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

Zarina Mamieva, Elena Poluektova, Valery Svistushkin, Vasily Sobolev, Oleg Shifrin, Francisco Guarner, Vladimir Ivashkin

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Chen F, Mi Y, Ren JY, Wang JH

Received: August 24, 2021
Peer-review started: August 24, 2021
First decision: November 7, 2021
Revised: December 1, 2021
Accepted: February 22, 2022
Article in press: February 22, 2022
Published online: March 28, 2022

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 complex interplay between antibiotics, gut microbiota, and the development of IBS.
understanding of the link between antibiotic use and the development of IBS.

**Key Words:** Gut microbiota; Irritable bowel syndrome; Antibiotics; Intestinal barrier; Gut motility; Gut sensitivity

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

---

**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.

---

**Citation:** Mamieva Z, Poluektova E, Svistushkin V, Sobolev V, Shifrin O, Guarner F, Ivashkin V. Antibiotics, gut microbiota, and irritable bowel syndrome: What are the relations? *World J Gastroenterol* 2022; 28(12): 1204-1219

**URL:** https://www.wjgnet.com/1007-9327/full/v28/i12/1204.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v28.i12.1204

---

**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.
| Bacterial phylum | Key representatives | Functions |
|------------------|--------------------|-----------|
| **Firmicutes**   | Members of the genera *Enterococcus*, *Ruminococcus*, *Clostridium*, *Lachnoclostridium*, *Faecalibacterium*, *Roseburia*, and *Escherichia* | 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[44]. Maintenance of a proper immune response[26,29] and intestinal epithelial barrier integrity[31]. Protection against enteric pathogens[33] |
| **Actinobacteria** | Members of the genera *Bifidobacterium* and *Coriobacterium* | 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 diarrhe-
Antibiotics, gut microbiota, and IBS

The physiological response to stress is mediated through the hypothalamic-pituitary-adrenal (HPA) axis [41]. 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.

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. 

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 (Gq, Gi and Gs) and activate different pathways known to regulate gene expression and promote exocytosis by raising intracellular Ca2+ 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.

DOI: 10.3748/wjg.v28.i12.1204 Copyright © The Author(s) 2022.
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 (ZO)s, 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-I\(^1,22,31,82,93\). 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-I\(^95\). 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 bacteria.
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  | IBS-D (n=16), IBS-C (n=15), Controls (n=15) | Real-time PCR   | Stool | No data | ↑ in IBS-D (Escherichia) | ↑ in IBS-C | -              |
| [145], 2016  |          |                            |                |           |                  |                   |                 |              |
| Ringel-Kulka et al | IBS (n=56), Controls (n=20) | 16S rRNA | Stool | No data | - | - | - |
| [109], 2016  |          |                            |                |           |                  |                   |                 | ↑            |
| Maharshak et al [102], 2018 | IBS-D (n=23), Controls (n=24) | 16S rRNA | Stool | ↓\(^1\) | ↓ | ↑ (unclassified genus) | - | - |
| 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 [109], 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 | ↓\(^3\) | ↓ (F. prausnitzii) | - | - |
|              |          |                            | Colonic biopsy |           |                  |                   |                 |              |

\(^1\)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\cite{110,111}. However, a growing number of studies have shown that inappropriate use of antibiotics promotes the development of antibiotic resistance\cite{112,113}. Furthermore, accumulating evidence indicates that antibiotic exposure in early life increases the risk of obesity and autoimmune and allergic diseases\cite{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\cite{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\cite{119-122}. 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\cite{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\cite{122}. Lipophilic antibiotics (e.g., lincosamides and macrolides) are eliminated mainly by biliary excretion and therefore cause profound changes in the intestinal microbiota\cite{125}. For example, treatment with clindamycin resulted in a reduction in microbial diversity and a decrease in Roseburia, Lachnospira, Coprococcus, Dorea, and Ruminococcus. Changes in microbial composition were observed throughout 12 mo after clindamycin exposure\cite{121}. In a recent study conducted by Haak et al\cite{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\cite{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\cite{127}.

