amelioration of symptoms remain unknown. The authors suggest that modulation of enteric neuronal function and tight junction expression, as well as the activation of serotonergic pathways in the colon, may play a role.

Secondary bile acids and SCFAs, which are mainly produced by *Eubacterium, Bacteroides*, and *Clostridium* (clusters IV, XI, XIII, and XIVa)[22], promote serotonin synthesis from colonic enterochromaffin cells[49]. Serotonin is an important neurotransmitter that, among its other functions, regulates gastrointestinal motility[50]. Serum serotonin levels were found to be increased in those with diarrhea-
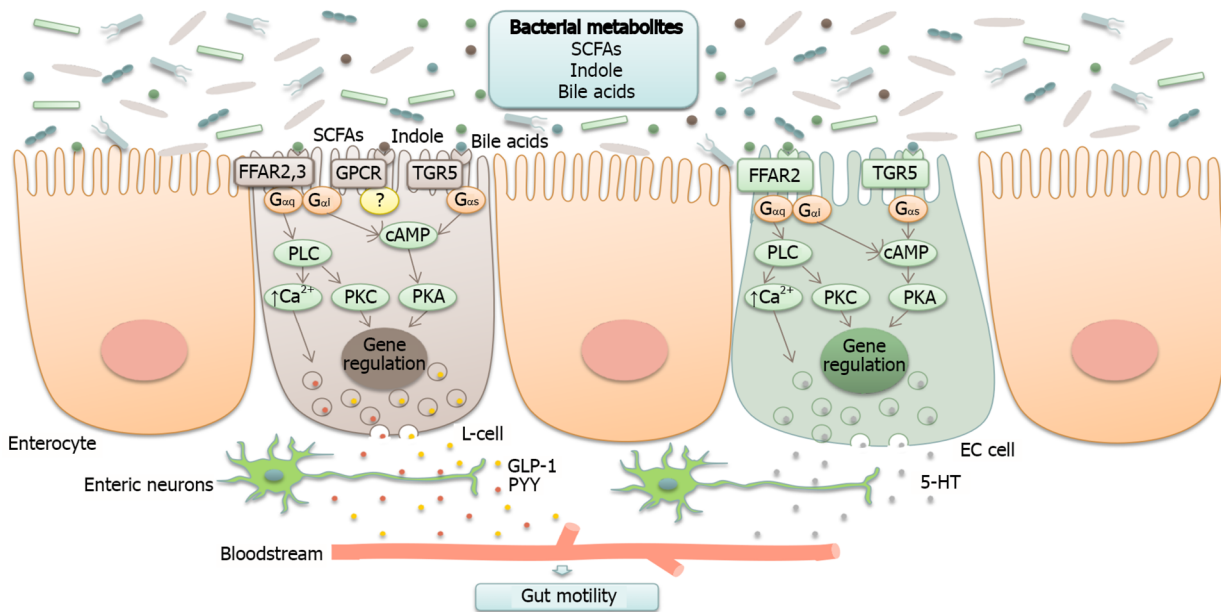
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Figure 1 Neurotransmitter modulation by gut microbiota (schematic illustration). Bacterial metabolites, such as short-chain fatty acids (SCFAs), secondary bile acids, and indole, are able to stimulate the production of neurotransmitters, including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and serotonin (5-HT). They act through G-protein coupled receptors (GPCRs) FFAR2, FFAR3, and TGR5 that are coupled to different types of G proteins ($G_{\alpha s}$, $G_{\alpha q}$, and $G_{\alpha i}$) and activate different pathways known to regulate gene expression and promote exocytosis by raising intracellular Ca^{2+} levels. SCFAs are recognized by FFAR2 and FFAR3. Enteroendocrine L-cells express both of these proteins, whereas enterochromaffin (EC) cells have been reported to express FFAR2. Bile acids are recognized by TGR5 receptors expressed in L-cells and EC cells. The sensing of indole remains elusive, although it is thought to act through GPCR. $G_{\alpha s}$ stimulates adenylate cyclase and elevates cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA). $G_{\alpha i}$ inhibits the cAMP pathway. $G_{\alpha q}$ stimulates phospholipase C (PLC), resulting in the generation of diacylglycerol (DAG) and inositol triphosphate (IP_3), which activate protein kinase C (PKC) and induce intracellular Ca^{2+} release[23,138-140]. SCFA: Short-chain fatty acids; GLP-1: Glucagon-like peptide-1; PYY: Peptide YY.

predominant IBS (IBS-D) and reduced in those with IBS-C[34].

The serotonin system represents a potential therapeutic target in IBS. The effects of serotonin are mediated through 5-HT receptors located on the surface of distinct cell types. Fourteen different serotonin receptor subtypes have been identified and classified into seven groups (5-HT_{1-7}), with 5-HT_3 and 5-HT_4 being the most investigated receptors in the intestine. Both receptor subtypes are expressed on neurons within the myenteric and submucosal plexuses of the enteric nervous system, intrinsic and extrinsic sensory neurons, interstitial cells of Cajal, enterocytes, and enterochromaffin cells[51]. 5-HT_3 receptors are involved in the contraction of intestinal smooth muscle and in gut-brain communication through vagal afferent fibers[52]. Activation of 5-HT_4 receptors induces neuronal release of acetylcholine and accelerates the peristaltic reflex[53]. 5-HT_3 receptor antagonists have been shown to improve abdominal pain and global IBS symptoms in patients with nonconstipated and IBS-D[54,55]. 5-HT_4 agonists have been shown to relieve overall and individual symptoms (abdominal pain/discomfort, stool frequency, stool consistency, and straining during defecation) in patients with IBS-C[56-58]. However, cardiovascular side effects were seen with these drugs, and they were either withdrawn from the market (cisapride) or approved for a limited population (tegaserod). Therefore, new safe and well-tolerated 5-HT_4 agonists are under development[59,60].

A number of animal studies have shown the prominent role of the gut microbiota in visceral hypersensitivity[41]. For example, colonization of germ-free rats with the gut microbiota from patients with IBS reduced the pain threshold to colorectal distension[42]. Furthermore, the beneficial effects of probiotic strains (*e.g.*, *Lactobacillus reuteri*, *Lactobacillus plantarum*, *Lactobacillus helveticus*, and *Bifidobacterium longum*) in alleviating visceral sensitivity have been documented[61-63].

Thus, the microbiota influences the main pathogenetic factors of IBS (*i.e.*, motility and sensitivity) both directly and through microbial metabolites.

Microbiota as a regulator of stress and emotional responses

The physiological response to stress is mediated through the hypothalamic-pituitary-adrenal (HPA) axis [64]. Activation of this axis results in the release of corticotropin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. CRH acts on the anterior pituitary and induces the production of adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal cortex to secrete cortisol.

Different types of stressors are known to contribute to the development, maintenance, and exacerbation of IBS symptoms[11]. The results of multiple studies suggest that there is HPA axis dysregulation in IBS. For instance, patients with IBS were found to have excess levels of ACTH in the plasma and cortisol in the serum in response to CRH infusion[65].

Growing evidence indicates that the gut microbiota is involved in the regulation of HPA axis activity. It has been shown that colonization with beneficial microorganisms in early life is of great importance for the normal development of this axis[66]. Moreover, alterations in the gut microbiota may influence the release of ghrelin and galanin, which are endocrine peptides contributing to the stress response through modulation of CRH, ACTH, and glucocorticoid secretion[40,67].

Dysfunction of the HPA axis, along with alterations in neurotransmitter metabolism, appear to be crucial factors in the development of psychiatric disorders, such as anxiety and depression[68,69]. A recent meta-analysis of 27 studies have reported elevated levels of anxiety and depression in patients with IBS as compared to those in healthy controls[70]. Comorbid emotional disorders lead to persistence of symptoms, drive patients to seek medical care, and contribute to poor outcomes[11].

A growing body of literature supports the association between microbial dysbiosis and the development of anxiety and depression. For instance, certain species within the *Lactobacillaceae* and *Bifidobacteriaceae* families are known to produce gamma-aminobutyric acid (GABA). GABA is the main inhibitory neurotransmitter of the central nervous system, playing an important role in the pathogenesis of mood disorders[49,71]. Interestingly, a specific type of GABA receptor (GABA-b) is localized on submucosal and myenteric neurons of the enteric nervous system[72] and is thought to be involved in the modulation of gut motility and sensitivity[37]. Furthermore, members of the genera *Bacillus* and *Escherichia* have been found to produce other neurotransmitters affecting mood and behavior, such as dopamine, serotonin, and norepinephrine[15,73]. In recent studies, germ-free mice have been widely used as a tool for assessing the role of intestinal microbes in brain function and behavior. Studies on germ-free and specific pathogen-free mice indicate that intestinal microbes can cause imbalances of the HPA axis, resulting in an anxiety-like behavioral phenotype[74]. Fecal microbiota transplantation studies have indicated the rodent-to-rodent and human-to-rodent transfer of anxiety-like behaviors[75, 76]. Moreover, animal studies have shown that transplantation of the microbiota from depressed patients to rodents is able to induce depression-like behavior. The authors linked microbiota-induced depression in mice to alterations in the cAMP-response element binding protein (CREB) signaling pathway in the olfactory bulb[77] and alterations in carbohydrate and amino acid metabolism[78].

