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REVIEW

Effects of Antibiotics on Intestinal Microbiota and Potential Treatment Options

Algül Dilara DOKUMACI

Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Medical Pharmacology, Kahramanmaraş, Türkiye.

ABSTRACT

The gut microbiota is a complex ecosystem that significantly impacts digestion, immunity, and overall health. Although antibiotics are valuable in treating infections, they can cause long-term harmful effects on the host by altering the composition and functions of the microbiota. These effects include reduced microbial diversity, changes in the functional attributes of the microbiota, and the formation of antibiotic-resistant strains. This situation can lead to other complications such as digestive issues, weakened immune system, obesity, diabetes, allergic and autoimmune diseases, neurodevelopmental disorders, and certain cancers. In recent years, the increase in antibiotic use has heightened the likelihood of these problems becoming more acute or prevalent in the future. Antibiotic resistance is a global crisis, and the rising use of antibiotics over time necessitates research into their effects on microbiota and health. This review highlights the adverse effects of antibiotics on gut health and emphasizes various strategies to mitigate these effects, such as probiotics, prebiotics, fecal microbiota transplantation, and phage therapy.

Keywords: Antibiotic. Gut Microbiota. Precision medicine. Fecal Microbiota Transplantation. Probiotics.

Antibiyotiklerin Barsak Mikrobiyotası Üzerindeki Etkileri ve Potansiyel Tedavi Seçenekleri

ÖZET

Barsak mikrobiyotası; sindirim, immünite ve genel sağlık üzerinde önemli bir etkiye sahip karmaşık bir ekosistemdir. Antibiyotikler, enfeksiyonları tedavi etmede önemli olmasına rağmen, mikrobiyota bileşimini ve işlevlerini değiştirerek konakçı için uzun vadeli zararlı etkilere neden olabilmektedir. Bu etkiler arasında mikrobiyal çeşitliliğin azalması, mikrobiyotanın işlevsel özelliklerinde değişiklikler ve antibiyotiğe dirençli suşların oluşması yer almaktadır. Bu durum, sindirim sorunları, immün sistemin zayıflaması, obezite, diyabet, alerjik ve otoimmün hastalıklar, nörogelişimsel bozukluklar ve bazı kanserler gibi diğer komplikasyonlara yol açabilir. Son yıllarda antibiyotik kullanımındaki artış, bu sorunların gelecekte daha akut veya yaygın hale gelme olasılığını artırmaktadır. Antibiyotik direnci küresel bir kriz olup, zamanla artan antibiyotik kullanımının mikrobiyota ve sağlık üzerindeki etkilerinin araştırılmasını gerektirmektedir. Bu derleme, antibiyotiklerin barsak sağlığı üzerindeki olumsuz etkilerini ve bu etkileri azaltmak için probiyotikler, prebiyotikler, fekal mikrobiyota transplantasyonu ve faj tedavisi gibi çeşitli stratejileri vurgulamaktadır.

Anahtar Kelimeler: Antibiyotik. Barsak Mikrobiyotası. Bireyselleştirilmiş Tıp. Fekal Mikrobiyota Transplantasyonu. Probiyotikler.

Antibiotics, the primary drugs used to treat bacterial diseases, have transformed modern medicine by significantly reducing morbidity and mortality associated with bacterial infections[1]. However, the indiscriminate and excessive use of antibiotics has led to serious global health issues, including antibiotic resistance. It has caused unintended consequences, such as alterations in the composition of the gut microbiome[2]. The gut microbiome is a complex system containing 10^{13}–10^{14} microbial cells, including bacteria, fungi, protozoa, and viruses[1]. Dysbiosis refers to an imbalance or disruption in the body's microbial community[3].

Since their discovery, antibiotics have been acknowledged as a key factor in increasing life expectancy during the 20th century, primarily by reducing the mortality caused by infectious diseases[4]. Despite their essential role in treating bacterial infections, antibiotics pose concerns because of their ability to disturb the delicate microbial balance within the gut[5]. Although they are specifically designed to target harmful pathogens, antibiotics often

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Dr. Algül Dilara DOKUMACI
Kahramanmaraş Sütçü İmam Üniversitesi
Tıp Fakültesi Tıbbi Farmakoloji Anabilim Dalı,
Kahramanmaraş, Türkiye.
Phone: 0344 300 26 69 / 0531 651 72 73
E-mail: dilaradokumaci@ksu.edu.tr

Yazarların Orcid Bilgileri
Algül Dilara DOKUMACI: 0000-0002-3703-3952

inadvertently damage the growth and colonization of diverse and beneficial bacterial communities in the gut[1].

The gut microbiome is a highly intricate and dynamic community of nearly 39 trillion microbial cells, including bacteria, viruses, and fungi. These microorganisms inhabit the gut and play a critical role in regulating cellular pathways such as glycolysis, amino acid metabolism, fatty acid metabolism, vitamin synthesis, and host immunity. These are essential for maintaining the ecological balance of the gut[1].