In a recent systematic review, Zimmerman et al\cite{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, lipopolysaccharides, 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\cite{129}. Moreover, expansion of bacteria belonging to the Enterobacteriaceae family was associated with inflammatory bowel diseases, both in animal models and in humans\cite{130,131}. Zimmerman et al\cite{128} reported that amoxicillin, piperacillin, ticarcillin, cephalosporins (except fifth generation cephalosporins), carbapenems, and lipopolysaccharides 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\cite{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\cite{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; \( P = 0.005 \))\cite{6}. A longitudinal study by Krogsgaard et al\cite{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)\cite{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 | ↓          | ↑ Escherichia, Shigella |
| Kabbani et al [137], 2017 | 16S RNA     | Amoxicillin-Clavulanate | 875/125 mg twice daily for 7 d | ↓          | ↑ Escherichia, Parabacteroides, Enterobacter ↓ Roseburia |
| Burdet et al [126], 2019 | 16S RNA     | Ceftriaxone     | 1 g once daily for 3 d | ↓          | ↓ Firmicutes, Actinobacteria, Bacteroidetes |
| Raymond et al [135], 2016 | Shotgun sequencing | Cefprozil    | 500 mg twice daily for 7 d | ↓          | ↑ Flavonifructos, Lachnoclostridium, Parabacteroides, Bifidobacteriaceae, Coriobacteriaceae, Eubacteriaceae, Oxalobacteriaceae, Pasteurellaceae, Veillonellaceae |
| Rashid et al [121], 2015 | Pyrosequencing | Ciprofloxacin   | 500 mg twice daily for 10 d | ↓          | ↑ Bacteroides ↓ Faecalibacterium, Alistipes, unculturable Ruminococcaceae |
| Isaac et al[122], 2017 | 16S RNA     | Vancomycin      | 250 mg per or 4 times daily for 2 wk | ↓          | ↑ Escherichia, Shigella, Klebsiella, ↓ Bacteroidetes, Faecalibacterium, Ruminococcus |

1OTU analysis.
2Rarefaction analysis.
3Chao index.
4Shannon index.
5Simpson 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
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

Author contributions: Mamieva Z and Poluektova E took the lead in writing the manuscript; Svistushkin V and Sobolev V contributed to interpreting the relevant literature, provided critical feedback, and helped shape the manuscript; Shifrin O, Guarner F, and Ivashkin V substantially contributed to the conception and design of the article and revised the paper; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/

Country/Territory of origin: Russia

ORCID number: Zarina Mamieva 0000-0002-5673-7920; Elena Poluektova 0000-0002-9038-3732; Valery Svistushkin 0000-0001-7614-1293; Vasily Sobolev 0000-0002-7372-3299; Oleg Shifrin 0000-0001-8148-2862; Francisco Guarner 0000-0002-4051-0836; Vladimir Ivashkin 0000-0002-6815-6015.

S-Editor: Fan JR
L-Editor: Wang TQ
P-Editor: Fan JR

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: 32800266 DOI: 10.1093/jac/dkaa350]

5. Villarreal AA, Abergler FJ, Benrud R, Gundrum JD. Use of broad-spectrum antibiotics and the development of irritable bowel syndrome. *JFMJ* 2012; 11: 17-20 [PMID: 22532311]

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. Klen 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, Khalifi F, 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, Burchardt J, Pommergaard HC, Rosenberg J. Irritable bowel syndrome, the microbiota and the gut-brain axis. *Gut Microbes* 2016; 7: 365-383 [PMID: 27472486 DOI: 10.1080/19490976.2016.1218583]

