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The Relevance and Necessity of Optimal Use of Antibacterial Drugs in the Prevention of Intestinal Microflora Imbalance

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Annotation: The human body, especially the gastrointestinal tract, is home to trillions of microorganisms that have coevolved with the host in a mutually beneficial relationship. Among other things, the gut microbiome's primary job is to ferment indigestible substrates and promote the growth of good bacteria that generate important antimicrobial metabolites like short-chain fatty acids, which stop the growth of harmful bacteria. By use of the colonization resistance mechanism, intestinal microbiota can stop pathogen colonization. Both pathogenic and benign microorganisms have a variety of resistomes. Exposure to both helpful and unfriendly gut microbiomes with antibiotics can cause a resistome response, which impacts colonization resistance. A mechanistic overview of the gut microbiome and how antibiotic therapy affects pathogen colonization and disease is given in the review that follows. Additionally, we go over the colonization and decontamination of multidrug-resistant organisms in the intestine, the epidemiology of immunocompromised people who are at high risk for nosocomial infections, and the direct and indirect mechanisms that control colonization resistance to the pathogens. Because of their ability to combat infections, antibiotics have been a staple of medical care during the past century. In the context of MDA, the effects of

antibiotic use on the gut flora are reviewed in this publication. It is now widely known that the gut microbiota plays a crucial role in human metabolism and physiology, and exposure to antibiotics may have a negative effect on host health through unintended consequences for the microbiota and its processes. We also review factors that affect the impact of antibiotic exposure on the microbiota, potential health outcomes of antibiotic-induced microbiota alterations, and strategies that may help alleviate these broader antibiotic-associated microbiota perturbations in order to better understand how gut microbiota respond to antibiotic perturbation and the implications for public health.

Keywords: infections, antibiotics, gut microbiota, colonization resistance, illnesses, probiotics, dysbiosis.

Introduction. Trillions of microorganisms, known as the microbiota, including bacteria, viruses, helminths, fungus, protozoa, and archaea, live in the gastrointestinal tracts (GIT) of humans and other mammals. As a result, the microbial makeup of microbiota members varies greatly from one another. Despite their diversity, the majority of intestinal microbiota belong to four phyla: *Proteobacteria, Firmicutes, Bacteroidetes* and *Actinobacteria.* Over 90% of the bacteria in the colon belong to the groups *Bacteroidetes* and *Firmicutes*. Below, we'll go over each of these phyla in brief and highlight key players to help you comprehend the makeup of the intestinal microbiota. Gram-positive, aerobic, anaerobic bacteria with a high G + C concentration in their genomic DNA are classified as members of the phylum Actinobacteria. Certain bacterial species that stick to the intestinal mucosa, such *Bifidobacteria spp.* (probiotics), have a mutually beneficial interaction when they coexist over an extended period of time. According to the World Health Organization, probiotics are live bacteria that, when given in enough quantities, boost the host's health [1,2,3,4]. Through a variety of mechanisms, such as competitive exclusion, bile salt hydrolase activity, support for nutritional metabolism, and immunological and digestive system modulation, probiotics shield the host from infections. However, the host offers nutrient-rich habitats to guarantee the survival of the microbiota. The rod-shaped, Gram-negative, aerobic, anaerobic, nonspore-forming bacteria that inhabit the intestine are members of the phylum *Bacteroidetes*. One of the most common genera that colonize the digestive system is *Bacteroides*. It is known that members of this genus may break down complex carbohydrates that the host's digestive enzymes cannot break down. The host uses tiny fatty acids like acetate, propionate, and butyrate for energy after complex polysaccharides are broken down [5,6,7]. Antibiotics are frequently used to treat bacterial infections. Epidemiological studies have shown that 71% of intensive care unit patients are on antibiotics. Long-term, excessive use of antibiotics can cause serious adverse consequences. Although antibiotics kill bacteria and inhibit their growth, they can also induce drug resistance. In addition, antibiotic use can temporarily or permanently alter the composition of the intestinal microbiota, promote colonization by intestinal pathogens, and trigger the development of some intestinal diseases [8,9]. Antibiotic-induced alteration of the gut microbiota has drawn more attention in recent years. Changes in the gut microbiota have been directly linked to the use of antibiotics, according to certain research. Mice treated with metronidazole, vancomycin, and clindamycin for a brief period of time, for instance,

are less likely to become infected with *Escherichia coli, vancomycin-resistant Enterococci, C. difficile* and *Klebsiella pneumonia*. To account for the majority of the bacterial components of the intestinal microbiota, we examined the effects of four widely used antibiotics in this study: metronidazole, which is commonly used to treat anaerobic bacterial infections; ampicillin and neomycin, which are typically used to treat Gram-negative bacterial infections; and vancomycin, which is typically used to treat infections with Gram-positive bacteria [10,11,12]. An enormous concern to world health is antimicrobial resistance. The role of altered gut microbiota during antibiotic treatment is supported by a significant quantity of data from animal models. Antibiotics' function as a catalyst in this relationship, whether as treatment or through low-dosage consumption through the food chain, is yet unclear. More advanced methods and randomized control trials are needed to clarify the connection and analyze the possibilities and difficulties of tackling the emerging AR epidemic. After conducting a comprehensive monitoring research on antibiotic resistance, the World Health Organization illustrates the gravity of the issue and stresses the need for coordinated efforts from all states and relevant entities to help society lessen the enormous threat posed by antimicrobial resistance. In addition, it is important to consider the financial costs associated with antibiotic resistance. Accordingly, international scientific cooperation will enable us to investigate and determine the best policy, as well as the most efficient procedure and approach, for the community and the environment [13,14,15,16].