Dysbiosis is characterized as a persistent disruption within the gut microbiota, marked by alterations in its composition and functionality. This imbalance is often driven by host-related or environmental factors that undermine a microbial ecosystem's capacity for resistance and resilience[6]. Research has consistently demonstrated connections between changes in the gut microbiota composition and a range of diseases, including recurrent diarrhea caused by *Clostridium difficile (C. difficile)*, certain bowel disorders such as inflammatory bowel disease (IBD), colorectal cancer, non-alcoholic steatohepatitis, type 2 diabetes, obesity, and advanced chronic liver disease[7,8].

Antibiotic use can cause dysbiosis, leading to digestive problems, weakened immune systems, and an increased risk of certain chronic diseases[9,10]. The primary impact of antibiotics on the gut microbiota is the disruption of microbial balance, often leading to the depletion of beneficial bacteria and the proliferation of opportunistic pathogens[3]. The indiscriminate use of antibiotics throughout an individual's lifetime can contribute to the emergence of antibiotic-resistant microorganisms such as *Vibrio, Acinetobacter, Escherichia, Klebsiella, and Clostridia* within the gut microbiota[1]. Narrow-spectrum antibiotics target specific bacterial groups, limiting their impact on microbiota and minimizing unintended alterations. On the other hand, broad-spectrum antibiotics can act on a wide array of bacterial species, posing a significant threat to microbiota stability[11]. By reducing gut microbial diversity, broad-spectrum antibiotics eliminate the intended pathogen and eradicate beneficial microbes, potentially leading to adverse effects on the host[12,13]. Although these effects may be temporary, there are concerns regarding their potential long-term consequences[13]. Research suggests that prolonged or repeated exposure to antibiotics can induce changes in microbial diversity, contributing to the development of chronic diseases, such as metabolic and autoimmune disorders[5].

This article explores the intricate interplay between antibiotics and the gut microbiota, highlighting short-term and potential long-term effects. Additionally, it investigates novel strategies that could reshape future therapeutic approaches in this field.

The Role and Importance of Gut Microbiota in Human Health

The human gut microbiota encompasses bacteria, archaea, eukaryotes (including fungi and protists), and viruses within the gastrointestinal tract, from the oral cavity to the rectum. It represents the body's largest microbial ecosystem, hosting an estimated 3.9 × 10 bacterial cells[14,15]. Although the domain Bacteria contains 55 recognized phyla, only seven to nine are consistently found in the human gut. *Bacteroidetes* and *Firmicutes* dominate, constituting approximately 90% of gut microbiota[16]. Other commonly identified phyla included *Proteobacteria, Actinobacteria, Fusobacteria*, and *Verrucomicrobia,* whereas archaeal species were relatively sparse[16].

This microbial community evolves in complexity over time and is influenced by numerous factors, including the birth method, age, nutritional habits, geographic location, ethnicity, and migration patterns[17]. Despite significant intra-individual fluctuations, such as those following an acute infectious diarrhea episode or antibiotic treatment, the gut microbiota generally returns to its original state over time, a phenomenon known as persistence[3].

Once thought to play a passive role, the gut microbiome is now recognized as an active and influential participant in human health, contributing to metabolism, immune system regulation, and brain function[1].

Digestion and Nutrient Absorption*:* The gut microbiota aids in breaking down complex carbohydrates and fibers, producing enzymes that facilitate digestion and nutrient absorption. Microorganisms also produce short-chain fatty acids, contributing to energy production and metabolic regulation[18].

Immune System Regulation*:* The gut microbiota helps develop and modulate the immune system from infancy. Microbiota-derived molecules influence immune system development and support the development of a balanced immune response, reducing the risk of allergies and autoimmune disorders[19].

Metabolism and Energy Homeostasis*:* The Gut microbiota influences metabolism by facilitating energy extraction from food and regulating metabolic processes. Metabolites produced by microbiota influence host metabolism and energy expenditure. Imbalances in the microbiota have been linked to pathologies, such as obesity and type 2 diabetes[20].

Gut-Brain Axis and Mental Health*:* The microbiota influences neurotransmitter production, affecting mood and behavior through the gut-brain axis. Changes in the microbiota composition have been

linked to conditions such as anxiety, depression, and neurodegenerative disorders[21,22].

***Protection Against Pathogens**:* A Healthy gut microbiota competes with harmful microorganisms and prevents colonization. Antimicrobial compounds produced by microbiota inhibit pathogen growth, and dysbiosis increases susceptibility to infection[23,24].

***Drug Metabolism and Detoxification**:* Some bacteria in the gut metabolize drugs, affecting their efficacy and side effects. The microbiota also contributes to detoxification by breaking down harmful compounds[25].