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. Holmman GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol* 2016; 1: 133-146 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 D, Gómez C, Renes E, Fresno JM, Tornadijo ME, Ross RP, Stanton C. Lactic Acid Bacteria and Bifidobacteria in the Gastrointestinal Tract: A Global Perspective Update September 2015. *J Clin Gastroenterol* 2016; 50: 704-713 [PMID: 27623513 DOI: 10.1097/MCG.0000000000000653]

17. 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]

18. 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/NEJMra1602626]

19. Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, Gordon JJ, Relman DA, Fraser-Liggett CM, Nelson KE. Metagenomic analysis of the human distal gut microbiome. *Science* 2006; 312: 1555-1559 [PMID: 16741115 DOI: 10.1126/science.1124234]
Smith PM, Howitt MR, Panikov N, Michaud H, 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.1244165]

Tedelind S, Westberg F, Kjerulf 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: 17599118 DOI: 10.3748/wjg.v13.i20.2826]

Wresnok L, Miqael S, Noordine ML, Bouet S, Joncquel Chevalier-Curt M, Robert V, Philippe C, Bridonneau C, Cherbuy C, Bobbie-Massolot C, Langella P, Thomas M. Bacteroides thetaiotaomicron and Faecalibacterium prausnitzii influence the production of mucosa 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]

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

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

Camilleri M, Ford AC. Irritable Bowel Syndrome: Pathophysiology and Current Therapeutic Approaches. Handb Exp Pharmacol 2017; 239: 75-113 [PMID: 27995391 DOI: 10.1007/16.2016_102]

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

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: 32327966 DOI: 10.3748/wjg.v26.i14.1564]

Hadjivassilis A, Tsiliotis C, Michalinos A, Nourakis D, Christodoulou DK, Agouridis AP. New insights into irritable bowel syndrome: from pathophysiology to treatment. Ann Gastroenterol 2019; 32: 554-566 [PMID: 31700231 DOI: 10.20524/ajag.2019.0428]

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

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/s41375-017-0073]

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/s13738-017-0585-0]

Cani PD, Knafu 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]

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]

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]

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]

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]

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 serotoninergic pathways in rats with neonatal colonic sensitivity. J Physiol Pharmacol 2014; 65: 349-357 [PMID: 24930566]

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]

Camilleri M, Vazquez-Roque M, Iuturino J, Boldingh A, Burton D, McKinzie S, Wong BS, Rao AS, Kenny E, Månsson T, Zinsmeister AR. Effect of a glucagon-like peptide 1 analog, ROSE-010, on GI motor functions in female patients with dysmotility in the Wistar Kyoto rat model of Irritable Bowel Syndrome. World J Gastroenterol 2020; 26: 759-755 [PMID: 32313554 DOI: 10.1177/1756284820910630]

Strandwitz P. Neurotransmitter modulation by the gut microbiota. Brain Res 2018; 1693: 128-132 [PMID: 29903615 DOI: 10.1016/j.brainres.2018.03.015]

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: 10.2174/138920101966180528094202]

Barnes NM, Ahern GP, Becamel C, Bockaert J, Camilleri M, Chaumont-Dubreuil S, Claesen S, Cunningham KA, Fone KC, Gershon M, Di Giovannella M, Hallerbrand AL, Hartley RM, Hassaine G, Herrick-Davis K, Hovius R, Lacivita E, Lambe EK, Leopoldo M, Levy FO, Lummis SCR, Marin P, Maroteaux L, McCready AC, Nelson DL, Neumaier JA, Newman-Tancredi A, Nury H, Roberts A, Roth BL, Roumier A, Sanger JJ, Teitel M, Sharp T, Villalón CM, Vogel H, Watts SW, Hoyer D. International Union of Basic and Clinical Pharmacology. CX. Classification of Receptors for S-hydroxytryptamine; Pharmacology and Function. Pharmacol Rev 2021; 73: 310-320 [PMID: 33370241 DOI: 10.1124/pr.118.115552]

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

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]
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.clg.2007.12.013]

Zheng Y, Yu T, Tang Y, Xiong W, Shun 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]