However, despite the data obtained, further research is needed to investigate the difference in emotional disorder levels in patients with postinfectious and other forms of IBS.
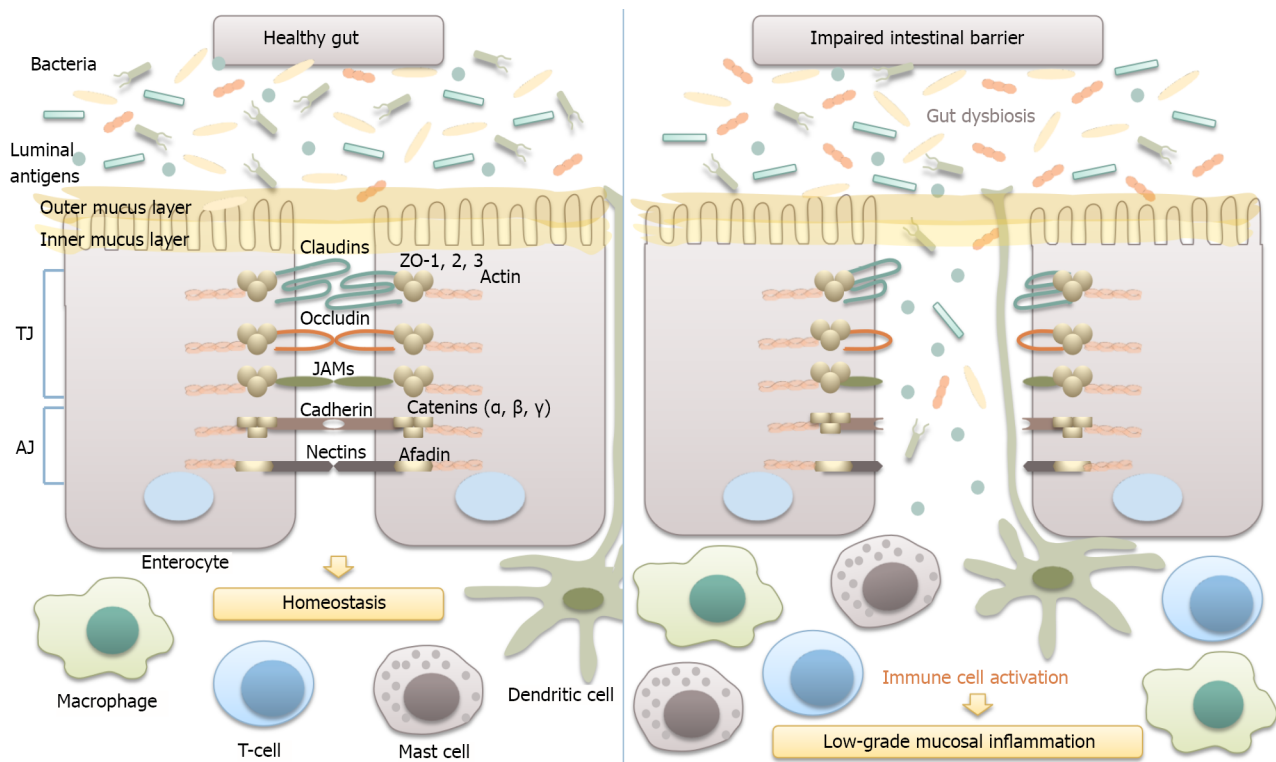
Microbiota and host immunity

Recently, considerable literature has grown around the theme of immune system activation in IBS. For instance, an increased number of mast cells located in close proximity to enteric nerve fibers have been found in colonic biopsies from patients with IBS and have been associated with the severity of symptoms[11,38,79]. Mast cells are thought to be key players in intestinal mucosal inflammation[79]. Their degranulation causes the release of inflammatory mediators (histamine, serotonin, and proteases), resulting in lymphocyte activation and cytokine imbalance[80]. Patients with IBS were found to have higher levels of proinflammatory interleukin (IL)-6, IL-8, IL-1β, and tumor necrosis factor-α (TNF-α) and lower levels of anti-inflammatory IL-10 in both serum and the intestinal mucosa[81,82]. These changes result in altered pain thresholds and visceral hypersensitivity[38,83]. In addition, mast cell degranulation has been shown to reduce the expression of tight junction proteins, probably through tryptase release[13]. Apart from mast cells, increased numbers of eosinophils and intraepithelial lymphocytes have been observed in colonic biopsies from patients with IBS[11,79].

Gut bacteria play an important role in the modulation of the immune response. For example, butyrate produced by members of the phylum *Firmicutes*[25] induces the differentiation of regulatory T cells[29, 84], thereby preventing an excessive immune response and autoimmunity[22,85]. Furthermore, *Lactobacilli* spp. metabolize dietary tryptophan into indole-3-aldehyde, which acts as an aryl hydrocarbon receptor (AHR) ligand[85]. AHR is a ligand-activated transcription factor that is expressed by immune cells and regulates the number of intraepithelial lymphocytes and IL-22 production[86]. Probiotic strains, such as *Lactobacillus rhamnosus*, *Lactobacillus casei*, and *Bifidobacterium breve*, were shown to induce IL-4 and IL-10 production, whereas *L. reuteri* and *L. plantarum* were found to downregulate the expression of TNF-α[87,88].

The importance of the interaction between the gut microbiota and host immune system in IBS is highlighted by a number of studies in patients with postinfectious IBS, indicating activation of the gastrointestinal immune system after acute gastroenteritis[89,90]. Moreover, animal studies have shown that stress-induced changes in the gut microbiota are associated with altered immune response and increased susceptibility to enteric pathogens[91,92].

Microbiota and intestinal barrier integrity

Intestinal epithelial barrier integrity is of great importance for gut homeostasis, as it prevents the translocation of luminal antigens to the mucosa, thus averting the development of low-grade mucosal inflammation in the gut wall (Figure 2).

Figure 2 Microbiota and intestinal barrier integrity. The intestinal barrier plays an essential role in maintaining host homeostasis. It is mainly composed of the mucus layer, the epithelial layer, and the underlying lamina propria. Intestinal epithelial cells are tightly attached to each other by junctional complexes. Tight junctions (TJs) are composed of several proteins, including occludin, claudins, zonula occludens (ZOs), and junctional adhesion molecules (JAMs), which interact with each other, as well as with the cytoskeleton. The adherence junction is composed of the nectin-afadin system and the E-cadherin-catenin system. Intestinal epithelial barrier integrity prevents the translocation of bacteria and luminal antigens to the mucosa, thus averting their interaction with the host immune system and the development of low-grade mucosal inflammation in the gut wall. TJ: Tight junctions; AJ: Adherence junction; JAM: Junctional adhesion molecules.

An increased density of epithelial gaps has been shown by electron microscopy in gut biopsies of patients with IBS[93]. Furthermore, histological examination of colonic biopsies revealed decreased expression of tight junction proteins, such as occludin; claudins 1, 3, and 5; and zonula occludens-1[13, 36,82,93]. Increased serum levels of anti-flagellin antibodies in patients with IBS further support the substantial role of intestinal permeability in the pathogenesis of IBS[94].

The gut microbiota is an important determinant of intestinal epithelial barrier integrity. In particular, certain gut bacteria, such as *Bacteroides thetaiotaomicron, Faecalibacterium prausnitzii,* and *Ruminococcus* spp., were shown to affect the mucus layer thickness and composition[1,22,31]. Moreover, SCFAs, which are produced predominantly by members of the genera *Eubacterium, Clostridium, Ruminococcus,* and *Faecalibacterium,* have been demonstrated to augment the expression of claudins 3 and 4 and occludin. Polyamines (putrescine, spermidine, and spermine), which are produced by certain species within the *Clostridium, Enterococcus, Streptococcus,* and *Lactobacillus* genera, have been shown to stimulate the production of E-cadherin and zonula occludens-1[95]. There is also evidence that probiotic strains of *Bifidobacterium* and *Lactobacillus* promote intestinal barrier function and prevent bacterial translocation [32,96].

Most likely, the preservation of the optimal composition of the microbiota (*e.g.,* a sufficient number of SCFA producers) may serve as a factor preventing the development of IBS.

GUT MICROBIAL COMPOSITION IN PATIENTS WITH IBS

A considerable amount of literature has been published on the compositional changes of the gut microbiota in patients with IBS. Although data from these studies are inconsistent and even conflicting, some common features can be found (Table 2). The discrepancy in findings is possibly due to differences in the population studied (*e.g.,* age, lifestyle, initial microbiota composition, prior antibiotic and/or probiotic use, and diagnostic criteria for IBS) and methodological issues, such as study design and methods for microbiota assessment and data analysis.

The majority of authors report decreased microbial diversity in patients with IBS[97-101]. Furthermore, a substantial number of studies have shown a lower abundance of butyrate-producing

Table 2 Compositional changes in gut microbiota in patients with irritable bowel syndrome (common threads)

Ref.	Subjects	Method	Specimen	Diversity	*Faecalibacterium*	*Enterobacteriaceae*	*Bifidobacterium*	*Lactobacillus*
Dior *et al* [145], 2016	IBS-D (n = 16), IBS-C (n =15), Controls (n = 15)	Real-time PCR	Stool	No data	–	↑ in IBS-D (*Escherichia*)	↑ in IBS-C	–
Ringel-Kulka *et al* [108], 2016	IBS (n = 56), Controls (n = 20)	16S rRNA	Stool	No data	–	–	–	↑
Maharshak *et al*[102], 2018	IBS-D (n = 23), Controls (n = 24)	16S rRNA	Stool	↓[1]	↓	↑ (*unclassified genus*)	–	–
			Colonic biopsy	–[1]	–	–	–	↑
Gobert *et al* [146], 2016	IBS-C (n = 33), Controls (n = 58)	16S rRNA	Stool	No data	–	↑	↓	–
Shukla *et al* [105], 2015	IBS (n = 47), Controls (n = 30)	16S rRNA; real-time PCR	Stool	No data	–	–	↓	–
Su *et al* [107], 2018	IBS-D (n = 40), Controls (n = 20)	16S rRNA; real-time PCR	Stool	No data	–	–	↓	↓
Zhuang *et al* [109], 2018	IBS-D (n = 30), Controls (n = 13)	16S rRNA	Stool	–[2]	–	–	–	↓
Zhong *et al* [147], 2019	IBS-D (n = 20), Controls (n = 16)	FISH	Colonic biopsy	No data	–	↑ (*E. coli*)	↓	–
Jeffery *et al* [100], 2020	IBS (n = 80), Controls (n = 65)	16S rRNA, shotgun sequencing	Stool	↓[2]	–	–	–	–
Rangel *et al* [148], 2015	IBS (n = 33), Controls (n = 16)	Microarray analysis	Stool	↓[2]	↓ (*F. prausnitzii*)	–	–	–
			Colonic biopsy	–[2]	–	–	–	–

[1]Rarefaction analysis.

[2]Shannon diversity index.