***Synthesis of Essential Compounds**:* Certain gut bacteria synthesize essential vitamins (e.g., B vitamins and vitamin K) and bioactive compounds that influence physiological functions[26].

The complex interactions between the gut microbiota and the body extend beyond digestion. A balanced and diverse microbiota is critical for overall health; disruptions caused by factors such as diet, antibiotics, and stress can lead to health problems[27]. Maintaining ~~a~~ healthy gut microbiota through a balanced diet and proactive measures can help prevent pathological conditions[28].

Antibiotics and the Gut Microbiome: A Complex Interaction

In recent years, the impact of antibiotics on gut microbiota has become a significant topic of interest and concern owing to its potential effects on human health[29]. Antibiotics are powerful antimicrobial agents used to treat bacterial infections and to target and kill specific bacteria. Although their primary goal is to eliminate harmful pathogens, antibiotics can also affect unintended bacteria in the gut microbiota. This secondary effect can disrupt the delicate balance between the different microbial species living in the gut[30].

Dysbiosis or dysfunction of the microbiota arises when microbial populations' diversity, biomass, and organization on or within the host are disrupted. These disturbances interfere with the coexistence and communication between bacteria and the host, significantly impairing host physiology, such as digestion and immune responses to pathogens[1].

The misuse of antibiotics, particularly their prolonged or irregular use, significantly reduces beneficial microbes. These adverse effects can be short- or long-term, resulting in microbial imbalances that render the intestinal environment more vulnerable to colonization by opportunistic pathogens usually checked by commensal bacteria[31].

The impact of antibiotics on the microbiome is further influenced by factors such as the type of antibiotic, dosage, and pharmacokinetic properties of the host. For instance, hydrophilic drugs (e.g., β-lactams, cephalosporins, penicillins, and rifampin) and hydrophobic drugs (e.g., macrolides: erythromycin, azithromycin, and clarithromycin) exhibit distinct routes of absorption and excretion, including epidermal, nasal, renal, and gastrointestinal pathways[32].

Both bactericidal and bacteriostatic antibiotics disrupt the balance between microbial populations and the host intestinal metabolism[33]. In comparative studies on mice, antibiotics commonly prescribed for *C. difficile* infections, such as metronidazole and vancomycin, eliminated the infection through different mechanisms. Metronidazole primarily reduces gram-negative bacteria, whereas vancomycin targets gram-positive bacteria, leading to imbalances in microbial density without significantly altering species composition[34].

Unlike vancomycin, antibiotics, such as ampicillin and clindamycin, exhibit long-term effects on the microbiota, increasing bacterial taxa such as *C. difficile* and decreasing others, including *Bacteroides, Subdoligranulum, and Faecalibacterium*[35,36]. Studies indicate that early and later in life, antibiotic usage causes imbalances within microbial communities, disrupting the symbiosis between bacterial species and the host. This imbalance is especially pronounced during the early life stages, from birth to early childhood[37,38].

Reduced Diversity: Antibiotic use is strongly associated with decreased microbial diversity. In children, microbial diversity reportedly recovers within approximately one month after antibiotic treatment[39]. In adults, the use of antibiotic combinations, including meropenem, gentamicin, and vancomycin, is associated with an increase in *Enterobacteriaceae* and other harmful pathogens, coupled with a reduction in beneficial microbes, such as *Bifidobacterium* and butyrate-producing species[40]. Although the overall composition of the microbiota showed significant recovery within approximately six weeks, some common bacterial species may remain absent for a six-month observational period[40].

Altered Metabolism: Low-dose antibiotic exposure in young mice has been shown to increase adiposity and elevate hormone levels associated with carbohydrate, lipid, and cholesterol metabolism[41]. Similarly, administering vancomycin-imipenem increased the arabinitol and sugars (e.g., sucrose) levels in fecal samples[42].

Antibiotic Resistance: Antibiotic resistance has become a pressing global public health concern. Between 2000 and 2015, the antibiotic consumption increased by 65% worldwide[43]. Projections indicate that by 2050, the annual fatalities linked to antibiotic resistance could reach approximately 317,000 in

North America, 390,000 in Europe, 392,000 in Latin America, 4,150,000 in Africa, and 4,730,000 in Asia[44]. The World Health Organization (WHO) estimates that the worldwide death toll due to antibiotic resistance may surpass 10 million annually by mid-century[45].

In summary, the relationship between antibiotics and the gut microbiota is a dynamic and multifaceted interaction with both short- and long-term effects on human health. As our knowledge of this interaction increases, so does the need to balance the benefits of antibiotic therapy with an understanding of its potential impact on the gut microbiota.

Antibiotics, a cornerstone of modern medicine in the fight against bacterial infections, exert their therapeutic effects through various mechanisms by targeting specific components of bacterial cells[46]. Additionally, antibiotics have a spectrum of activities and can effectively combat bacterial species' diversity[47].