The main purpose of the presented balloon is to briefly analyze the relevance and necessity of optimal use of antibacterial drugs in the prevention of intestinal microflora imbalance based on the results of reputable scientific papers.

Intestinal Microbiota Metabolites Prevent Pathogenic Bacteria. The gut microbiota produces metabolites that prevent harmful bacteria from growing. Healthy gut microbiota produces short-chain fatty acids (SCFAs), which offer protection from enteric infections. Vitamins, soluble dietary lipids, and unabsorbed starch are all fermented by intestinal bacteria. In adults, SCFAs are produced by *Bacteroidetes* and *Clostridium,* components of the intestinal microbiota. The main fermenters are Bacteroidetes, which convert complex carbs into organic acids and SCFA. *Clostridium utilizes* the organic acids to produce more SCFAs. By reducing intracellular pH and permeating bacterial membranes, SCFAs exhibit direct antibacterial action. SCFAs' antibacterial properties make them potentially useful for human health and food safety. Important metabolites called *Clostridium SCFAs* prevent the growth of *S. Typhimurium* in the intestines of mice, dangerous strains of *E. coli* in mice treated with streptomycin and *C. difficile* in humans [17,18,19].. Bile acids are amphipathic compounds produced from cholesterol that are secreted by the gut microbiota. Before being stored in the gall bladder, bile acids undergo conjugation with taurine or glycine after being produced in the liver. Bile acids are then released into the small intestine, where they emulsify fat and vitamins that are soluble in fat so that they can be absorbed. In humans, the distal ileum reabsorbs around 95% of bile acids, with the remaining 5% being converted or deconjugated to secondary bile acids such lithocholic acid and deoxycholic acid. As seen in the instance of *C. difficile enterocolitis*, pathogens proliferate when commensals that produce deoxycholic acid are absent. Increased bile acid levels (from diets or therapy) inhibit *Bacteroidetes* and *Actinobacteria* and encourage the growth of *Firmicutes* and *Clostridium species* involved in bile acid deconjugation. High amounts of bile acid can prolong the survival of certain bacterial infections, including *S. Typhimurium*. The gut microbiota also contributes to the development of colon cancer and cholesterol gallstones caused by excess bile acids, such as deoxycholic acid. The growth of bile acid-intolerant microorganisms is inhibited by secondary bile acids because they change the integrity of the microbial cell membrane, causing intracellular contents to leak out [7,9,10,18].

Related health effects. It is crucial to remember that healing by itself might not shield the host from the possible long-term consequences of antibiotic-induced microbiome disruptions. Antibiotic use has been linked in epidemiologic research to a number of illnesses, including obesity, colorectal cancer, asthma, allergies, and atopy. One significant explanation behind these

relationships has been suggested to be the alteration of the gut flora caused by antibiotics. The majority of research, however, has examined the connections between antibiotic usage, the makeup or function of the gut microbiota, and health outcomes independently. In order to show a direct correlation between antibiotic modulation of the gut microbiota and health effects, or the precise antibiotic-induced alterations to the microbiome that may be involved, recent reviews have found few, if any, studies that evaluated and reported antibiotic use, microbiota composition, and host health outcomes in the same study population. In this part, I address such research with regard to the MDA studies' findings in order to obtain a better understanding of the health implications of microbiome disturbance caused by MDA with antibiotics [11-19].

Encouraging preventative actions to safeguard the microbiome. To lessen the negative effects of antibiotic use on the microbiome, a few viable strategies have been proposed. One such tactic is the co-administration of prebiotics to encourage commensal bacterial growth. Complex oligosaccharides found in human milk are abundant in babies and act as substrates for *Bifidobacterium spp.* growth and to help other species cross-feed. In one observational cohort, breastfeeding is linked to a faster recovery of microbiome α-diversity in newborns exposed to IAP. Beyond its prebiotic value, nursing may have other advantages. While azithromycin alone increased the abundance of proinflammatory Streptococci up to 60 days after treatment, co-administration of lactulose and azithromycin in children helped restore the relative abundance of *Lactobacillus, Enterococcus, Anaerostipes, Blautia* and *Roseburia* within 18 days of treatment. Adult probiotic and antibiotic co-administration has also demonstrated some promise in reducing antibiotic selection for genetic resistance factors. However, due to host and autochthonous microbiome characteristics, the degree of effective gut colonization by probiotic bacteria taken orally has varied significantly by individual, gut area, and probiotic strain [1-7]. The potential protective effects of probiotics may also be further limited if the probiotic strains lack resistance to the administered antibiotic, which could worsen selection for antibiotic resistance in the microbiome. Although it might not be as feasible for LMICs, fecal microbiota transplantation utilizing a self-provided, healthy fecal samples obtained before antibiotic therapy might be a more successful method of microbiome restoration. In order to generate more species-specific effects than single antibiotic treatments, another tactic is to use antibiotic-drug combos. One study, for instance, tested over a thousand medications to find potential candidates that lessen antibiotics' broad-spectrum activity without compromising their ability to combat pertinent bacteria. Another known antibiotic that is produced by Bacillus thuringiensis is called Thuricin-CD. In a fecal-culture system that mimics the human colon, it has been demonstrated to be effective against Clostridium difficile without affecting the composition of the microbiota. In order for narrow-spectrum options to maximize desired results while reducing undesirable hazards, a fuller knowledge of the mechanisms by which mass drug administration (MDA) with antibiotics cause health benefits or unpleasant side-effects would be necessary for the development of such therapies. Lastly, during crucial developmental stages, there might be significant microbial elements in the environment that aid in preventing dysbiosis or restoring physiologically significant subgroups of the gut microbiome. Finding these elements could direct the creation and evaluation of mitigation measures [8-14].