↓: Decreased abundance; ↑: Increased abundance; –: No significant differences found; IBS: Irritable bowel syndrome; IBS-D: Diarrhea-predominant irritable bowel syndrome; IBS-C: Constipation-predominant irritable bowel syndrome; FISH: Fluorescence *in situ* hybridization; *E. coli*: *Escherichia coli*; *F. prausnitzii*: *Faecalibacterium prausnitzii*.

bacteria from the genus *Faecalibacterium*, mainly *F. prausnitzii*,[97,98,102,103] as well as an increase in the abundance of the *Enterobacteriaceae* family, including pathogens such as *Escherichia coli* and *Enterobacter* spp.[98,104-106]. Moreover, patients with IBS were found to have a reduced prevalence of *Bifidobacterium,* providing a range of beneficial properties to the host[98,103,104,106,107]. Significant differences in *Lactobacillus* numbers were also observed between patients with IBS and healthy controls, but the findings of different studies were not consistent. Some authors reported an increased amount of *Lactobacillus*[98,99,102,108], while others documented a decrease in the abundance of this commensal[103,104,106,107,109].

Overall, there seems to be some evidence to indicate that patients with IBS have decreased numbers of bacteria contributing to the maintenance of host homeostasis and proper immune response, as well as increased numbers of microbes with proinflammatory properties.

ANTIBIOTICS, GUT MICROBIOTA, AND IBS

Effects of antibiotics on gut microbiota composition

The discovery of antibiotics in the early 20th century was a great milestone in the history of medicine, as

it changed the natural course of most infectious diseases and saved countless lives[110,111]. However, a growing number of studies have shown that inappropriate use of antibiotics promotes the development of antibiotic resistance[112,113]. Furthermore, accumulating evidence indicates that antibiotic exposure in early life increases the risk of obesity and autoimmune and allergic diseases[114-117].

During the past four decades, there has been an increasing interest in the impact of antibiotics on the composition of the gut microbiota. A substantial number of studies in this area were conducted in the 1980s and 1990s and relied on culture-based techniques. However, researchers indicate that up to 80% of gut bacteria are nonculturable[118]. Therefore, the focus has shifted to culture-independent approaches mainly based on 16S rRNA gene sequence analysis.

Extensive research has established that antibiotic treatment induces a dramatic loss of diversity and remarkable shifts in community composition (Table 3), with the time of recovery varying substantially [119-123].

The inconsistency in the results of various studies can be attributed to substantial heterogeneity in sample characteristics (age, ethnicity, diet, *etc.*) and study methodology. Furthermore, antibiotic characteristics, such as their class, pharmacokinetics (absorption and excretion), range of action, and dosing regimen, have been shown to shape the response of the gut microbiota to antibiotic perturbation[124]. For instance, vancomycin is poorly absorbed when administered orally, resulting in high fecal concentrations. Therefore, it significantly alters the composition of the gut microbiota by increasing pathogenic *Proteobacteria*, such as *Klebsiella*, *Escherichia*, and *Shigella*, and decreasing members of the *Bacteroidetes* phylum[122]. Lipophilic antibiotics (*e.g.,* lincosamides and macrolides) are eliminated mainly by biliary excretion and therefore cause profound changes in the intestinal microbiota[125]. For example, treatment with clindamycin resulted in a reduction in microbial diversity and a decrease in *Roseburia, Lachospira, Coprococcus, Dorea,* and *Ruminococcus*. Changes in microbial composition were observed throughout 12 mo after clindamycin exposure[121]. In a recent study conducted by Haak *et al*[123], it was shown that treatment with broad-spectrum antibiotics (ciprofloxacin, vancomycin, and metronidazole) promotes the growth of *Streptococcus* and *Lactobacillus*. Furthermore, the authors found reduced numbers of anaerobes producing SCFAs, such as *Bacteroides*, *Subdoligranulum*, and *Faecalibacterium*. Interestingly, a return toward baseline was observed between 8 and 31 mo, but the composition of the microbiota often remained changed from its initial state.

There is some evidence that antibiotics can indirectly affect the composition of the gut microbiota. This is due to interdependence among different microbial taxa, as they have a variety of shared metabolic pathways[124,126]. Thus, the loss or reduction of certain taxa affects the growth of other members of the community. As an example, vancomycin treatment reduces the number of Gram-negative commensals, although this drug selectively targets Gram-positive bacteria[127].

In a recent systematic review, Zimmerman *et al*[128] summarized data from 129 studies on the effect of antibiotics on the composition of the gut microbiota. The authors concluded that the majority of 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[129]. Moreover, expansion of bacteria belonging to the *Enterobacteriaceae* family was associated with inflammatory bowel diseases, both in animal models and in humans [130,131]. Zimmerman *et al*[128] reported that amoxicillin, piperacillin, ticarcillin, cephalosporins (except fifth generation cephalosporins), carbapenems, and lipoglycopeptides facilitate the overgrowth of *Enterococcus,* while treatment with macrolides and doxycycline results in decreased numbers of these bacteria. It has conclusively been shown that piperacillin, ticarcillin, carbapenems, macrolides, clindamycin, and quinolones markedly reduce the abundance of anaerobic bacteria. Finally, the authors documented that the most long-lasting changes in the community structure are caused by ciprofloxacin (1 year), clindamycin (2 years), and clarithromycin plus metronidazole (4 years).

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[33,124].

Antibiotics as a risk factor for IBS

Data from large cohort and case-control studies indicate that antibiotics are a risk factor for functional gastrointestinal disorders and IBS in particular. A retrospective study on more than 26000 patients showed that exposure to macrolides and tetracyclines may be associated with the development of IBS [5]. Similarly, a prospective case-control study found that antibiotic treatment of nongastrointestinal infections was associated with the development of IBS [odds ratio (OR) = 2.30; 95% confidence interval (CI): 1.22-4.33; *P* = 0.01] and other functional gastrointestinal disorders (OR = 1.90; 95%CI: 1.21-2.98; *P* = 0.005)[6]. A longitudinal study by Krogsgaard *et al*[7] also identified that the use of antibiotics was a predictor for IBS (OR = 1.8; 95%CI: 1.0-3.2). Additionally, a recent meta-analysis showed that the use of antibiotics for infectious enteritis was associated with an increased risk of IBS (OR = 1.69; 95%CI: 1.20-2.37)[8].

Table 3 Effects of antibiotics on gut microbiota composition (based on culture-independent approaches)

Ref.	Method	Antibiotic	Dosing regimen	Diversity	Compositional changes
Pallav *et al* [136], 2014	Pyrosequencing	Amoxicillin	250 mg 3 times daily for 7 d	—[1,2]	↑ *Escherichia, Shigella*
Kabbani *et al* [137], 2017	16S rRNA	Amoxicillin-Clavulanate	875/125 mg twice daily for 7 d	↓[1,3]	↑ *Escherichia, Parabacteroides, Enterobacter* ↓ *Roseburia*
Burdet *et al* [120], 2019	16S rRNA	Ceftriaxone	1 g once daily for 3 d	↓[1,4]	↓ *Firmicutes, Actinobacteria, Bacteroidetes*
Raymond *et al* [135], 2016	Shotgun sequencing	Cefprozil	500 mg twice daily for 7 d	↓[5]	↑*Flavonifractor, Lachnoclostridium, Parabacteroides,* ↓*Bifidobacteriaceae, Coriobacteriaceae, Eubacteriaceae, Oxalobacteraceae, Pasteurellaceae, Veillonellaceae*
Rashid *et al* [121], 2015	Pyrosequencing	Ciprofloxacin	500 mg twice daily for 10 d	↓[1]	↑ *Bacteroides*↓ *Faecalibacterium, Alistipes,* unculturable *Ruminococcaceae*
		Clindamycin	150 mg 4 times daily for 10 d	↓[1]	↓ *Roseburia, Lachospira, Coprococcus, Dorea, Ruminococcus*
Isaac *et al*[122], 2017	16S rRNA	Vancomycin	250 mg *per os* 4 times daily for 2 wk	↓[1,4]	↑ *Escherichia, Shigella, Klebsiella,* ↓ *Bacteroidetes, Faecalibacterium, Ruminococcus*

[1]OTU analysis.
[2]Rarefaction analysis.
[3]Chao1 index.
[4]Shannon index.
[5]Simpson index.

However, nonabsorbable antibiotics can be used to treat IBS. In a double-blind, randomized, placebo-controlled study, treatment with neomycin resulted in a 35% improvement in composite scores of IBS symptoms, compared with only 11% for placebo (*P* < 0.05)[132]. Nonetheless, the use of this antibiotic is limited by the risk for *C.difficile* infection and systemic adverse events. A recent meta-analysis of four studies and 1803 patients showed that rifaximin was more effective than placebo in the overall improvement of IBS symptoms (OR = 1.19; 95%CI: 1.08-1.32 and OR = 1.36; 95%CI: 1.18–1.58, respectively, *P* < 0.05 for both). There was no difference in adverse events between rifaximin and placebo[133]. Due to its safety, rifaximin was approved by the Food and Drug Administration for the treatment of IBS-D.

Similarities in gut microbiota between patients with IBS and those after antibiotic exposure

Analysis of data on changes in the gut microbiota in patients with IBS and those after antibiotic exposure uncovers some common features and trends. For instance, decreased microbial diversity[97-99, 121,128] and a reduction in the abundance of *Faecalibacterium,* particularly *F. prausnitzii*[97,98,102,121, 122], have been observed in both cases. *F. prausnitzii* is one of the most abundant bacterial species in the gut, exhibiting anti-inflammatory effects through inhibition of IL-8 production, promotion of IL-10 secretion, and upregulation of regulatory T cells[134]. Moreover, patients with IBS were shown to have reduced numbers of *Bifidobacterium*[98,103,104,106,107]. Likewise, several studies have reported a decreased abundance of these commensals after antibiotic exposure[121,128,135]. Most members of the genus *Bifidobacterium* are known to exert beneficial effects on host health, including competitive exclusion of enteric pathogens, metabolism of dietary compounds, and regulation of the immune response[22,26,33]. Furthermore, both IBS and antibiotic exposure are characterized by overgrowth of *Enterobacteriaceae*[98,104,106,136,137]. The *Enterobacteriaceae* family includes pathogenic bacteria (*e.g., Escherichia, Shigella, Klebsiella,* and *Enterobacter)* with proinflammatory properties that may contribute to low-grade inflammation in the gut wall[98].