The Spectrum of Activity of Antibiotics

Antibiotics are crucial in combating bacterial infections, but their effects extend beyond the target pathogens, influencing the host microbiota. Choosing between narrow-spectrum and broad-spectrum antibiotics significantly affects microbiota composition, resilience, and susceptibility to dysbiosis[48].

Narrow-Spectrum Antibiotics and Microbiota: Narrow-spectrum antibiotics are designed to target specific bacterial species or groups, thereby minimizing collateral damage to the microbiota. These antibiotics are preferred when the causative pathogen is known, as they help to preserve microbial diversity and reduce the risk of antibiotic resistance.

- ***Selective Action*:** Narrow-spectrum antibiotics primarily affect a limited range of bacteria, allowing the microbiota to maintain balance.
- ***Reduced Dysbiosis Risk*:** Since fewer bacterial species are disrupted, the likelihood of dysbiosis, a microbial imbalance associated with conditions such as IBD and metabolic disorders, is lower[49].

Broad-Spectrum Antibiotics and Microbiota: Broad-spectrum antibiotics target many bacterial species, including gram-positive and gram-negative bacteria. Although effective in treating infections of unknown origin, they pose a greater risk to microbiota stability[50].

- ***Widespread Disruption:*** Broad-spectrum antibiotics can significantly reduce microbial diversity, leading to loss of beneficial bacteria[50].
- ***Increased Risk of Opportunistic Infections:*** Depleting protective microbiota can allow opportunistic pathogens, such as *C. difficile*, to proliferate, increasing the risk of infections[51].
- ***Potential Long-Term Effects:*** Prolonged use may lead to persistent alterations in microbiota composition, affecting immune function and metabolic health[3].

The selection of narrow-spectrum and broad-spectrum antibiotics should be guided by infection specificity, patient health status, and concerns regarding antibiotic resistance. While narrow-spectrum antibiotics are preferable for targeted therapy, broad-spectrum antibiotics remain essential in situations that require immediate intervention.

Understanding the differing effects of narrow-spectrum and broad-spectrum antibiotics on microbiota is crucial for optimizing antibiotic therapy while mitigating unintended consequences. The indiscriminate use of broad-spectrum antibiotics can disrupt the balance of gut microbiota and contribute to antibiotic resistance[5]. Therefore, narrow-spectrum antibiotics should be prioritized whenever possible to minimize these risks.

Although antibiotics play a vital role in infection treatment, their rational use, considering mechanisms of action and activity spectra, is essential for preserving their long-term effectiveness and reducing their impact on the microbiota.

Antibiotics: A Double-Edged Sword – Therapeutic Benefits and Secondary Harms

Regarded as life-saving interventions, antibiotics indeed possess a double-edged sword nature. Although their therapeutic benefits in treating bacterial infections are undeniable, the secondary harms they can cause to targeted and non-targeted microorganisms must be carefully considered. This delicate balance between healing and unwanted outcomes underscores the complex nature of antibiotic therapy[47].

Therapeutic Benefits of Antibiotics

- **Elimination of Infection:** Antibiotics are considered the cornerstone agents in the fight against bacterial infections, eliminating pathogens and saving countless lives[46].
- **Transforming Medical Practices:** Antibiotics have transformed medical practices, enabling safer surgical procedures, organ transplants, and cancer treatments by effectively preventing or managing infections[52].
- **Reduced Mortality Rates:** The advent of antibiotics has significantly reduced the mortality rates from infections that were once fatal, marking a monumental achievement in modern medicine[53].

Secondary Harms Caused by Antibiotics

- **Reduction of Beneficial Microorganisms**: Because antibiotics do not distinguish between harmful and beneficial bacteria, their use can reduce diversity within the gut microbiota, affecting its functionality[2,13].
- **Antibiotic Resistance**: Prolonged or inappropriate use of antibiotics can trigger the development of antibiotic-resistant bacteria, making these drugs less effective over time and posing a threat to global health[54].
- **Opportunistic Infections**: Antibiotics can increase the risk of opportunistic infections such as *C. difficile*-associated colitis by eliminating beneficial microorganisms that limit pathogen growth[5].
- **Microbiota Dysbiosis**: Changes in gut microbiota due to antibiotics have been linked to various pathologies, including metabolic disorders, allergies, and immune disorders[55].
- **Long-term Effects**: The effects of antibiotics on the gut microbiota extend beyond the short term. Research has shown that repeated or prolonged antibiotic exposure can lead to deeper and more lasting changes in microbial composition. This raises concerns about potential long-term health effects, including an increased risk of conditions such as obesity, metabolic syndrome, and autoimmune diseases[19,20]. The mechanisms underlying these relationships are complex and multifaceted, involving interactions between the gut microbiota, host physiology, and immune system[56]. There are potential links between early life exposure to antibiotics and the development of chronic diseases such as obesity and asthma[57,58].