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: 31302037 DOI: 10.1016/j.cgh.2019.07.007]

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: 17949307 DOI: 10.1002/14651858.CD003960.pub3]

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: 10.1038/s41410-019-00001-1313]

Fukudo S, Nakamura M, Hamatani T, Kazumori K, Miwa H. Efficacy and Safety of 5-HT4 Receptor Agonist Minapriside for Irritable Bowel Syndrome with Constipation in a Randomized Controlled Trial. *Clin Gastroenterol Hepatol* 2021; 19: 538-546.e6 [PMID: 32184185 DOI: 10.1016/j.cgh.2020.03.019]

Hamatani T, Noda T, Takagaki T, Yodo Y, Kawai H, Kakuyma H, Kaji Y, Fuyuo J. Thorough QT/QTc Study Shows That a Novel 5-HT4 Receptor Partial Agonist Minapriside Has No Effect on QT Prolongation. *Clin Pharmacol Drug Dev* 2020; 9: 938-951 [PMID: 32087003 DOI: 10.1002/cpdd.778]

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]

Ait-Belgnaoui A, Payard I, Rolland C, Harkat C, Braniste V, Théodora 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/jnm161677]

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

Wei P, Keller C, Li L. Neuropeptides in gut-brain 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]

Kano M, Muratsubaki T, Van Oudenhoove L, Morishita J, Yoshizawa M, Kolho 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]

Sudo N, Chida Y, Aita Y, Sonoda J, Oyama N, Xu 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: 10.1111/j.1469-7793.2004.03385.x]

Rea K, Dinan TG, Cryan JF. The microbiome: A key regulator of stress and neuroinflammation. *Neurobiol Stress* 2016; 4: 23-33 [PMID: 27981817 DOI: 10.1016/j.jnstr.2016.03.001]

Keller J, Gomez R, Williams G, Lembke A, Lazzeroni L, Alazzroni 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]

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.i11.13]

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]

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]

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

Kawase T, Nagasawa M, Ikeda H, Yassou 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]

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]

De Palma G, Blennnerhassett P, Lu D, 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 genetically separated mice. *Nat Commun* 2015; 6: 7735 [PMID: 26218677 DOI: 10.1038/ncomms8735]

De Palma G, Lynch MD, Lu J, Dang VT, Deng Y, Jury J, Umeh G, Miranda PM, Pigrau Pastor M, Sidiani S, Pinto-Sanchez MJ, Philip V, McLean PG, Hagelsieb MG, Surette MG, Bergonzelli GE, Verdu EF, Birtz-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: 366ra151 [PMID: 28251905 DOI: 10.1126/scitranslmed.aaf6397]

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*
O'Toole PW. Differences in Fecal Microbiomes and Metabolomes of People With Irritable Bowel Syndrome-A Systematic Review. Gut 2016; 65: 155-168. DOI: 10.1136/gutjnl-2015-309151

Chaghakhorl R, Abbassnezhad A, Hasanvand A, Amrani R. Inflammatory cytokines and oxidative stress biomarkers in irritable bowel syndrome: Association with digestive symptoms and quality of life. Cytokine 2017; 93: 34-43. DOI: 10.1016/j.cyt.2017.05.005

Barbalho SM, Goulart RA, Araújo AC, Guiguer EL, 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. DOI: 10.1080/17474744.2019.1570137

Farzaei MH, Bahramosltani 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. DOI: 10.4049/jnm160011

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. DOI: 10.1038/nature12331

Blachier E, Levy M, Tatirovsky E, Elinar E. Microbiome-Modulated Metabolites at the Interface of Host Immunity. J Immunol 2019; 198: 572-580. DOI: 10.4049/jimmunol.1601247

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. DOI: 10.3389/fcimb.2018.00013

Azad MA, Sarkar M, Wan D. Immunomodulatory Effects of Probiotics on Cytokine Profiles. Biomed Res Int 2018; 2018: 8063647. DOI: 10.1155/2018/8063647

