Antibiotic-associated Gut Dysbiosis

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**Abstract**

The human gut microbiota plays a crucial role in maintaining overall health. However, the widespread use of antibiotics has raised concerns about its impact on the microbial ecosystem. This review explores the multifaceted relationship between antibiotics and gut dysbiosis, highlighting the mechanisms underlying these interactions and their implications for human health. Antibiotics, while invaluable in treating infections, disrupt the gut microbiota by indiscriminately targeting both harmful and beneficial microorganisms. This disturbance leads to a reduction in microbial diversity, altered metabolite production, and compromised immune responses, resulting in a state referred to as dysbiosis. Broad-spectrum antibiotics tend to induce more severe dysbiosis compared to narrow-spectrum agents. Antibiotic-induced dysbiosis has been linked to the onset and progression of these disorders, emphasizing the far-reaching consequences of microbial imbalance. The review highlights various strategies to mitigate the adverse effects of antibiotics on gut health, like probiotics, fecal microbiota transplantation (FMT), and phage therapy, as promising approaches to restore and maintain a balanced gut microbiota.

**An Overview of Human Gut Microbiota**

The human gut microbiota plays a critical role in supporting the integrity and functionality of the gastrointestinal (GI) tract and immunological and metabolic systems. The $10^{14}$ naturally occurring bacterial cells normally present in the human intestine and colon belong to around 500–1,000 species that have a mutually beneficial relationship, and they colonize the human gut. Over 90% of the total bacterial population that lives in the gut belongs to five major bacterial phyla: Verrucomicrobia, Proteobacteria, Actinobacteria, Bacteroidetes, and Firmicutes. Fusobacteria and Fibrobacteres are less abundant bacteria. The dynamic ecosystem upholds a two-way connection with the host, a relationship crucial for both the normal physiological and pathophysiological state. Microbiota helps in processing nutrients, producing essential compounds, shaping the immune system, and maturing the GI system. Microbiota is constantly altered by several factors like genetics, sex, diet, lifestyle, age, and medicine. The microbial denizens of the gut have many interactions; some are cooperative, such as sharing of nutrients, and others inhibitory, such as bacteriocins. In a healthy individual, a balance is maintained between beneficial and aggressive microbial communities, a state that is referred to as eubiosis. An imbalance between possibly detrimental and helpful bacteria leads to a state called alteration of the normal composition of gut microbes, causing intestinal dysbiosis, which may, in turn, lead to pathological abnormalities and inflammation. This intestinal dysbiosis has been linked to various diseases, both intestinal and extraintestinal. This review examines the role of antibiotics in inducing prolonged changes in the gut microbiome and the potential association of such changes with disease states.

**Antibiotic-Associated Changes in the Gut Microbiota**

One of the foremost achievements in medicine of the 20th century was the discovery of antibiotics, which completely changed how infectious diseases were treated. Nevertheless, their impact extends beyond the targeted pathogens, as they indiscriminately stop the proliferation of helpful microorganisms, including those inhabiting the gut. This reduction in microbiota diversity caused by antibiotics undermines interactions between the host and microbes, disrupts the equilibrium of the immune system, and weakens the body’s ability to resist the colonization of harmful bacteria. The influence of antibiotics on gut dysbiosis and their potential function in disease, even after brief usage, may cause long-term dysbiosis, which is marked by loss of important taxa, change of diversity, and metabolic changes. These changes may lead to impaired colonization resistance against intestinal pathogens, most clearly demonstrated in the emergence of *Clostridiodes difficile* (*C. difficile*)-associated diseases, even after short-term antibiotic administration in susceptible individuals. Numerous medical conditions have been investigated and shown to cause dysbiosis of the gut microbiota. The interaction between gut health and microbiota is thought to have a role in the pathogenesis and seriousness of metabolic conditions, autoimmune disorders, infections, and cancer malignancies and is expected to play a role in the pathogenesis and severity of these diseases. Despite this, a 65% increase in the consumption of antibiotics worldwide was observed between 2000 and 2015. It has been estimated that nearly 50% of the time antibiotics are prescribed unnecessarily.