Antibiotics truly exhibit the characteristics of a double-edged sword; although they provide vital benefits in the treatment of infections, they can also potentially cause unwanted outcomes[47].

Research has shown that chronic changes in gut microbiota diversity due to antibiotic use are associated with pathologies, such as obesity, IBD, and allergies[55]. Long-term diversity reductions can also impair the microbiome by inhibiting the growth of pathogenic species, leading to an increased susceptibility to infections[59].

Connections between Antibiotics, Microbiota, and Autoimmune Diseases: Metabolic Syndrome, Obesity, and Metabolic Effects

Antibiotics have attracted increasing attention recently because of the complex interplay between them, the gut microbiota, and autoimmune disorders[60].

Antibiotics, microbiota changes, and autoimmunity: Long-term or repeated exposure to antibiotics can change the composition and diversity of gut microbiota. Dysbiosis resulting from such changes has been linked to the dysregulation of immune responses that can promote the development of autoimmune diseases. Impaired immune tolerance and the potential for molecular mimicry between the host and microbial antigens have been reported as mechanisms that drive autoimmune responses[61].

Metabolic syndrome and obesity: Gut microbiota plays a role in developing metabolic syndrome and obesity. Dysbiosis from antibiotic exposure can contribute to low-grade inflammation, insulin resistance, and altered energy metabolism, leading to obesity and its associated metabolic complications[20].

Immunity-metabolism cross-talk: Emerging evidence suggests that gut microbiota-mediated immunity-metabolism cross-talk plays a critical role in maintaining metabolic health. Antibiotic-induced changes in microbial communities can disrupt this interplay, promoting a pro-inflammatory environment and disrupting the metabolic balance. Such changes can create an environment conducive to autoimmune diseases and metabolic dysfunctions[62].

Potential Therapeutic Strategies

Recognition of the connection between antibiotics, gut microbiota, and autoimmune-metabolic interactions has opened new avenues for therapeutic exploration. Probiotics, prebiotics, and dietary interventions to restore gut microbial balance may help reduce the risk of autoimmune diseases and metabolic complications[63]. Precision medicine approaches considering an individual's microbial profile can offer personalized interventions[64].

1. Antibiotic management and long-term health: Balancing the need for antibiotic treatment with ~~the~~ potential long-term consequences on gut microbiota and health is critical. Antibiotic stewardship programs should be designed to minimize gut microbiome disruption while optimizing treatment efficacy[65,66].

Healthcare providers must be equipped with knowledge to balance the necessity of antibiotics with their potential impact on the gut microbiota. Educating patients is pivotal in promoting responsible antibiotic use, emphasizing adherence to prescribed courses, and increasing awareness of dysbiosis symptoms. Antibiotic stewardship programs that address the broader consequences of antimicrobial therapy can guide appropriate prescription practices and mitigate the risk of antimicrobial resistance[53].

Furthermore, reforming or establishing complementary public health measures can significantly reduce the reliance on antibiotics. As

highlighted by Laxminarayan, improving sanitation, expanding vaccine usage, and enhancing hospital infection control are proven strategies for reducing the demand for antibiotic therapies[67]. Additionally, minimizing the unnecessary use of antibiotics in agricultural practices should be prioritized[2].

Given the pivotal role of microbiota in regulating host physiology and the drawbacks of antibiotic use, it is imperative to explore alternative or complementary infection-fighting strategies. Promising avenues for research include antimicrobial peptides, innate defense regulatory peptides, bacteriocins, antisense antimicrobial therapeutics, predatory bacteria, monoclonal antibodies, antimicrobial nanoparticles, and CRISPR-Cas9[53].

2. Future Directions in Treatment: Microbiota-Medicine Interaction: Microbiome research advances have revealed gut microbiota's central role in human health and disease. The dynamic interaction between gut microbiota and human health has expanded our understanding of disease mechanisms and treatment approaches[19]. Microbiota-medicine interactions will enable the emergence of new therapeutic applications that leverage the potential of the gut microbiome to improve the treatment outcomes[68,69].

3. Microbiome applications in personalized medicine: The era of personalized medicine includes microbiome-based applications. A precise microbiome profile allows for individualized interventions that consider individual microbial composition and function differences. Treatments, such as fecal microbiota transplantation (FMT), are being explored for various diseases to restore healthy microbial balance[70].

4. Synthetic microbiota modulation*:* Advances in synthetic biology offer exciting opportunities to engineer microbial communities with health benefits. Engineered probiotics and prebiotics can deliver therapeutic molecules, modulate immune responses, and correct dysbiosis[71]. These innovative approaches hold promise for targeted applications in various pathological conditions, ranging from inflammatory disorders to metabolic diseases[72].

5. Microbiome as a therapeutic target: A changing perspective views the microbiome as a therapeutic target[73]. Small molecules produced by microbiota, known as postbiotics, exhibit various bioactive properties[74]. Developing postbiotics as therapeutic agents offers a new dimension to microbiota-targeted therapies by overcoming the challenges associated with live microbial interventions[75,76].