CONCLUSION

There is 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 findings. To date, there is still no consensus on distinct microbiome signatures in IBS. Although some common threads reviewed here were found, prospective large-scale studies need to be carried out to shed light on this issue. Independent analysis of the gut microbiota and its metabolites will help to develop novel microbiota-based treatment strategies that target the
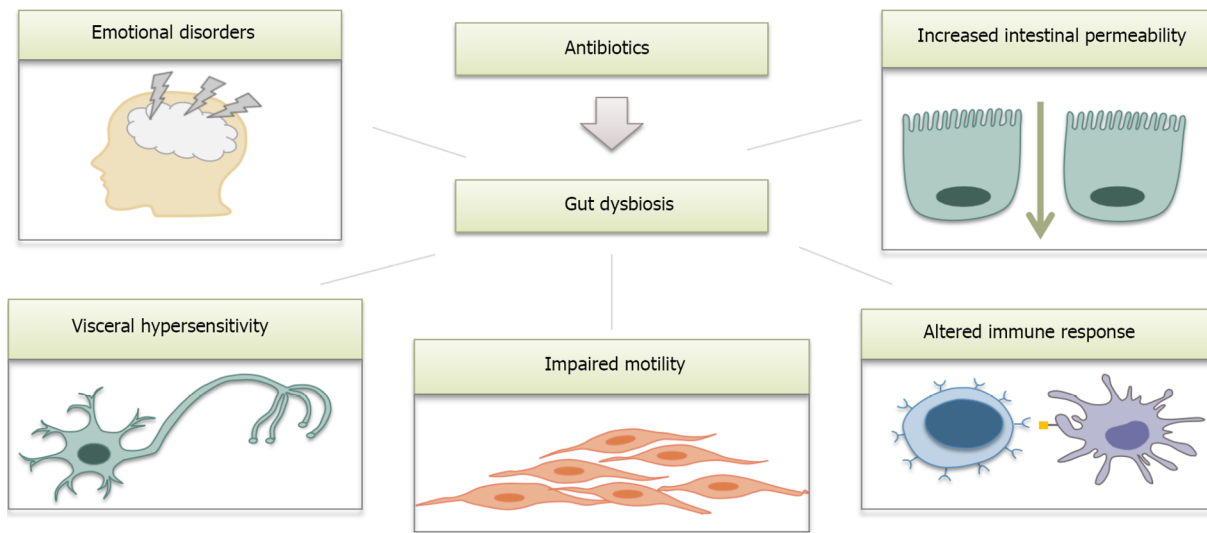
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Figure 3 Possible link between antibiotic use and the development of irritable bowel syndrome (schematic illustration). Antibiotics cause profound changes in the gut microbiota and therefore contribute to all mechanisms involved in the pathogenesis of irritable bowel syndrome.

underlying pathophysiology of IBS rather than focusing on symptom alleviation.

A number of recent studies have addressed the effects of antibiotics on gut microbiota composition, and these effects were found to be quite similar to those observed in IBS. We suggest that the Rome V criteria could provide a new definition of postantibiotic IBS. As major disruptors of the gut microbiota, antibiotics seem to contribute to all aspects of IBS pathogenesis (Figure 3). However, further research in this area is definitely warranted.

FOOTNOTES

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REFERENCES

1   **Thursby E**, Juge N. Introduction to the human gut microbiota. *Biochem J* 2017; **474**: 1823-1836 [PMID: 28512250 DOI: 10.1042/BCJ20160510]

2   **Hasan N**, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. *PeerJ* 2019; **7**: e7502 [PMID: 31440436 DOI: 10.7717/peerj.7502]

3   **Klein EY**, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, Goossens H, Laxminarayan R. Global increase

and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A* 2018; **115**: E3463-E3470 [PMID: 29581252 DOI: 10.1073/pnas.1717295115]

4   **Miranda C**, Silva V, Capita R, Alonso-Calleja C, Igrejas G, Poeta P. Implications of antibiotics use during the COVID-19 pandemic: present and future. *J Antimicrob Chemother* 2020; **75**: 3413-3416 [PMID: 32830266 DOI: 10.1093/jac/dkaa350]

5   **Villarreal AA**, Aberger FJ, Benrud R, Gundrum JD. Use of broad-spectrum antibiotics and the development of irritable bowel syndrome. *WMJ* 2012; **111**: 17-20 [PMID: 22533211]

6   **Paula H**, Grover M, Halder SL, Locke GR 3rd, Schleck CD, Zinsmeister AR, Talley NJ. Non-enteric infections, antibiotic use, and risk of development of functional gastrointestinal disorders. *Neurogastroenterol Motil* 2015; **27**: 1580-1586 [PMID: 26303310 DOI: 10.1111/nmo.12655]

7   **Krogsgaard LR**, Engsbro AL, Bytzer P. Antibiotics: a risk factor for irritable bowel syndrome in a population-based cohort. *Scand J Gastroenterol* 2018; **53**: 1027-1030 [PMID: 30189148 DOI: 10.1080/00365521.2018.1500638]

8   **Klem F**, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, Singh S, Grover M. Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. *Gastroenterology* 2017; **152**: 1042-1054.e1 [PMID: 28069350 DOI: 10.1053/j.gastro.2016.12.039]

9   **Quigley EM**, Fried M, Gwee KA, Khalif I, Hungin AP, Lindberg G, Abbas Z, Fernandez LB, Bhatia SJ, Schmulson M, Olano C, LeMair A; Review Team:. World Gastroenterology Organisation Global Guidelines Irritable Bowel Syndrome: A Global Perspective Update September 2015. *J Clin Gastroenterol* 2016; **50**: 704-713 [PMID: 27623513 DOI: 10.1097/MCG.0000000000000653]

10   **Black CJ**, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 473-486 [PMID: 32296140 DOI: 10.1038/s41575-020-0286-8]

11   **Raskov H**, Burcharth J, Pommergaard HC, Rosenberg J. Irritable bowel syndrome, the microbiota and the gut-brain axis. *Gut Microbes* 2016; **7**: 365-383 [PMID: 27472486 DOI: 10.1080/19490976.2016.1218585]

12   **Mari A**, Abu Baker F, Mahamid M, Sbeit W, Khoury T. The Evolving Role of Gut Microbiota in the Management of Irritable Bowel Syndrome: An Overview of the Current Knowledge. *J Clin Med* 2020; **9** [PMID: 32143424 DOI: 10.3390/jcm9030685]

13   **Holtmann GJ**, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol* 2016; **1**: 133-146 [PMID: 28404070 DOI: 10.1016/S2468-1253(16)30023-1]

14   **Rhee SH**, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 306-314 [PMID: 19404271 DOI: 10.1038/nrgastro.2009.35]

15   **Baj A**, Moro E, Bistoletti M, Orlandi V, Crema F, Giaroni C. Glutamatergic Signaling Along The Microbiota-Gut-Brain Axis. *Int J Mol Sci* 2019; **20** [PMID: 30934533 DOI: 10.3390/ijms20061482]

16   **Cryan JF**, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE, Jaggar M, Long-Smith CM, Lyte JM, Martin JA, Molinero-Perez A, Moloney G, Morelli E, Morillas E, O'Connor R, Cruz-Pereira JS, Peterson VL, Rea K, Ritz NL, Sherwin E, Spichak S, Teichman EM, van de Wouw M, Ventura-Silva AP, Wallace-Fitzsimons SE, Hyland N, Clarke G, Dinan TG. The Microbiota-Gut-Brain Axis. *Physiol Rev* 2019; **99**: 1877-2013 [PMID: 31460832 DOI: 10.1152/physrev.00018.2018]

17   **Quigley EMM**. The Gut-Brain Axis and the Microbiome: Clues to Pathophysiology and Opportunities for Novel Management Strategies in Irritable Bowel Syndrome (IBS). *J Clin Med* 2018; **7** [PMID: 29301380 DOI: 10.3390/jcm7010006]

18   **Herndon CC**, Wang YP, Lu CL. Targeting the gut microbiota for the treatment of irritable bowel syndrome. *Kaohsiung J Med Sci* 2020; **36**: 160-170 [PMID: 31782606 DOI: 10.1002/kjm2.12154]

19   **Lynch SV**, Pedersen O. The Human Intestinal Microbiome in Health and Disease. *N Engl J Med* 2016; **375**: 2369-2379 [PMID: 27974040 DOI: 10.1056/NEJMra1600266]

20   **Gill SR**, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, Gordon JI, Relman DA, Fraser-Liggett CM, Nelson KE. Metagenomic analysis of the human distal gut microbiome. *Science* 2006; **312**: 1355-1359 [PMID: 16741115 DOI: 10.1126/science.1124234]

21   **Qin J**, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Jian M, Zhou Y, Li Y, Zhang X, Qin N, Yang H, Wang J, Brunak S, Doré J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J; MetaHIT Consortium, Bork P, Ehrlich SD, Wang J. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010; **464**: 59-65 [PMID: 20203603 DOI: 10.1038/nature08821]

22   **Adak A**, Khan MR. An insight into gut microbiota and its functionalities. *Cell Mol Life Sci* 2019; **76**: 473-493 [PMID: 30317530 DOI: 10.1007/s00018-018-2943-4]

23   **Roager HM**, Licht TR. Microbial tryptophan catabolites in health and disease. *Nat Commun* 2018; **9**: 3294 [PMID: 30120222 DOI: 10.1038/s41467-018-05470-4]

24   **Oliphant K**, Allen-Vercoe E. Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. *Microbiome* 2019; **7**: 91 [PMID: 31196177 DOI: 10.1186/s40168-019-0704-8]

25   **Blaak EE**, Canfora EE, Theis S, Frost G, Groen AK, Mithieux G, Nauta A, Scott K, Stahl B, van Harsselaar J, van Tol R, Vaughan EE, Verbeke K. Short chain fatty acids in human gut and metabolic health. *Benef Microbes* 2020; **11**: 411-455. [PMID: 32865024 DOI: 10.3920/BM2020.0057]

26   **Linares DM**, Gómez C, Renes E, Fresno JM, Tornadijo ME, Ross RP, Stanton C. Lactic Acid Bacteria and Bifidobacteria with Potential to Design Natural Biofunctional Health-Promoting Dairy Foods. *Front Microbiol* 2017; **8**: 846 [PMID: 28572792 DOI: 10.3389/fmicb.2017.00846]