In 2010, India stood as the foremost consumer of antibiotics for human health. Sometimes, inappropriate and irrational use of antibiotics against infectious diseases is found to be the highest in India and is considered a major driver of resistance. In a survey by Basu et al., the doctors participating in the study identified infants and children under 5 years as the most susceptible group to potential negative effects of antibiotics stemming from disruptions in the gut microbiome. Another age group that is susceptible to developing dysbiosis is the geriatric population. In the elderly, the makeup of the gut microbiota changes, leading to a mild inflammatory state. This transformation can be further intensified by various internal and external factors, including the consumption of antibiotics and dietary choices. The excessive utilization of broad-spectrum antibiotics for conditions that could be effectively treated with narrow-spectrum agents has been steadily rising. This irrational, extended, and relentless use contributes to the emergence of dysbiosis, which subsequently gives rise to pathological complications in the host. This disturbance in the equilibrium of gut microbiota is accompanied by the loss of some essential taxa that can cause metabolic shifts, a rise in

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Antibiotic treatment is the most immediate and drastic exposure that causes dysbiosis.

In this review, we have summarized the most recent research on the gut microbiome and its alterations in relation to antibiotics, along with the impact of antibiotic-associated dysbiosis in specific conditions and strategies to reduce this dysbiosis. A literature search of published articles in the English language was conducted using search engines like PubMed and Google Scholar from 2010 to 2021. A total of 150 abstracts were identified using the relevant search terms such as antibiotic-associated dysbiosis, the impact of antibiotics on gut microbiota, gut dysbiosis, classes of antibiotic, antibiotic-associated diarrhea (AAD), C. difficile-associated diarrhea, inflammatory bowel disease (IBD), atopic disorders, allergy, coronavirus disease 2019 (COVID-19), and treatment for antibiotic-associated dysbiosis. The manual reference and review article searches were conducted in addition to the computerized search. Full-text articles and those describing the results on human subjects of all age groups were considered. Research related to various methodologies investigating alterations in the microbiome linked to specific antibiotic usage, diseases connected with antibiotic-associated dysbiosis, and strategies like fecal microbiota transplantation (FMT), probiotics, and phage therapy were included in the search. Animal studies were a part of the exclusion criteria. After applying the predetermined criteria for inclusion and exclusion, a total of 62 pertinent articles were ultimately selected for use.

**The Direct and Indirect Effects of Antibiotics on Gut Microbiota**

Antibiotics exert their effect on gut microbiota through either direct or indirect mechanisms. Direct action involves reducing pathogenic bacteria; however, due to their wide-ranging effects, antibiotics can also eliminate or hinder certain groups of beneficial microbes that inhabit the gut. Broad-spectrum antibiotics have been reported to affect 30% of gut bacteria, leading to a prompt and significant decrease in evenness, diversity, and taxonomic richness.18–20

The indirect effect of antibiotics on the gut microbiome is discussed below:

- **Effects on bacterial metabolism:** Different subsets of gut microbiota universally exhibit symbiosis and codependency. A homeostatic state is maintained by the microbiota under normal physiological conditions. The secondary compounds produced by certain microbiota species might offer essential nutritional value to other colonizing organisms. If not, some metabolites may accumulate in the gut and exhibit toxicity toward other microorganisms. The microbial biotransformation of these toxic metabolites is species-specific. Hence, disturbance in the microbiota can lead to changes in metabolites and the gut’s microenvironment, subsequently impacting the growth of other constituents within the gut microbiota.3 Antibiotic treatment also causes the loss of Firmicutes, Bacteroidetes, and Proteobacteria, diminishes the healthy combination of phyla, which in turn causes metabolic shifts, makes the gut more prone to colonization, and stimulates the development of bacterial antibiotic resistance.5,17

  Metabonomic analysis suggested that lipids, bile acids, amino acids, and amino acid-related materials are affected greatly by antibiotics in the gut. An alteration in the short-chain fatty acids (SCFA) production is the primary route through which microbiota dysbiosis induces their effects on immunity and metabolism.