6. Microbiota-drug interactions**:** Recognizing the impact of the microbiota on drug metabolism and efficacy is critical. Understanding microbiota-mediated drug interactions can guide the optimization of treatment regimens. Developing drugs that interact synergistically with the microbiota can also improve therapeutic outcomes[69].

Advances in Fundamental Treatments

Microbiota-based treatments have gained momentum as innovative strategies to restore microbial balance and improve human health. Various methods such as prebiotics, probiotics, postbiotics, synbiotics, and FMT, are currently used[1].

1. Treatment of microbiome damage following antibiotic use

Antibiotic use is known to alter microbial composition, often with potentially harmful effects on the host. Several strategies can be implemented during or after antibiotic therapy to expedite the recovery of microbial balance. Probiotics are frequently employed for this purpose as they have been shown to boost the population of beneficial microorganisms, stabilize the microbial ecosystem, and mitigate the adverse effects of antibiotics[5]. Additionally, engineered probiotics and prebiotics offer targeted solutions that promote the growth of beneficial bacteria and aid in restoring microbial diversity. Furthermore, probiotics, prebiotics, and fecal microbiota transplantation are being actively investigated to enhance microbial resilience and diversity after antibiotic exposure[77].

2. Probiotics

Probiotics were first identified in the early 1900s and have been shown to transform the gut microbiota, replacing “rotting” bacteria with beneficial ones, thereby improving various disease conditions[5]. Over time, our understanding of probiotics has evolved, recognizing their role beyond regulating the microbiota to include enhancing immunity and improving general physiological functions.

Probiotics exert their effects through several mechanisms, including promoting antimicrobial peptide production, synthesizing bacteriocins, suppressing the growth of non-commensal bacteria by competing for nutrients and receptors on the intestinal mucosa, improving gut barrier function, and modulating immune responses. However, it should be noted that probiotic use may not completely restore the gut microbiota[5].

The therapeutic application of probiotics has shown significant success in balancing microbial configurations. For instance, *Lactobacillus acidophilus* has demonstrated immune modulation in mice via TLR2-dependent IFN-β pathways, enhanced intestinal barrier integrity (maintaining the mucosal layer), and inhibited pathogen colonization[78].

Engineered probiotics represent an innovative advancement in genetically modifying existing

probiotic strains through gene-editing techniques to produce novel microorganisms with desired properties. These modifications allow researchers to directly verify the changes in genetic material, proteins, and functional roles[79]. The progression of gene-editing technologies—from homologous recombination to Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), and the widely recognized CRISPR-associated systems (CRISPR-Cas)— highlights the rapid advancements in genetic engineering tools in recent years[80].

Emerging gene-editing techniques have shown exceptional promise in developing synthetic engineered probiotics for diagnosing and treating various diseases. Engineered probiotics are being investigated for their application in managing conditions such as cancer, inflammation, and infections. Researchers have aimed to enhance these probiotics' efficacy, safety, and cost-effectiveness compared with conventional therapies or wild-type strains, benefiting a wider range of patients and their families[81].

The advantages of engineered probiotics, including improved stability, specificity, selectivity, affordability, and relative safety, make them promising alternatives for treating various health conditions. However, despite their benefits, several challenges hinder their broader clinical adoption. Addressing concerns related to safety, ethical considerations, and regulatory frameworks is crucial for their successful integration into healthcare practices[82].

3. Prebiotics as microbial growth promoters: Mechanisms and applications

Prebiotics were first introduced in 1995, defining them as non-digestible food components that promote host health by selectively stimulating the growth and activity of specific beneficial bacteria in the colon[83]. This definition has evolved, and according to the International Scientific Association for Probiotics and Prebiotics (ISAPP), prebiotics are now recognized as dietary substances that are selectively utilized by beneficial microorganisms within the host, ultimately contributing to overall health[84].

Prebiotics include various compounds, such as inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and lactulose. These beneficial substances are naturally present in foods, such as whole grains, onions, garlic, and bananas[85]. Their primary role is to serve as a nutritional source for the beneficial gut bacteria. Since prebiotics are resistant to digestion by human enzymes, they pass through the digestive system largely intact until they reach the colon, where they undergo fermentation by the gut microbiota[86].

Prebiotic fermentation produces short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, contributing to gut health[87]. Prebiotics support microbiota balance by selectively promoting the proliferation and activity of beneficial bacterial species such as Bifidobacteria and Lactobacilli while suppressing the growth of pathogenic microorganisms[88]. In addition to maintaining gut microbial equilibrium, prebiotic-derived metabolites play essential roles in cellular energy production, immune modulation, reinforcement of gut barrier integrity, and neurological processes through the gut–brain axis[72].