Yousefi B, Esfandiari S, Ghaseemian A, Kokhaki P, Salek Farrokhhi A, Darabi N. Probiotics importance and their immunomodulatory properties. J Cell Physiol 2019; 234: 8008-8018. DOI: 10.1002/jcp.27559

Kim HS, Lim JH, Park H, Lee SL. Increased immunoeendocrine cells in intestinal mucosa of postinfectious irritable bowel syndrome patients 3 years after acute Shigella infection—an observation in a small case control study. Yonset Med J 2010; 51: 45-51. DOI: 10.5056/jyjm.2010.51.1.45

Swan C, Durodier 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 patients 3 years after acute Shigella infection–an observation in a small case control study. J Cell Physiol 2016; 231: 572-583. DOI: 10.1002/jcp.27559

Chang T, 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. DOI: 10.3892/mmr.2015.3808

van Tuyl 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. DOI: 10.1152/ajpgi.00196.2019

Bailey MT, Dow 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. DOI: 10.1016/j.bbi.2010.10.023

Sharara AI, Aoun E, Abdul-Baki H, Mourenz R, Sidiqi S, Elhaij J. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. Am J Gastroenterol 2006; 101: 326-333. DOI: 10.1111/j.1572-0241.2006.00458.x

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. DOI: 10.3892/mmr.2015.3808

van Tuyl 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. DOI: 10.1152/ajpgi.00196.2019

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

Ait-Belgnaoui A, Durand H, Cartier C, Chaumaz G, Eutamene H, Ferrier L, Houdeau E, Fioramonti J, Bueno, 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. DOI: 10.1016/j.pynen.2012.03.024

Vich Vila I, Immann F, Collij V, Janikpersadsing SA, Gurry T, Mujagic Z, Kurilshikov A, Monder MJ, Jiang X, Tigchelaar EF, Dekens J, Peters V, Voiskuil MD, Visschedijk MC, van Dullemen HM, Keszthelyi D, Swertz MA, Franke L, Alberts R, Festen EAM, Dijskstra G, Massee AAM, Holker MH, Xavier RJ, Aln 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: DOI: 10.1126/scitranslmed.aap9814

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. DOI: 30940523 DOI: 10.1053.j.gastro.2019.03.049

Duan R, Zhu S, Wang B, Duan L. Alterations of Gut Microbiota in Patients With Irritable Bowel Syndrome Based on 16S RNA-Targeted Sequencing: A Systematic Review. Clin Transl Gastroenterol 2018; 10: e00012. DOI: 30829191 DOI: 10.14309/jctg.2018.11.023

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. DOI: 31843589 DOI: 10.1153/jnm160011

Mamieva Z et al. Antibiotics, gut microbiota, and IBS
Antibiotics, gut microbiota, and IBS

Mamieva Z et al. 

10.1053/j.gastro.2019.11.301

Pozuelo M, Panda S, Santiago A, Mendez S, Accarino A, Santos J, Guarnier 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/rep12693]

Maharshak N, Ringel Y, Katibian D, Lundqvist A, Sartor RB, Carroll IM, Ringel-Kulka T. Fecal and Muco-associated Intestinal Microbiota in Patients with Diarrhea-Predominant Irritable Bowel Syndrome. *Dig Dis Sci* 2018; 63: 1890-1899 [PMID: 29777439 DOI: 10.1007/s00412-018-8690-6]

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.2017.01.042]

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]

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]

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

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]

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]

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]

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.2018.10.010]

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.2016.01.001]

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

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]

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]

Scheer S, Medina TS, Murison A, Taves MD, Antignano F, Chenery A, Somas KW, Perona-Wright G, Lupien M, Arrowsmith CH, De Carvalho DD, Zap 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: 10.1118/jlb.3MA0716-334RR]