- **Impact on host immune system:** Molecules derived from luminal gut microbes trigger the immune response. For example, microbial-associated molecular patterns are sensed by innate immune receptors on epithelial cells and dendritic cells. These toll-like receptors (TLRs) influence cells in the lamina propria to elaborate cytokines and chemokines. They also influence the maturation of naïve T-cells in the intestinal mucosa and direct their differentiation to different classes of T-helper (Th) cells (such as Th1, Th2, Th17, etc.) or T-regulatory cells. In a healthy state, it is believed that a preponderance of the T-regulatory cells maintains immune homeostasis and prevents unbridled inflammation within the intestine and further systemic circulation. The microbial imbalance caused by antibiotic use leads to dysregulation of immune response, which can potentially manifest as a minor systemic inflammatory state or as an inflammation in a variety of end-organs. SCFA results in a lower frequency of Th and Treg cells, which are considered critical for immune homeostasis. Deregulation of gut microbiota disturbs this balance, which impairs the immune responses, hence leading to a variety of disease outcomes.18 Antibiotics affect the immunity of the host by changing the metabolites of bacteria and specifically inhibiting bacterial colonies. Intestinal epithelial cells identify the signals communicated from the gut microbiota to the host, and intestinal immunity may skew the immune response to cause inflammation or allergic reactions.3 The hygiene hypothesis specifies that, as hygiene improves, autoimmune and allergic diseases become more prevalent in society, and a large component of this is mediated by changes in gut microbiota. Recent research has shown that the reduction of resident microbiota affects systemic immunity, innate immunity, and adaptive immunity.5,21 Antibiotic-induced dysbiosis promotes sustained T-cell-mediated dysfunction, thereby increasing the susceptibility to inflammation and infections by meddling with regulation dependent on the microbiota of intestinal innate immunity.1 Antibiotics also have a profound impact on group 3 innate lymphoid cell recruitment and development, which in turn reduces interleukin 22 (IL-22) production and makes the host more susceptible to invading pathogens.22 The effect of antibiotics/dysbiosis on immune cells in humans is explored by relatively fewer studies.23 In a specific subset of full-term infants, Oosterloo et al. investigated how neonatal antibiotic treatment influenced the expression of 84 distinct markers on circulating immune cells. The findings revealed a notable correlation between the use of broad-spectrum antibiotics and the presence of immune-inflammatory markers [such as heat shock protein 70, soluble form of vascular endothelial growth factor receptor 1, IL-1R1, soluble cluster of differentiation 19 (sCD19), sCD14, and soluble vascular cell adhesion molecule-1] at the age of 1 year.23

The host’s adaptive immunity against hepatitis B virus (HBV) infection was also depleted due to dysbiosis. Antibiotics-treated patients showed a decline in interferon-γ production and impaired clearance of HBV.24 Figure 125 describes the mechanism of immunomodulation caused by antibiotics.

- **Increased susceptibility to infection:** An excess of inflammatory vs anti-inflammatory microbial species is also related to low microbial richness, which in turn causes inflammation of the intestine and disruption of the mucosal barrier.5,26 Antibiotic-associated dysbiosis leads to a plethora of imbalances in the immune system like (1) impairment of pulmonary defense against pathogens,
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Dysbiosis induced by antibiotics has been linked to the genesis of several disorders, including obesity, AAD, *C. difficile*-associated diarrhea, IBD, atopic disorders, allergy, and COVID-19. The aforementioned conditions are discussed in detail below:

- Antibiotic-associated diarrhea (AAD): The prevalence among patients receiving antibiotics is about 5–35%. While certain antibiotics may induce diarrhea through effects on motility, modification in the variety of the gut microbiota is supposedly