Microencapsulation technology is used to enhance the stability of prebiotics and ensure their delivery to targeted intestinal regions. This method involves encasing prebiotic components in a protective coating, which increases their resistance to stomach acids and enables more effective utilization in the intestines. Advances in biotechnology have made it possible to produce prebiotics more efficiently using genetic engineering and fermentation techniques. Notably, studies focusing on probiotic-prebiotic synergy have aimed to increase the prebiotic content of fermented foods[89].

Synbiotics, which combine prebiotics and probiotics, have shown promising results. For instance, in middle-aged individuals receiving a synbiotic containing *Bifidobacterium animalis lactis* and fructooligosaccharides, improved abdominal discomfort, enhanced intestinal motility, and better bowel movement regularity were observed[90]. Another synbiotic, comprising probiotics (*Lactobacillus acidophilus*, *B. lactis*, *B. longum*, and *B. bifidum*) combined with a prebiotic (galactooligosaccharide mix), demonstrated improvements in blood glucose levels, initially linked to an increase in *Lactobacillus*, and subsequent reductions in BMI and body fat mass, which were associated with a decrease in *Bifidobacterium* levels[91].

5. Fecal Microbiota Transplantation as a Restoration Strategy

FMT involves the transfer of fecal microbiota from a healthy donor to a recipient to restore a diverse and balanced microbial community. Its therapeutic potential extends beyond gastrointestinal disorders, offering promise for autoimmune, metabolic, and neurological diseases—the primary mechanisms underlying FMT microbial reconstitution, immune modulation, and metabolite production[92].

Research has demonstrated that FMT can reduce *C. difficile* infection by inhibiting bacterial overgrowth and regulating bile acid metabolism[93]. A systematic review indicated that FMT has been used in clinical settings worldwide to treat 85 specific diseases between 2011 and 2021[94]. FMT has shown remarkable

efficacy in managing recurrent *C. difficile* infections, with an approximate cure rate of 90%[95].

Four randomized trials assessed fecal transplantation as an induction therapy for achieving remission in active ulcerative colitis, demonstrating statistically significant improvements compared to control treatments. By week 8, remission was achieved in 37% of the participants receiving FMT compared to 18% in the control group[96].

A significant milestone in FMT's advancement is regulatory approval. The prepared fecal microbiota was recognized as a live biotherapeutic product in Australia and the United States in 2022 and 2023, respectively[97]. In addition, the United States Food and Drug Administration (FDA) approved spores isolated from donor feces in 2023[98].

Despite its promise, several factors, such as efficacy, cost, and suitability, make FMT an attractive therapeutic option. However, further research is necessary to optimize its application and explore its potential therapeutic benefits beyond gut-related disorders[100]. Moreover, the success and safety of FMT rely on meticulous donor selection, standardization, and adherence to stringent safety protocols[101].

6. Unveiling the potential of phage therapy for microbiota modulation*:* Phage therapy, using bacteriophages to target bacterial populations selectively, has gained renewed interest as a promising approach to microbiota modulation[101]. Bacteriophages are viruses that infect and lyse specific bacterial species. By selectively eliminating harmful bacteria, phages can restore the microbial balance, enhance gut health, and mitigate inflammatory responses. Recent studies have highlighted their ability to shape the microbiota composition, influence immune function, and reduce antibiotic-resistant bacterial populations[102].

Phage therapy has been investigated for its efficacy in reducing biofilms and addressing lung infections, particularly in mouse models, where its successful application in treating respiratory diseases caused by *Pseudomonas aeruginosa* has been demonstrated[103,104]. Personalized phage therapy has also effectively cleared multidrug-resistant *Acinetobacter baumannii* infections, with documented treatment success in clinical cases[105]. Additionally, case studies have indicated pathogen eradication and symptomatic improvement in patients with bacterial prostatitis, septicemia, and acute kidney injury after undergoing phage therapy[106,107]. In another study, phage therapy was associated with healing in wounds and ulcers of 67 out of 96 patients, demonstrating a significant reduction in pathogenic bacteria[108]. Engineered bacteriophages have shown promise in combating drug-resistant *Mycobacterium abscessus*, leading to clinical improvement in patients with cystic fibrosis[109]. Moreover, phage-derived lytic proteins have emerged as potent antimicrobial agents, positioning phages as compelling alternative antibiotics in the fight against resistant pathogens[5].

Phage therapy offers advantages such as precise targeting and reduced antibiotic use. Phage therapy can particularly benefit patients with antibiotic-resistant infections, dysbiosis-related disorders, and immunocompromised patients. Despite its potential, phage therapy faces challenges like phage stability, immune response interactions, and regulatory hurdles. Advances in genetically engineered phages and personalized phage therapy are expected to enhance their efficacy and broaden their clinical application[101].

In summary, microbiota-based treatments, including FMT, engineered probiotics, prebiotics, and phage therapy, represent exciting avenues for innovations in healthcare. Each approach offers distinct mechanisms and applications for microbiota modulation, reflecting a new era of personalized and precise medicine[75].