27   **Biesalski HK**. Nutrition meets the microbiome: micronutrients and the microbiota. *Ann N Y Acad Sci* 2016; **1372**: 53-64 [PMID: 27362360 DOI: 10.1111/nyas.13145]

28   **Grigg JB**, Sonnenberg GF. Host-Microbiota Interactions Shape Local and Systemic Inflammatory Diseases. *J Immunol* 2017; **198**: 564-571 [PMID: 28069751 DOI: 10.4049/jimmunol.1601621]

29   **Smith PM**, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 2013; **341**: 569-573 [PMID: 23828891 DOI: 10.1126/science.1241165]

30   **Tedelind S**, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. *World J Gastroenterol* 2007; **13**: 2826-2832 [PMID: 17569118 DOI: 10.3748/wjg.v13.i20.2826]

31   **Wrzosek L**, Miquel S, Noordine ML, Bouet S, Joncquel Chevalier-Curt M, Robert V, Philippe C, Bridonneau C, Cherbuy C, Robbe-Masselot C, Langella P, Thomas M. Bacteroides thetaiotaomicron and Faecalibacterium prausnitzii influence the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic model rodent. *BMC Biol* 2013; **11**: 61 [PMID: 23692866 DOI: 10.1186/1741-7007-11-61]

32   **Ahl D**, Liu H, Schreiber O, Roos S, Phillipson M, Holm L. Lactobacillus reuteri increases mucus thickness and ameliorates dextran sulphate sodium-induced colitis in mice. *Acta Physiol (Oxf)* 2016; **217**: 300-310 [PMID: 27096537 DOI: 10.1111/apha.12695]

33   **Kim S**, Covington A, Pamer EG. The intestinal microbiota: Antibiotics, colonization resistance, and enteric pathogens. *Immunol Rev* 2017; **279**: 90-105 [PMID: 28856737 DOI: 10.1111/imr.12563]

34   **Camilleri M**, Ford AC. Irritable Bowel Syndrome: Pathophysiology and Current Therapeutic Approaches. *Handb Exp Pharmacol* 2017; **239**: 75-113 [PMID: 27995391 DOI: 10.1007/164_2016_102]

35   **Ford AC**, Lacy BE, Talley NJ. Irritable Bowel Syndrome. *N Engl J Med* 2017; **376**: 2566-2578 [PMID: 28657875 DOI: 10.1056/NEJMra1607547]

36   **D'Antongiovanni V**, Pellegrini C, Fornai M, Colucci R, Blandizzi C, Antonioli L, Bernardini N. Intestinal epithelial barrier and neuromuscular compartment in health and disease. *World J Gastroenterol* 2020; **26**: 1564-1579 [PMID: 32327906 DOI: 10.3748/wjg.v26.i14.1564]

37   **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**: 554-564 [PMID: 31700231 DOI: 10.20524/aog.2019.0428]

38   **Casado-Bedmar M**, Keita ÅV. Potential neuro-immune therapeutic targets in irritable bowel syndrome. *Therap Adv Gastroenterol* 2020; **13**: 1756284820910630 [PMID: 32313554 DOI: 10.1177/1756284820910630]

39   **Worthington JJ**, Reimann F, Gribble FM. Enteroendocrine cells-sensory sentinels of the intestinal environment and orchestrators of mucosal immunity. *Mucosal Immunol* 2018; **11**: 3-20 [PMID: 28853441 DOI: 10.1038/mi.2017.73]

40   **Lach G**, Schellekens H, Dinan TG, Cryan JF. Anxiety, Depression, and the Microbiome: A Role for Gut Peptides. *Neurotherapeutics* 2018; **15**: 36-59 [PMID: 29134359 DOI: 10.1007/s13311-017-0585-0]

41   **Cani PD**, Knauf C. How gut microbes talk to organs: The role of endocrine and nervous routes. *Mol Metab* 2016; **5**: 743-752 [PMID: 27617197 DOI: 10.1016/j.molmet.2016.05.011]

42   **Lin L**, Zhang J. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. *BMC Immunol* 2017; **18**: 2 [PMID: 28061847 DOI: 10.1186/s12865-016-0187-3]

43   **O'Malley D**. Endocrine regulation of gut function - a role for glucagon-like peptide-1 in the pathophysiology of irritable bowel syndrome. *Exp Physiol* 2019; **104**: 3-10 [PMID: 30444291 DOI: 10.1113/EP087443]

44   **Halim MA**, Degerblad M, Sundbom M, Karlbom U, Holst JJ, Webb DL, Hellström PM. Glucagon-Like Peptide-1 Inhibits Prandial Gastrointestinal Motility Through Myenteric Neuronal Mechanisms in Humans. *J Clin Endocrinol Metab* 2018; **103**: 575-585 [PMID: 29177486 DOI: 10.1210/jc.2017-02006]

45   **Li ZY**, Zhang N, Wen S, Zhang J, Sun XL, Fan XM, Sun YH. Decreased glucagon-like peptide-1 correlates with abdominal pain in patients with constipation-predominant irritable bowel syndrome. *Clin Res Hepatol Gastroenterol* 2017; **41**: 459-465 [PMID: 28215540 DOI: 10.1016/j.clinre.2016.12.007]

46   **Yang Y**, Cui X, Chen Y, Wang Y, Li X, Lin L, Zhang H. Exendin-4, an analogue of glucagon-like peptide-1, attenuates hyperalgesia through serotonergic pathways in rats with neonatal colonic sensitivity. *J Physiol Pharmacol* 2014; **65**: 349-357 [PMID: 24930506]

47   **O'Brien R**, O'Malley D. The Glucagon-like peptide-1 receptor agonist, exendin-4, ameliorated gastrointestinal dysfunction in the Wistar Kyoto rat model of Irritable Bowel Syndrome. *Neurogastroenterol Motil* 2020; **32**: e13738 [PMID: 31602785 DOI: 10.1111/nmo.13738]

48   **Camilleri M**, Vazquez-Roque M, Iturrino J, Boldingh A, Burton D, McKinzie S, Wong BS, Rao AS, Kenny E, Månsson M, Zinsmeister AR. Effect of a glucagon-like peptide 1 analog, ROSE-010, on GI motor functions in female patients with constipation-predominant irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G120-G128 [PMID: 22517769 DOI: 10.1152/ajpgi.00076.2012]

49   **Strandwitz P**. Neurotransmitter modulation by the gut microbiota. *Brain Res* 2018; **1693**: 128-133 [PMID: 29903615 DOI: 10.1016/j.brainres.2018.03.015]

50   **Ge X**, Pan J, Liu Y, Wang H, Zhou W, Wang X. Intestinal Crosstalk between Microbiota and Serotonin and its Impact on Gut Motility. *Curr Pharm Biotechnol* 2018; **19**: 190-195 [PMID: 29804531 DOI: 10.2174/1389201019666180528094202]

51   **Barnes NM**, Ahern GP, Becamel C, Bockaert J, Camilleri M, Chaumont-Dubel S, Claeysen S, Cunningham KA, Fone KC, Gershon M, Di Giovanni G, Goodfellow NM, Halberstadt AL, Hartley RM, Hassaine G, Herrick-Davis K, Hovius R, Lacivita E, Lambe EK, Leopoldo M, Levy FO, Lummis SCR, Marin P, Maroteaux L, McCreary AC, Nelson DL, Neumaier JF, Newman-Tancredi A, Nury H, Roberts A, Roth BL, Roumier A, Sanger GJ, Teitler M, Sharp T, Villalón CM, Vogel H, Watts SW, Hoyer D. International Union of Basic and Clinical Pharmacology. CX. Classification of Receptors for 5-hydroxytryptamine; Pharmacology and Function. *Pharmacol Rev* 2021; **73**: 310-520 [PMID: 33370241 DOI: 10.1124/pr.118.015552]

52   **Gros M**, Gros B, Mesonero JE, Latorre E. Neurotransmitter Dysfunction in Irritable Bowel Syndrome: Emerging Approaches for Management. *J Clin Med* 2021; **10** [PMID: 34362210 DOI: 10.3390/jcm10153429]

53   **Mawe GM**, Hoffman JM. Serotonin signalling in the gut--functions, dysfunctions and therapeutic targets. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 473-486 [PMID: 23797870 DOI: 10.1038/nrgastro.2013.105]

54   **Andresen V**, Montori VM, Keller J, West CP, Layer P, Camilleri M. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. *Clin Gastroenterol Hepatol* 2008; **6**: 545-555 [PMID: 18242143 DOI: 10.1016/j.cgh.2007.12.015]

55   **Zheng Y**, Yu T, Tang Y, Xiong W, Shen X, Jiang L, Lin L. Efficacy and safety of 5-hydroxytryptamine 3 receptor antagonists in irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2017; **12**: e0172846 [PMID: 28291778 DOI: 10.1371/journal.pone.0172846]

56   **Black CJ**, Burr NE, Ford AC. Relative Efficacy of Tegaserod in a Systematic Review and Network Meta-analysis of Licensed Therapies for Irritable Bowel Syndrome With Constipation. *Clin Gastroenterol Hepatol* 2020; **18**: 1238-1239.e1 [PMID: 31302307 DOI: 10.1016/j.cgh.2019.07.007]

57   **Evans BW**, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. *Cochrane Database Syst Rev* 2007; CD003960 [PMID: 17943807 DOI: 10.1002/14651858.CD003960.pub3]

58   **Shah ED**, Lacy BE, Chey WD, Chang L, Brenner DM. Tegaserod for Irritable Bowel Syndrome With Constipation in Women Younger Than 65 Years Without Cardiovascular Disease: Pooled Analyses of 4 Controlled Trials. *Am J Gastroenterol* 2021; **116**: 1601-1611 [PMID: 34047303 DOI: 10.14309/ajg.0000000000001313]

59   **Fukudo S**, Nakamura M, Hamatani T, Kazumori K, Miwa H. Efficacy and Safety of 5-HT4 Receptor Agonist Minesapride for Irritable Bowel Syndrome with Constipation in a Randomized Controlled Trial. *Clin Gastroenterol Hepatol* 2021; **19**: 538-546.e8 [PMID: 32184185 DOI: 10.1016/j.cgh.2020.03.019]