Impact of Different Antibiotic Classes on Gut Microbiota

The usage of antibiotics is one of many elements that may disturb the balance between human hosts and related microorganisms. The effect of antibiotics on intestine microbiota varies among different classes of these drugs. The extent to which antibiotics can alter the microbiota depends on factors like (1) the spectrum of the agent, (2) the duration and dosage of treatment, (3) the pharmacodynamic and pharmacokinetic properties of the agent, and (4) the route of administration. To increase the spectra of antibacterial activity, usually a combination of antibiotics is used, but this produces severe dysbiosis compared to treatment with a single antibiotic. Treatment with cefazolin, ampicillin, and vancomycin in humans has been shown to decrease the population of Firmicutes (Clostridium cluster IV and XIVa, *Eubacterium* and *Subdoligranulum*, *Anaerobutyricum hallii* and *Faecalibacterium prausnitzii*) with a simultaneous rise in the abundance of Proteobacteria. The importance of this observation lies in the fact that *Clostridium* clusters IV and XIV, *Eubacterium*, *Roseburia*, and *Faecalibacterium prausnitzii* are important for producing SCFA, particularly butyrate, while phylum Proteobacteria contains potentially pathogenic microbe including *Escherichia coli*, *Vibrio cholerae*, and *Shigella* species.

Clindamycin, a broad-spectrum antibiotic that is excreted in bile and mainly concentrated in the feces, is known to target anaerobic bacteria. Clindamycin has an adverse impact on the gut microbiota by diminishing its ability to resist colonization by harmful pathogens and promoting the proliferation of *C. difficile*. Additionally, it also causes inflammation of the lining of the stomach and diarrhea. These disruptions in regular bowel function may cause bloating and discomfort in the abdomen. On the other hand, β-lactams are known to double the average microbial burden. The patients undergoing moxifloxacin treatment experienced a decrease in the abundance of *Bacteroides* and *Faecalibacterium* genera. However, in the early stages of treatment, there was an active presence of other bacteria that produce butyrate, such as *Roseburia* and *Lachnospiraceae incertae*) as well as *Blautia*, *Collinsella*, and *Bifidobacterium*. These bacteria provide energy to the host’s epithelial cells lining the colon. When a combination of clindamycin and penicillin G was used, a marked decrease in *Blautia* and *Bacteroides* genera was observed in the active microbiota. These were some common examples of the perturbations caused by antibiotics. Table 1 lists more such examples.

Impact of Antibiotic-Associated Dysbiosis in the Following Conditions

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**Fig. 1:** Pathophysiology of dysbiosis associated changes. DC, dendritic cells; DAMP, damage-associated molecular patterns; PMNs, polymorphonuclear leukocytes; PAMP, pathogen-associated molecular patterns; Th, T helper cells
Table 1: Impact of antibiotics on gut microbiota and immunity

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Class</th>
<th>Resistance mechanism</th>
<th>Effect on gut microbiota</th>
<th>Effect on immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>β-lactam</td>
<td>Altered target, β-lactamase</td>
<td>Reduction of <em>Enterobacteria</em></td>
<td>NA</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>β-lactam</td>
<td>Altered target, β-lactamase inhibitors</td>
<td>Greater prevalence of <em>Enterobacter</em> spp. and decreased bacterial diversity</td>
<td>Reduced immune cell</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>β-lactam (third generation cephalosporin)</td>
<td>Altered target</td>
<td>Reduction in the number of bacterial cells; decline in the abundance of anaerobic and <em>Enterobacter</em> species</td>
<td>NA</td>
</tr>
<tr>
<td>Ceftriaxon</td>
<td>β-lactam (third generation cephalosporin)</td>
<td>NA</td>
<td>Increase in gram-positive bacteria, reduction in <em>Enterobacteria</em></td>
<td>Decrease in slgA</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Fluoroquinolone</td>
<td>Altered target, efflux</td>
<td>Decreased abundance of <em>Enterobacteria</em>; lower bacterial diversity, decrease in short-chain fatty acid (SCFA) producers</td>
<td>Decrease in antimicrobial peptide</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Lincosamide</td>
<td>Altered target</td>
<td>Initially decreased abundance of <em>Enterococc</em>, <em>Streptococcus</em>, and anaerobic bacteria, subsequent recovery of abundance of <em>Streptococcus</em> and anaerobic bacteria; reduced diversity of <em>Bacteroides</em> spp.; decrease in an abundance of bacteria producing short-chain fatty acids</td>
<td>Not reported</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Glycopeptide</td>
<td>Altered peptidoglycan target</td>
<td>Decreased bacterial diversity</td>
<td>Decrease in antimicrobial peptide, immune cells, and intestinal lymphoid follicles</td>
</tr>
<tr>
<td>Amoxicillin/ampicillin</td>
<td>Penicillins with β-lactamase inhibitors</td>
<td>NA</td>
<td>Increase in aerobic gram-positive coccic and <em>Enterobacteria</em></td>
<td>Decrease in antimicrobial peptide and antigen-presenting capacity</td>
</tr>
<tr>
<td>Clarithromycin/metronidazole</td>
<td>Macrolide (clarithromycin) and nitroimidazole (metronidazole)</td>
<td>Altered target/drug inactivation (clarithromycin) and efflux (metronidazole)</td>
<td>Reduction in an abundance of <em>Actinobacteria</em>, partial recovery of pretreatment state; increase in <em>enterobacteria</em></td>
<td>Decrease in antimicrobial peptide and intestinal innate immune cells</td>
</tr>
</tbody>
</table>