Genetic Factors Influencing Antibiotic-Microbiota Interactions: Personalized Therapeutic Approaches

The gut microbiota of each individual comprises numerous unique strains that are absent from others, with inter-individual variations in microbiota composition being significantly greater than intra-individual variations[110]. Factors, such as sex, ethnicity, and geographic location, influence the taxonomic composition of the microbiome[111]. For instance, the fecal microbiota of adults residing in the metropolitan regions of Europe and North America is less diverse than that of adults in rural populations in Africa and South America[112,113].

Individual genetic differences influence responses to antibiotics and their subsequent effects on the gut microbiota. Understanding these interactions is critical for optimizing treatment outcomes while minimizing disruption to microbial communities[59].

1. Genetics Shapes Antibiotic Responses

Genetic polymorphisms, which refer to variations in DNA sequences among individuals, play a significant role in modulating the effects of antibiotics on human microbiota. These genetic differences can influence drug metabolism, efficacy, and extent of microbiota disruption, leading to variability in therapeutic outcomes and susceptibility to dysbiosis-related conditions[114].

Genetic polymorphisms in enzymes, such as cytochrome P450 (CYP) and UDP-glucuronosyltransferases (UGTs), affect the metabolism of antibiotics. For instance, variants in CYP enzymes can alter the breakdown and bioavailability of antibiotics, affecting their

concentration in the gut and, consequently, their effect on the microbiota. Slow metabolizers may experience prolonged exposure to antibiotics, increasing the risk of microbiota imbalance and the development of resistance[115].

Polymorphisms in transporter genes such as ABCB1 (P-glycoprotein) influence the distribution of antibiotics within the body. These variations can affect the concentration of antibiotics in the gut, altering their impact on microbial communities[116]. Genetic differences in immune-related genes, such as those encoding Toll-like receptors (TLRs), can affect the host response to antibiotic-induced microbiota changes. Variations in TLRs may influence inflammation and microbial resilience, shaping the recovery of the microbiota after antibiotic treatment. Variations in genes associated with antibiotic resistance mechanisms, such as efflux pumps and β-lactamases, can contribute to the emergence of resistant strains within the microbiota[114].

Understanding the role of genetic polymorphisms in the effects of antibiotics on microbiota is crucial for personalized medicine. Tailoring antibiotic therapies based on genetic profiles can minimize microbiota disruption, reduce the risk of antibiotic resistance, and enhance therapeutic efficacy. Pharmacogenomics and microbiome research advances are paving the way for personalized approaches to antibiotic therapy. Integrating genetic testing into clinical practice can help predict individual responses to antibiotics and guide the development of microbiota-friendly treatments.

2. Microbiome Profiling for Personalized Therapeutic Strategies

High-throughput sequencing and multi-omics approaches provide microbiome profiles, offering insights into the microbial composition and functional potential. Integrating genetic data with microbiome profiles allows for identifying conditions related to drug response and susceptibility to dysbiosis. Such profiles can inform personalized therapeutic applications, aid~~ing~~ in predicting patient-specific outcomes and guiding antibiotic selection[64,69].

3. Developing Algorithms for Personalized Antibiotic Prescribing

Advances in computational biology and machine learning have enabled the development of algorithms to predict optimal antibiotic regimens based on genetic and microbiome data. These algorithms can assist clinicians in making evidence-based antibiotic choices by considering an individual's genetic makeup and microbial composition. This approach can help minimize the risk of adverse effects and improve the treatment efficacy[117,118].

Integrating genetic and microbiome data into clinical practice poses significant data integration, interpretation, and privacy challenges. To facilitate seamless adoption of personalized therapeutic strategies, collaborative efforts among researchers, clinicians, and bioinformaticians are required to develop standardized protocols and tools. Genetic factors influencing antibiotic-microbiome interactions are critical determinants of individual responses to antibiotics and subsequent outcomes[119].

Ethical Considerations and Regulatory Frameworks

As microbiome-based applications evolve, it is imperative to address the ethical implications. Establishing regulatory frameworks is crucial for ensuring safety, efficacy, and equitable access to these applications. Collaboration among researchers, clinicians, and ethicists is essential for appropriately developing and utilizing microbiota-targeted therapies. Microbiome-medicine interaction represents a transformative paradigm in healthcare. Future directions include personalized applications, synthetic microbiota modulation, and microbiome-centered therapies[120].

Conclusion

In conclusion, the dynamic relationship between antibiotics and gut microbiota highlights the need for precision in prescribing practices and the development of innovative therapies. By considering this complex interplay, healthcare professionals can help preserve both the efficacy of antibiotics and the delicate balance of gut microbiota. This can lead to better health outcomes for individuals and the broader population. Further research in this area will enable the optimization of antibiotic use and the development of new approaches to protect microbiota health.

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