60   **Hamatani T**, Noda N, Takagaki T, Yodo Y, Kawai H, Kakuyama H, Kaji Y, Fujio Y. Thorough QT/QTc Study Shows That a Novel 5-HT$_4$ Receptor Partial Agonist Minesapride Has No Effect on QT Prolongation. *Clin Pharmacol Drug Dev* 2020; **9**: 938-951 [PMID: 32087003 DOI: 10.1002/cpdd.778]

61   **Pusceddu MM**, Gareau MG. Visceral pain: gut microbiota, a new hope? *J Biomed Sci* 2018; **25**: 73 [PMID: 30309367 DOI: 10.1186/s12929-018-0476-7]

62   **Ait-Belgnaoui A**, Payard I, Rolland C, Harkat C, Braniste V, Théodorou V, Tompkins TA. *Bifidobacterium longum* and *Lactobacillus helveticus* Synergistically Suppress Stress-related Visceral Hypersensitivity Through Hypothalamic-Pituitary-Adrenal Axis Modulation. *J Neurogastroenterol Motil* 2018; **24**: 138-146 [PMID: 29291614 DOI: 10.5056/jnm16167]

63   **Zhang J**, Song L, Wang Y, Liu C, Zhang L, Zhu S, Liu S, Duan L. Beneficial effect of butyrate-producing Lachnospiraceae on stress-induced visceral hypersensitivity in rats. *J Gastroenterol Hepatol* 2019; **34**: 1368-1376 [PMID: 30402954 DOI: 10.1111/jgh.14536]

64   **Wei P**, Keller C, Li L. Neuropeptides in gut-brain axis and their influence on host immunity and stress. *Comput Struct Biotechnol J* 2020; **18**: 843-851 [PMID: 32322366 DOI: 10.1016/j.csbj.2020.02.018]

65   **Kano M**, Muratsubaki T, Van Oudenhove L, Morishita J, Yoshizawa M, Kohno K, Yagihashi M, Tanaka Y, Mugikura S, Dupont P, Ly HG, Takase K, Kanazawa M, Fukudo S. Altered brain and gut responses to corticotropin-releasing hormone (CRH) in patients with irritable bowel syndrome. *Sci Rep* 2017; **7**: 12425 [PMID: 28963545 DOI: 10.1038/s41598-017-09635-x]

66   **Sudo N**, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu X-N, Kubo C, Koga Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol* 2004; **558**: 263-275. [PMID: 15133062 DOI: 10.1113/jphysiol.2004.063388]

67   **Rea K**, Dinan TG, Cryan JF. The microbiome: A key regulator of stress and neuroinflammation. *Neurobiol Stress* 2016; **4**: 23-33 [PMID: 27981187 DOI: 10.1016/j.ynstr.2016.03.001]

68   **Keller J**, Gomez R, Williams G, Lembke A, Lazzeroni L, Murphy GM Jr, Schatzberg AF. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. *Mol Psychiatry* 2017; **22**: 527-536 [PMID: 27528460 DOI: 10.1038/mp.2016.120]

69   **Faravelli C**, Lo Sauro C, Godini L, Lelli L, Benni L, Pietrini F, Lazzeretti L, Talamba GA, Fioravanti G, Ricca V. Childhood stressful events, HPA axis and anxiety disorders. *World J Psychiatry* 2012; **2**: 13-25 [PMID: 24175164 DOI: 10.5498/wjp.v2.i1.13]

70   **Lee C**, Doo E, Choi JM, Jang SH, Ryu HS, Lee JY, Oh JH, Park JH, Kim YS; Brain-Gut Axis Research Group of Korean Society of Neurogastroenterology and Motility. The Increased Level of Depression and Anxiety in Irritable Bowel Syndrome Patients Compared with Healthy Controls: Systematic Review and Meta-analysis. *J Neurogastroenterol Motil* 2017; **23**: 349-362 [PMID: 28672433 DOI: 10.5056/jnm16220]

71   **Sarkar A**, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the Manipulation of Bacteria-Gut-Brain Signals. *Trends Neurosci* 2016; **39**: 763-781 [PMID: 27793434 DOI: 10.1016/j.tins.2016.09.002]

72   **Auteri M**, Zizzo MG, Serio R. GABA and GABA receptors in the gastrointestinal tract: from motility to inflammation. *Pharmacol Res* 2015; **93**: 11-21 [PMID: 25526825 DOI: 10.1016/j.phrs.2014.12.001]

73   **Kawase T**, Nagasawa M, Ikeda H, Yasuo S, Koga Y, Furuse M. Gut microbiota of mice putatively modifies amino acid metabolism in the host brain. *Br J Nutr* 2017; **117**: 775-783 [PMID: 28393748 DOI: 10.1017/S0007114517000678]

74   **Huo R**, Zeng B, Zeng L, Cheng K, Li B, Luo Y, Wang H, Zhou C, Fang L, Li W, Niu R, Wei H, Xie P. Microbiota Modulate Anxiety-Like Behavior and Endocrine Abnormalities in Hypothalamic-Pituitary-Adrenal Axis. *Front Cell Infect Microbiol* 2017; **7**: 489 [PMID: 29250490 DOI: 10.3389/fcimb.2017.00489]

75   **De Palma G**, Blennerhassett P, Lu J, Deng Y, Park AJ, Green W, Denou E, Silva MA, Santacruz A, Sanz Y, Surette MG, Verdu EF, Collins SM, Bercik P. Microbiota and host determinants of behavioural phenotype in maternally separated mice. *Nat Commun* 2015; **6**: 7735 [PMID: 26218677 DOI: 10.1038/ncomms8735]

76   **De Palma G**, Lynch MD, Lu J, Dang VT, Deng Y, Jury J, Umeh G, Miranda PM, Pigrau Pastor M, Sidani S, Pinto-Sanchez MI, Philip V, McLean PG, Hagelsieb MG, Surette MG, Bergonzelli GE, Verdu EF, Britz-McKibbin P, Neufeld JD, Collins SM, Bercik P. Transplantation of fecal microbiota from patients with irritable bowel syndrome alters gut function and behavior in recipient mice. *Sci Transl Med* 2017; **9** [PMID: 28251905 DOI: 10.1126/scitranslmed.aaf6397]

77   **Huang C**, Yang X, Zeng B, Zeng L, Gong X, Zhou C, Xia J, Lian B, Qin Y, Yang L, Liu L, Xie P. Proteomic analysis of olfactory bulb suggests CACNA1E as a promoter of CREB signaling in microbiota-induced depression. *J Proteomics*

2019; **194**: 132-147 [PMID: 30521978 DOI: 10.1016/j.jprot.2018.11.023]

78   **Zheng P**, Zeng B, Zhou C, Liu M, Fang Z, Xu X, Zeng L, Chen J, Fan S, Du X, Zhang X, Yang D, Yang Y, Meng H, Li W, Melgiri ND, Licinio J, Wei H, Xie P. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Mol Psychiatry* 2016; **21**: 786-796 [PMID: 27067014 DOI: 10.1038/mp.2016.44]

79   **Enck P**, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, Niesler B, Quigley EM, Rajilić-Stojanović M, Schemann M, Schwille-Kiuntke J, Simren M, Zipfel S, Spiller RC. Irritable bowel syndrome. *Nat Rev Dis Primers* 2016; **2**: 16014 [PMID: 27159638 DOI: 10.1038/nrdp.2016.14]

80   **Wouters MM**, Vicario M, Santos J. The role of mast cells in functional GI disorders. *Gut* 2016; **65**: 155-168 [PMID: 26194403 DOI: 10.1136/gutjnl-2015-309151]

81   **Choghakhori R**, Abbasnezhad A, Hasanvand A, Amani R. Inflammatory cytokines and oxidative stress biomarkers in irritable bowel syndrome: Association with digestive symptoms and quality of life. *Cytokine* 2017; **93**: 34-43 [PMID: 28506572 DOI: 10.1016/j.cyto.2017.05.005]

82   **Barbalho SM**, Goulart RA, Araújo AC, Guiguer ÉL, Bechara MD. Irritable bowel syndrome: a review of the general aspects and the potential role of vitamin D. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 345-359 [PMID: 30791775 DOI: 10.1080/17474124.2019.1570137]

83   **Farzaei MH**, Bahramsoltani R, Abdollahi M, Rahimi R. The Role of Visceral Hypersensitivity in Irritable Bowel Syndrome: Pharmacological Targets and Novel Treatments. *J Neurogastroenterol Motil* 2016; **22**: 558-574 [PMID: 27431236 DOI: 10.5056/jnm16001]

84   **Atarashi K**, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, Fukuda S, Saito T, Narushima S, Hase K, Kim S, Fritz JV, Wilmes P, Ueha S, Matsushima K, Ohno H, Olle B, Sakaguchi S, Taniguchi T, Morita H, Hattori M, Honda K. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature* 2013; **500**: 232-236 [PMID: 23842501 DOI: 10.1038/nature12331]

85   **Blacher E**, Levy M, Tatirovsky E, Elinav E. Microbiome-Modulated Metabolites at the Interface of Host Immunity. *J Immunol* 2017; **198**: 572-580 [PMID: 28069752 DOI: 10.4049/jimmunol.1601247]

86   **Gao J**, Xu K, Liu H, Liu G, Bai M, Peng C, Li T, Yin Y. Impact of the Gut Microbiota on Intestinal Immunity Mediated by Tryptophan Metabolism. *Front Cell Infect Microbiol* 2018; **8**: 13 [PMID: 29468141 DOI: 10.3389/fcimb.2018.00013]

87   **Azad MAK**, Sarker M, Wan D. Immunomodulatory Effects of Probiotics on Cytokine Profiles. *Biomed Res Int* 2018; **2018**: 8063647 [PMID: 30426014 DOI: 10.1155/2018/8063647]

88   **Yousefi B**, Eslami M, Ghasemian A, Kokhaei P, Salek Farrokhi A, Darabi N. Probiotics importance and their immunomodulatory properties. *J Cell Physiol* 2019; **234**: 8008-8018 [PMID: 30317594 DOI: 10.1002/jcp.27559]