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an underlying factor of AAD. One of the mechanisms by which AAD can occur is due to the decrease of advantageous metabolic activities of intestinal microbes. By altering global colonic metabolism, alterations in the composition and amount of the intestinal microbiota (even in the absence of excess growth of pathogenic microorganisms) may lead to AAD. Since the colon cannot absorb carbohydrates, anaerobic colonic bacteria metabolize them as an important source of energy, creating lactic acid and SCFAs that the colon can easily absorb. Due to antibiotic treatment, such bacteria are lost, which leads to an increase in the amounts of carbohydrates in the lumen, further causing osmotic diarrhea. A meta-analysis by Szajewska, Kolodziej et al. revealed that certain strains of probiotics, such as those composed of *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii* might be useful for the prevention of AAD.

- **Clostridium difficile**—associated diarrhea: *C. difficile*, an anaerobic, gram-positive bacillus, possesses resilient spores resistant to extreme temperatures, chemicals, and desiccation. It generates toxins A and B, capable of damaging the gut mucosa. Antibiotics such as clindamycin, cefoperazone, and vancomycin produce an environment that is favorable for the development of *C. difficile* by increasing the levels of carbohydrates like mannitol and sorbitol, reducing SCFAs and glucose, creating an increase in tauro-conjugated primary BAs and levels of glycine in the intestinal lumen.

- **Obesity**: Obesity and obesity-related metabolic disorders are linked to dysbiosis of the gut microbiota. Diets, in addition to genetics, both have a significant impact on obesity. Over the past 3 decades, there has been a rise in the number of cases of obesity, which has been linked to changes in the composition of the intestinal microbiota. Obesity is related to changed microbial profile, including diminished diversity, increased abundance of pro-inflammatory bacteria, and decreased abundance of anti-inflammatory bacteria.

In comparison to their lean counterparts, obese people have fewer Bacteroidetes, *Christensenellaceae*, and *Akkermansia* and a higher concentration of *Firmicutes*. Numerous studies have consistently linked antibiotic-induced alterations in the gut microbiota to either children being overweight or adiposity. Evidence indicates that early antibiotic exposure can trigger long-term and substantial changes in an infant’s gut microbiota. It has been noted that antibiotic use in infants under 6 months of age is linked to higher body mass index in later life. Changes in metabolic function, an increase in adipose tissue in the body, and childhood obesity have all been linked to altered gut microbiota. Since the published results are not causal, the mechanism that underlies the linking of early childhood antibiotic use, being obese, and gut microbiota is unknown.

- **Inflammatory bowel disease (IBD)**: A close connection between altered gut microbiota and IBD can be made from several clinical observations.
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population-based study by Kronman et al. stated that infants receiving anti-anerobic antibiotics in the first year of life had higher chances of being diagnosed with IBD than those who were not treated with antibiotics. A Danish (Hviid et al.) study observed that the probability of IBD was highest in the initial 3 months after usage of antibiotics and in children who had received at least seven courses of antibiotics. Antibiotic-induced dysbiosis may contribute to the onset and progression of IBD. The widespread presence of supposedly immune-protective bacteria from the phylum Firmicutes, especially F. prausnitzii and Akkermansia muciniphila, is decreasing, whereas adherent, invasive Escherichia coli is increasing. F. prausnitzii secretes anti-inflammatory metabolites that block nuclear factor-κB activation and IL-8 development by epithelial cells, resulting in anti-inflammatory effects in cellular and animal models of colitis. F. prausnitzii and A. muciniphila contain the SCFAs butyrate and propionate, which maintain the integrity of the mucosal barrier in addition to their direct anti-inflammatory effects. In line with the idea that antibiotic exposure will lead to a decrease in abundance and the extinction of certain taxa, the overall decrease in Firmicutes and F. prausnitzii is linked to an increased risk of recrudescence of CD, ulcerative colitis (UC), and IBD.