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

Rasmussen SH, Shrestha S, Bjerggaard LG, Angquist LH, Baker JL, Jess T, Allin KH. Antibiotic exposure in early life is Associated with High Risk of Diarrhea-Predominant Irritable Bowel Syndrome. *Front Microbiol* 2018; 9: 1600 [PMID: 30090090 DOI: 10.3389/fmicb.2018.01600]

Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal flora. *Science* 2005; 308: 1635-1638 [PMID: 15581718 DOI: 10.1126/science.1110591]

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: e95474 [PMID: 24783487 DOI: 10.1371/journal.pone.0095476]

Burdet C, Grall N, Linard M, Bridier-Nahmias A, Benhayoun M, Bourabia K, Magnan M, Clermont O, d'Humières C, Tenailleau O, Denaurm E, Massias L, Tubiana S, Alavoine L, Andremont A, Mentre 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]

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]

Isaac S, Scher JU, Djkovovic A, Jiménez N, Littman DR, Abramson SB, Parmar 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]

Haak BW, Lankelma JM, Hugenholzt 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]

Janiro G, Tülg 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]

Baietto L, Coricione 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: 10.2174/138920215666140605013093]

Becattini S, Taur Y, Parmer EG. Antibiotic-Induced Changes in the Intestinal Microbiota and Disease. *Trends Mol Med*
The interplay between bile acid metabolism and microbiota in irritable bowel syndrome.

*Gastroenterology* 2016; 10.1111/j.1574-6968.2009.01531.x

M, Ito S, Yokota A. Conversion of cholic acid and chenodeoxycholic acid into their 7-oxo derivatives by Bacteroides. *J Physiol* 2012; 10.1113/jphysiol.2011.22482725

Ford AC, Bergeron MG, Corbeil J. The initial state of the human gut microbiome determines its reshaping by antibiotics. *MBio* 2016; 10.1128/mBio.00507-15

Pimentel M, Inderdonk 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 DOI: 10.1016/j.chom.2010.08.004

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

Baldelli V. Scaldaferri F, Patignani L, Del Chierico F. The Role of Enterobacteriaceae in Gut Microbiota Dysbiosis in Inflammatory Bowel Diseases. *Microorganism* 2021; 9 DOI: 10.3380/microorganisms9040697

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 DOI: 10.1186/gb-2012-13-9-79

Garrett WS, Galliani CA, Yatsunenko T, Michaud M, DuBois A, Delaney ML, Punti 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 DOI: 10.1016/j.chom.2010.08.004

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 DOI: 10.1111/j.1574-6968.2004.04723.x

Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of probiotics, prebiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther* 2018; 48: 1044-1060 DOI: 10.1111/ajp.14972

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 DOI: 10.1038/ismej.2016.176

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

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

Kabbani TA, Pallav K, Dowd SE, Villafuerte-Galvez J, Varga 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: clinical, microbial, and maternally transmitted colitis. *Am J Gastroenterol* 2019; 114: 79-89 DOI: 10.14309/ajg.2019.994

Vangel MS, Inderdonk 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 DOI: 10.1016/j.chom.2010.08.004

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

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

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 DOI: 10.1016/j.molmet.2018.03.004

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

Fukuia S, Arata M, Kawashima H, Yoshida D, Kaneko M, Minamida K, Watanebe 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 DOI: 10.1111/j.1574-6968.2009.01531.x

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

Fortune 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

Dior M, Delagrèverie H, Duboc H, Jouve P, Coffin B, Brot L, Humbert L, Trugnan G, Seksik P, Sokol H, Rainteau D, Scaldaferri F, Putignani L, Del Chierico F. The Role of Enterobacteriaceae in Gut Microbiota Dysbiosis in Inflammatory Bowel Diseases. *Microorganism* 2021; 9 DOI: 10.3380/microorganisms9040697

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

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

1211-1221 [PMID: 27178527 DOI: 10.1016/j.molmed.2016.04.003]

124: 458-478 [PMID: 27178527 DOI: 10.1016/j.molmed.2016.04.003]