89   **Kim HS**, Lim JH, Park H, Lee SI. Increased immunoendocrine cells in intestinal mucosa of postinfectious irritable bowel syndrome patients 3 years after acute Shigella infection--an observation in a small case control study. *Yonsei Med J* 2010; **51**: 45-51 [PMID: 20046513 DOI: 10.3349/ymj.2010.51.1.45]

90   **Swan C**, Duroudier NP, Campbell E, Zaitoun A, Hastings M, Dukes GE, Cox J, Kelly FM, Wilde J, Lennon MG, Neal KR, Whorwell PJ, Hall IP, Spiller RC. Identifying and testing candidate genetic polymorphisms in the irritable bowel syndrome (IBS): association with TNFSF15 and TNFα. *Gut* 2013; **62**: 985-994 [PMID: 22684480 DOI: 10.1136/gutjnl-2011-301213]

91   **Bailey MT**, Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain Behav Immun* 2011; **25**: 397-407 [PMID: 21040780 DOI: 10.1016/j.bbi.2010.10.023]

92   **Sharara AI**, Aoun E, Abdul-Baki H, Mounzer R, Sidani S, Elhajj I. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. *Am J Gastroenterol* 2006; **101**: 326-333 [PMID: 16454838 DOI: 10.1111/j.1572-0241.2006.00458.x]

93   **Cheng P**, Yao J, Wang C, Zhang L, Kong W. Molecular and cellular mechanisms of tight junction dysfunction in the irritable bowel syndrome. *Mol Med Rep* 2015; **12**: 3257-3264 [PMID: 25998845 DOI: 10.3892/mmr.2015.3808]

94   **van Thiel IAM**, de Jonge WJ, Chiu IM, van den Wijngaard RM. Microbiota-neuroimmune cross talk in stress-induced visceral hypersensitivity of the bowel. *Am J Physiol Gastrointest Liver Physiol* 2020; **318**: G1034-G1041 [PMID: 32308040 DOI: 10.1152/ajpgi.00196.2019]

95   **Rooks MG**, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol* 2016; **16**: 341-352 [PMID: 27231050 DOI: 10.1038/nri.2016.42]

96   **Ait-Belgnaoui A**, Durand H, Cartier C, Chaumaz G, Eutamene H, Ferrier L, Houdeau E, Fioramonti J, Bueno L, Theodorou V. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology* 2012; **37**: 1885-1895 [PMID: 22541937 DOI: 10.1016/j.psyneuen.2012.03.024]

97   **Vich Vila A**, Imhann F, Collij V, Jankipersadsing SA, Gurry T, Mujagic Z, Kurilshikov A, Bonder MJ, Jiang X, Tigchelaar EF, Dekens J, Peters V, Voskuil MD, Visschedijk MC, van Dullemen HM, Keszthelyi D, Swertz MA, Franke L, Alberts R, Festen EAM, Dijkstra G, Masclee AAM, Hofker MH, Xavier RJ, Alm EJ, Fu J, Wijmenga C, Jonkers DMAE, Zhernakova A, Weersma RK. Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. *Sci Transl Med* 2018; **10** [PMID: 30567928 DOI: 10.1126/scitranslmed.aap8914]

98   **Pittayanon R**, Lau JT, Yuan Y, Leontiadis GI, Tse F, Surette M, Moayyedi P. Gut Microbiota in Patients With Irritable Bowel Syndrome-A Systematic Review. *Gastroenterology* 2019; **157**: 97-108 [PMID: 30940523 DOI: 10.1053/j.gastro.2019.03.049]

99   **Duan R**, Zhu S, Wang B, Duan L. Alterations of Gut Microbiota in Patients With Irritable Bowel Syndrome Based on 16S rRNA-Targeted Sequencing: A Systematic Review. *Clin Transl Gastroenterol* 2019; **10**: e00012 [PMID: 30829919 DOI: 10.14309/ctg.0000000000000012]

100   **Jeffery IB**, Das A, O'Herlihy E, Coughlan S, Cisek K, Moore M, Bradley F, Carty T, Pradhan M, Dwibedi C, Shanahan F, O'Toole PW. Differences in Fecal Microbiomes and Metabolomes of People With *vs* Without Irritable Bowel Syndrome and Bile Acid Malabsorption. *Gastroenterology* 2020; **158**: 1016-1028.e8 [PMID: 31843589 DOI:

10.1053/j.gastro.2019.11.301]

101   **Pozuelo M**, Panda S, Santiago A, Mendez S, Accarino A, Santos J, Guarner F, Azpiroz F, Manichanh C. Reduction of butyrate- and methane-producing microorganisms in patients with Irritable Bowel Syndrome. *Sci Rep* 2015; **5**: 12693 [PMID: 26239401 DOI: 10.1038/srep12693]

102   **Maharshak N**, Ringel Y, Katibian D, Lundqvist A, Sartor RB, Carroll IM, Ringel-Kulka T. Fecal and Mucosa-Associated Intestinal Microbiota in Patients with Diarrhea-Predominant Irritable Bowel Syndrome. *Dig Dis Sci* 2018; **63**: 1890-1899 [PMID: 29777439 DOI: 10.1007/s10620-018-5086-4]

103   **Liu HN**, Wu H, Chen YZ, Chen YJ, Shen XZ, Liu TT. Altered molecular signature of intestinal microbiota in irritable bowel syndrome patients compared with healthy controls: A systematic review and meta-analysis. *Dig Liver Dis* 2017; **49**: 331-337 [PMID: 28179092 DOI: 10.1016/j.dld.2017.01.142]

104   **Zhuang X**, Xiong L, Li L, Li M, Chen M. Alterations of gut microbiota in patients with irritable bowel syndrome: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2017; **32**: 28-38 [PMID: 27300149 DOI: 10.1111/jgh.13471]

105   **Shukla R**, Ghoshal U, Dhole TN, Ghoshal UC. Fecal Microbiota in Patients with Irritable Bowel Syndrome Compared with Healthy Controls Using Real-Time Polymerase Chain Reaction: An Evidence of Dysbiosis. *Dig Dis Sci* 2015; **60**: 2953-2962 [PMID: 25784074 DOI: 10.1007/s10620-015-3607-y]

106   **Wang L**, Alammar N, Singh R, Nanavati J, Song Y, Chaudhary R, Mullin GE. Gut Microbial Dysbiosis in the Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Case-Control Studies. *J Acad Nutr Diet* 2020; **120**: 565-586 [PMID: 31473156 DOI: 10.1016/j.jand.2019.05.015]

107   **Su T**, Liu R, Lee A, Long Y, Du L, Lai S, Chen X, Wang L, Si J, Owyang C, Chen S. Altered Intestinal Microbiota with Increased Abundance of *Prevotella* Is Associated with High Risk of Diarrhea-Predominant Irritable Bowel Syndrome. *Gastroenterol Res Pract* 2018; **2018**: 6961783 [PMID: 29967640 DOI: 10.1155/2018/6961783]

108   **Ringel-Kulka T**, Benson AK, Carroll IM, Kim J, Legge RM, Ringel Y. Molecular characterization of the intestinal microbiota in patients with and without abdominal bloating. *Am J Physiol Gastrointest Liver Physiol* 2016; **310**: G417-G426 [PMID: 26702134 DOI: 10.1152/ajpgi.00044.2015]

109   **Zhuang X**, Tian Z, Li L, Zeng Z, Chen M, Xiong L. Fecal Microbiota Alterations Associated With Diarrhea-Predominant Irritable Bowel Syndrome. *Front Microbiol* 2018; **9**: 1600 [PMID: 30090090 DOI: 10.3389/fmicb.2018.01600]

110   **Durand GA**, Raoult D, Dubourg G. Antibiotic discovery: history, methods and perspectives. *Int J Antimicrob Agents* 2019; **53**: 371-382 [PMID: 30472287 DOI: 10.1016/j.ijantimicag.2018.11.010]

111   **Aminov R**. History of antimicrobial drug discovery: Major classes and health impact. *Biochem Pharmacol* 2017; **133**: 4-19 [PMID: 27720719 DOI: 10.1016/j.bcp.2016.10.001]

112   **Zaman SB**, Hussain MA, Nye R, Mehta V, Mamun KT, Hossain N. A Review on Antibiotic Resistance: Alarm Bells are Ringing. *Cureus* 2017; **9**: e1403 [PMID: 28852600 DOI: 10.7759/cureus.1403]

113   **Sultan I**, Rahman S, Jan AT, Siddiqui MT, Mondal AH, Haq QMR. Antibiotics, Resistome and Resistance Mechanisms: A Bacterial Perspective. *Front Microbiol* 2018; **9**: 2066 [PMID: 30298054 DOI: 10.3389/fmicb.2018.02066]

114   **Turta O**, Rautava S. Antibiotics, obesity and the link to microbes - what are we doing to our children? *BMC Med* 2016; **14**: 57 [PMID: 27090219 DOI: 10.1186/s12916-016-0605-7]

115   **Scheer S**, Medina TS, Murison A, Taves MD, Antignano F, Chenery A, Soma KK, Perona-Wright G, Lupien M, Arrowsmith CH, De Carvalho DD, Zaph C. Early-life antibiotic treatment enhances the pathogenicity of CD4^{+} T cells during intestinal inflammation. *J Leukoc Biol* 2017; **101**: 893-900 [PMID: 28034915 DOI: 10.1189/jlb.3MA0716-334RR]

116   **Gustafsson J**, McDonald KG, Newberry R.   Disruption of the gut microbiota by antibiotics exposure during early life promotes spontaneous Th2 responses and loss of tolerance to dietary antigens. e-pub ahead of print 2016

117   **Rasmussen SH**, Shrestha S, Bjerregaard LG, Ängquist LH, Baker JL, Jess T, Allin KH. Antibiotic exposure in early life and childhood overweight and obesity: A systematic review and meta-analysis. *Diabetes Obes Metab* 2018; **20**: 1508-1514 [PMID: 29359849 DOI: 10.1111/dom.13230]

118   **Eckburg PB**, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. *Science* 2005; **308**: 1635-1638 [PMID: 15831718 DOI: 10.1126/science.1110591]