- Allergy and atopic disorders: Allergies are a very common chronic disease where there is hyperactivation of Th2 of the adaptive immune response. Important components of the gut microbiota are necessary for the development of the immune system’s regulatory components as well as for maintaining homeostasis at the gut epithelium. It is assumed that dysbiosis due to antibiotics can affect the response of Th2, making it more vulnerable to allergies. Multiple studies have revealed that the first 6 months of life are the most important for the development of the immune system, suggesting host-microbiome interactions play an important factor. In a study by Kummeling et al., an investigation into the connection between infants being exposed to antibiotics within their first 6 months of life and the occurrence of eczema, wheezing, and allergies at the age of 2 was conducted. The study revealed that antibiotics were associated with an elevated likelihood of recurrent and extended wheezing, although no significant links were observed with allergic sensitization or eczema. According to Stensballe et al., children born to asthmatic mothers having a higher risk of asthma were linked to maternal antibiotics used during the third trimester of pregnancy. The widespread use of antibiotics may be one of the factors leading to the dramatic rise in autoimmunity and allergies over the last few decades.

- Coronavirus disease 2019 (COVID-19): Prescribing antibiotics to prevent/treat superinfections in COVID-19 patients might have a significant effect on the patient’s gut microbiota. COVID-19 patients have demonstrated a more heterogeneous microbiome configuration, and there is a shift of gut microbiota toward an unhealthier spectrum. A study conducted by Zuo et al. concluded that even in patients with COVID-19 naïve to antibiotic therapy, depletion of beneficial commensals was a peculiar characteristic. Azithromycin showed a higher potential to rapidly worsen the already weak microbiota of elderly and COVID patients with comorbid conditions because of its ability to rapidly reduce bacterial richness (23%) and Shannon diversity (13%). However, further research is needed to figure out the effect of antibiotic-associated dysbiosis on COVID patients.

Strategies to Reduce Antibiotic-induced Gut Microbial Dysbiosis and Immune Disorders

Overuse of antibiotics must be moderated due to the numerous adverse effects that come with the consumption of antibiotics. The use of antibiotics cannot be abandoned, especially when patients have severe infections. Hence, multiple approaches have been proposed to lessen immunological diseases and dysbiosis caused due to antibiotics. Some of these strategies are mentioned below:

- Probiotics: Live probiotics are generally administered to restore the balance of microbiota in the gut and to promote anti-inflammatory responses. Lactobacillus, Saccharomyces, Bifidobacterium, and Enterococcus are the most frequently used probiotics. Goldenberg et al. revealed that probiotics may be useful to prevent C. difficile infection in patients who are being administered antibiotics. Multiple studies have observed that oral administration of a combination of probiotics, such as Bifidobacterium, L. acidophilus, L. casei, and L. rhamnosus, can decrease the risk of AAD. Interestingly, there are also reports of probiotics being effective for the treatment of IBD. Some studies have demonstrated the synergistic role against two methicillin-resistant pathogens and, hence, can be coadministrated to treat complex infections and the prevalent antimicrobial resistance. Because of the strain-specific effects of probiotics, it is essential to emphasize on development of new personalized probiotic supplementation approaches rather than the general ones. Yeast probiotics, especially S. boulardii, are now gaining a lot of popularity for the treatment of dysbiosis. A recent review confirmed that treatment with S. boulardii NCIM 1-745 in dysbiosis results in a faster reestablishment of healthy microbiota. S. boulardii, being yeast, is resistant to antibiotics, and the administration of S. boulardii NCIM 1-745 after antibiotic therapy has been reported to accelerate the recovery of the intestinal microbiota at the initial level. Therefore, the use of yeast probiotics can be further explored for the treatment of antibiotic-associated dysbiosis.