119   **Panda S**, El khader I, Casellas F, López Vivancos J, García Cors M, Santiago A, Cuenca S, Guarner F, Manichanh C. Short-term effect of antibiotics on human gut microbiota. *PLoS One* 2014; **9**: e95476 [PMID: 24748167 DOI: 10.1371/journal.pone.0095476]

120   **Burdet C**, Grall N, Linard M, Bridier-Nahmias A, Benhayoun M, Bourabha K, Magnan M, Clermont O, d'Humières C, Tenaillon O, Denamur E, Massias L, Tubiana S, Alavoine L, Andremont A, Mentré F, Duval X; CEREMI Group. Ceftriaxone and Cefotaxime Have Similar Effects on the Intestinal Microbiota in Human Volunteers Treated by Standard-Dose Regimens. *Antimicrob Agents Chemother* 2019; **63** [PMID: 30936104 DOI: 10.1128/AAC.02244-18]

121   **Rashid MU**, Zaura E, Buijs MJ, Keijser BJ, Crielaard W, Nord CE, Weintraub A. Determining the Long-term Effect of Antibiotic Administration on the Human Normal Intestinal Microbiota Using Culture and Pyrosequencing Methods. *Clin Infect Dis* 2015; **60** Suppl 2: S77-S84 [PMID: 25922405 DOI: 10.1093/cid/civ137]

122   **Isaac S**, Scher JU, Djukovic A, Jiménez N, Littman DR, Abramson SB, Pamer EG, Ubeda C. Short- and long-term effects of oral vancomycin on the human intestinal microbiota. *J Antimicrob Chemother* 2017; **72**: 128-136 [PMID: 27707993 DOI: 10.1093/jac/dkw383]

123   **Haak BW**, Lankelma JM, Hugenholtz F, Belzer C, de Vos WM, Wiersinga WJ. Long-term impact of oral vancomycin, ciprofloxacin and metronidazole on the gut microbiota in healthy humans. *J Antimicrob Chemother* 2019; **74**: 782-786 [PMID: 30418539 DOI: 10.1093/jac/dky471]

124   **Ianiro G**, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. *Gut* 2016; **65**: 1906-1915 [PMID: 27531828 DOI: 10.1136/gutjnl-2016-312297]

125   **Baietto L**, Corcione S, Pacini G, Perri GD, D'Avolio A, De Rosa FG. A 30-years review on pharmacokinetics of antibiotics: is the right time for pharmacogenetics? *Curr Drug Metab* 2014; **15**: 581-598 [PMID: 24909419 DOI: 10.2174/1389200215666140605130935]

126   **Becattini S**, Taur Y, Pamer EG. Antibiotic-Induced Changes in the Intestinal Microbiota and Disease. *Trends Mol Med*

2016; **22**: 458-478 [PMID: 27178527 DOI: 10.1016/j.molmed.2016.04.003]

127 **Ubeda C**, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, Viale A, Socci ND, van den Brink MR, Kamboj M, Pamer EG. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. *J Clin Invest* 2010; **120**: 4332-4341 [PMID: 21099116 DOI: 10.1172/JCI43918]

128 **Zimmermann P**, Curtis N. The effect of antibiotics on the composition of the intestinal microbiota - a systematic review. *J Infect* 2019; **79**: 471-489 [PMID: 31629863 DOI: 10.1016/j.jinf.2019.10.008]

129 **Baldelli V**, Scaldaferri F, Putignani L, Del Chierico F. The Role of Enterobacteriaceae in Gut Microbiota Dysbiosis in Inflammatory Bowel Diseases. *Microorganisms* 2021; **9** [PMID: 33801755 DOI: 10.3390/microorganisms9040697]

130 **Morgan XC**, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, Reyes JA, Shah SA, LeLeiko N, Snapper SB, Bousvaros A, Korzenik J, Sands BE, Xavier RJ, Huttenhower C. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol* 2012; **13**: R79 [PMID: 23013615 DOI: 10.1186/gb-2012-13-9-r79]

131 **Garrett WS**, Gallini CA, Yatsunenko T, Michaud M, DuBois A, Delaney ML, Punit S, Karlsson M, Bry L, Glickman JN, Gordon JI, Onderdonk AB, Glimcher LH. Enterobacteriaceae act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis. *Cell Host Microbe* 2010; **8**: 292-300 [PMID: 20833380 DOI: 10.1016/j.chom.2010.08.004]

132 **Pimentel M**, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2003; **98**: 412-419 [PMID: 12591062 DOI: 10.1111/j.1572-0241.2003.07234.x]

133 **Ford AC**, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther* 2018; **48**: 1044-1060 [PMID: 30294792 DOI: 10.1111/apt.15001]

134 **Lopez-Siles M**, Duncan SH, Garcia-Gil LJ, Martinez-Medina M. Faecalibacterium prausnitzii: from microbiology to diagnostics and prognostics. *ISME J* 2017; **11**: 841-852 [PMID: 28045459 DOI: 10.1038/ismej.2016.176]

135 **Raymond F**, Ouameur AA, Déraspe M, Iqbal N, Gingras H, Dridi B, Leprohon P, Plante PL, Giroux R, Bérubé È, Frenette J, Boudreau DK, Simard JL, Chabot I, Domingo MC, Trottier S, Boissinot M, Huletsky A, Roy PH, Ouellette M, Bergeron MG, Corbeil J. The initial state of the human gut microbiome determines its reshaping by antibiotics. *ISME J* 2016; **10**: 707-720 [PMID: 26359913 DOI: 10.1038/ismej.2015.148]

136 **Pallav K**, Dowd SE, Villafuerte J, Yang X, Kabbani T, Hansen J, Dennis M, Leffler DA, Newburg DS, Kelly CP. Effects of polysaccharopeptide from Trametes versicolor and amoxicillin on the gut microbiome of healthy volunteers: a randomized clinical trial. *Gut Microbes* 2014; **5**: 458-467 [PMID: 25006989 DOI: 10.4161/gmic.29558]

137 **Kabbani TA**, Pallav K, Dowd SE, Villafuerte-Galvez J, Vanga RR, Castillo NE, Hansen J, Dennis M, Leffler DA, Kelly CP. Prospective randomized controlled study on the effects of Saccharomyces boulardii CNCM I-745 and amoxicillin-clavulanate or the combination on the gut microbiota of healthy volunteers. *Gut Microbes* 2017; **8**: 17-32 [PMID: 27973989 DOI: 10.1080/19490976.2016.1267890]

138 **Covasa M**, Stephens RW, Toderean R, Cobuz C. Intestinal Sensing by Gut Microbiota: Targeting Gut Peptides. *Front Endocrinol (Lausanne)* 2019; **10**: 82 [PMID: 30837951 DOI: 10.3389/fendo.2019.00082]

139 **Reimann F**, Tolhurst G, Gribble FM. G-protein-coupled receptors in intestinal chemosensation. *Cell Metab* 2012; **15**: 421-431 [PMID: 22482725 DOI: 10.1016/j.cmet.2011.12.019]

140 **Lund ML**, Egerod KL, Engelstoft MS, Dmytriyeva O, Theodorsson E, Patel BA, Schwartz TW. Enterochromaffin 5-HT cells - A major target for GLP-1 and gut microbial metabolites. *Mol Metab* 2018; **11**: 70-83 [PMID: 29576437 DOI: 10.1016/j.molmet.2018.03.004]

141 **Cantarel BL**, Lombard V, Henrissat B. Complex carbohydrate utilization by the healthy human microbiome. *PLoS One* 2012; **7**: e28742 [PMID: 22719820 DOI: 10.1371/journal.pone.0028742]

142 **Fukiya S**, Arata M, Kawashima H, Yoshida D, Kaneko M, Minamida K, Watanabe J, Ogura Y, Uchida K, Itoh K, Wada M, Ito S, Yokota A. Conversion of cholic acid and chenodeoxycholic acid into their 7-oxo derivatives by Bacteroides intestinalis AM-1 isolated from human feces. *FEMS Microbiol Lett* 2009; **293**: 263-270 [PMID: 19243441 DOI: 10.1111/j.1574-6968.2009.01531.x]

143 **Kimura I**, Inoue D, Hirano K, Tsujimoto G. The SCFA Receptor GPR43 and Energy Metabolism. *Front Endocrinol (Lausanne)* 2014; **5**: 85 [PMID: 24926285 DOI: 10.3389/fendo.2014.00085]

144 **Portune K**, Beaumont M, Davila A, Tomé D, Blachier F, Sanz Y. Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin. *Trends Food Sci Technol* 2016 [DOI: 10.1016/J.TIFS.2016.08.011]

145 **Dior M**, Delagrèverie H, Duboc H, Jouet P, Coffin B, Brot L, Humbert L, Trugnan G, Seksik P, Sokol H, Rainteau D, Sabate JM. Interplay between bile acid metabolism and microbiota in irritable bowel syndrome. *Neurogastroenterol Motil* 2016; **28**: 1330-1340 [PMID: 27060367 DOI: 10.1111/nmo.12829]

146 **Gobert AP**, Sagrestani G, Delmas E, Wilson KT, Verriere TG, Dapoigny M, Del'homme C, Bernalier-Donadille A. The human intestinal microbiota of constipated-predominant irritable bowel syndrome patients exhibits anti-inflammatory properties. *Sci Rep* 2016; **6**: 39399 [PMID: 27982124 DOI: 10.1038/srep39399]

147 **Zhong W**, Lu X, Shi H, Zhao G, Song Y, Wang Y, Zhang J, Jin Y, Wang S. Distinct Microbial Populations Exist in the Mucosa-associated Microbiota of Diarrhea Predominant Irritable Bowel Syndrome and Ulcerative Colitis. *J Clin Gastroenterol* 2019; **53**: 660-672 [PMID: 29210899 DOI: 10.1097/MCG.0000000000000961]

148 **Rangel I**, Sundin J, Fuentes S, Repsilber D, de Vos WM, Brummer RJ. The relationship between faecal-associated and mucosal-associated microbiota in irritable bowel syndrome patients and healthy subjects. *Aliment Pharmacol Ther* 2015; **42**: 1211-1221 [PMID: 26376728 DOI: 10.1111/apt.13399]