- Fecal microbiota transplantation (FMT): FMT is considered to be a novel method to control multidrug-resistant pathogens and to avoid potential or future severe infections, and is generally used to treat patients whose gut is colonized with such pathogens as C. difficile or for patients who are at greater risk of infection after treatment with antibiotics. FMT controls intestinal inflammation and maintains the balance of gut microbiota through several mechanisms, such as increasing the production of IL-10 by APCs, INKT cells, and CD4+ T-cells, restoration of secondary bile acid metabolism, provision of signals for epithelial regeneration, and stimulation of secretion of antimicrobial peptide. Selective transfer of Clostridium scindens has demonstrated considerable advantages in addressing recurrent or recalcitrant C. difficile infections, yielding a notable cure rate ranging from, approximately, 87 to 90%. This beneficial outcome arises from the augmentation of host resistance against the infection, as C. scindens possesses the capability to enzymatically transform primary bile salts into secondary bile salts, which exhibit potent inhibitory properties against the colonization of C. difficile. Lastly, autologous FMT also increases the
diversity of microbiota and restores the gut microbiota in healthy adults, patients, and mice ingested antibiotics.53

- Phage therapy: Along with bacterial diversity, the human gut is also a host to a fascinating viral community that exerts its effect on microbiota as well as the host.33 Phage therapy was the choice of treatment before the advent of antibiotics and is now gaining popularity either for restoring microbial equilibrium in chronic health conditions or for compassionate intervention in acute cases.33,35 Phage therapy capitalizes on the intrinsic capacity of bacteriophages to selectively target specific bacteria, harnessing both lytic and temperate phages as agents for microbiome intervention to engineer and manipulate the microbiota within its specific ecological niche to attain a state of well-balanced and health-promoting microflora.33,55 Phages are now recommended because of (1) their high specificity to the target bacteria, which helps in reducing the off-target impacts on broader microbiota and (2) their inherent self-replicative nature, thereby contributing to the cost-effective production of phage-centered therapeutics.33 Genetically engineered phages show an improved function in modulating the gut ecosystem.57 One such example is the incorporation of a biofilm-degrading enzyme into the genetic makeup of T7 phages. It allowed for the reduction of the biofilm and lysis of the bacteria simultaneously in a positive feedback manner.59 Many active phages like those against E. faecalis,59 Bacillus cereus,60 and P. aeruginosa61 have been discovered. A study by Yosef et al. identified the use of phage therapy to treat antibiotic resistance.62 On the basis of these reports, phage therapy is recommended to be used for diseases in which (1) the bacterial cause is well defined, (2) refractory to antibiotics, and (3) phages are accessible.52 However, more research needs to be done on resistance to both phages and engineered nucleases. Nonetheless, natural and engineered phages are promising future tools in the battle against pathogens and the state of the dysbiotic community.62

### Conclusion and Future Directions

The gut, housing a vast community of trillions of microbes known as the gut microbiota, plays a pivotal role in maintaining equilibrium within the body. It accomplishes this by safeguarding against diseases modulating both the immune response and energy utilization. Despite being one of the most often prescribed medications, the excess dependence on them can be a serious problem as they can disrupt the equilibrium of the gut microorganisms and further lead to serious disorders. Antibiotics have extreme effects on the gut microbiota as they diminish the plethora of useful commensals and increase the abundance of harmful pathogens or commensals. These adverse effects of antibiotics are particularly a major concern to infants and should be carefully considered while it is prescribed without affecting the clinical practice. Disturbances in microbiota equilibrium triggered by antibiotics can have adverse health implications. These perturbations may amplify vulnerability to infections and disrupt immune homeostasis, potentially leading to heightened allergies, IBD, colorectal cancer, obesity, and asthma. However, recent advances bring a new road map for combating disease—causing bacteria while minimizing harm to the microbiota. The forthcoming emergence of targeted antivirulence agents, alongside a revitalized exploration of probiotics, phage therapy, and FMTs, promises to revolutionize treatment approaches for dysbiosis. Furthermore, advancements in our understanding of antibiotics can give us a better insight to fight pathogenic bacteria.

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