Instead of treating a specific infection, this narrative review is limited to studies of antibiotics used as part of a mass drug administration program or policy to lower morbidity and mortality in particular at-risk target populations. I concentrated on antibiotics used in these settings because of the ongoing public health interest in using MDA with antibiotics to lower childhood morbidity and death in light of global targets, as well as the historical interest in trachoma and yaws elimination initiatives. Because there are guidelines and recommendations for use, I also concentrated on intrapartum antibiotic prophylaxis and antibiotic prophylaxis in people living with HIV [5-11]. These articles are scarce and restricted to pregnant women, children, and babies, which limits their generalizability to populations outside of these risk groups or to other therapeutic indications. More thorough examination of antibiotic-associated taxonomic changes

was not possible because the majority of these studies only documented antibiotic effects on α- and β-diversity metrics. I also talked about studies that examined antibiotic use, gut microbiota, and health outcomes in the same study population, as well as studies that documented the characteristics that influence how gut microbiota respond to antibiotic disruption, in order to better understand the findings of these MDA studies. Additionally, there weren't many of these investigations, which limited the conclusions that could be made. Last but not least, the majority of the studies examined here employed 16S amplicon sequencing and offered no details on the microbiome's functional capacity, which would have shed more light on the mechanisms behind antibiotic-induced changes in health [12-17].

Discussion. The microorganisms that live in the human gut collectively, known as the gut microbiota, are essential for defending the body against potentially dangerous substances like bacteria, poisons, and antigens. One One could consider the relationship between sepsis and the microbiota to be a bidirectional one that is yet poorly understood. The microbiota is disrupted by the illness state of sepsis, but the treatments given to these critically ill patients during clinical care also act as external modulators of the microbiota. Modern research is focused on the topic of intestinal flora. Maintaining a healthy intestinal microbiota is crucial for maintaining homeostasis, and dysbiosis—a disruption in the microbiota's makeup and functions—is linked to a variety of illnesses, including UTIs. Antimicrobial medication raises the risk of recurrent urinary tract infections and significantly alters the gut microbiome. To restore the microbiota's structural and functional integrity, it is crucial to research microbiota repair techniques [3,5,6,11].The findings of multiple studies support the necessity of considering the impact of instant messaging on the occurrence of urinary tract infections. Correcting the gut microbiota may prove to be a useful strategy for both preventing and treating illness. Dietary treatments, FMT, and pro/prebiotics have all showed promising outcomes. The viability of additional study in this area is determined by the fact that there is currently insufficient evidence to provide trustworthy recommendations on the application of such correction techniques in the treatment and prevention of UTIs [4,12].In addition to a decrease in Bifidobacterium species and an increase in Enterobacteriaceae with prenatal or neonatal exposure, the most consistently observed effect of MDA with antibiotics has been a decrease in microbiota α-diversity in infants and children. Depending on the type of antibiotic used, the microbiome's original makeup, or the sources and frequency of recolonization, the microbiome might not completely recover to its original state. The timing of antibiotic exposure and the particular setting may determine the possible effect on host health. Although they need more research, interventions to lessen or track the effects of antibiotic usage on the microbiota appear promising. More thorough research is needed to completely characterize the possible mechanisms of antibiotic-induced changes in the human gut microbiome and their effects on host health, as well as to guide their translation into alternative treatments and public health initiatives. Antibiotic-induced microbiome alteration is a complicated process [12,13,19]. The health of the world is seriously threatened by antibiotic resistance. Animal models have provided a significant amount of evidence about the role of altered gut microbiota after antibiotic treatment. It is yet unclear how antibiotics, either as treatment or through low-dosage consumption through the food chain, work as a stimulant in this interaction. To clarify the relationship and investigate the possibilities and difficulties for battling the emerging AR epidemic, new, state-of-the-art methods and more complex, randomized control studies are needed. Following a lengthy surveillance study of antibiotic resistance, the World Health Organization highlights the gravity of the issue and stresses that all states and relevant organizations must work together to reduce the enormous threat posed by antimicrobial resistance [9-13].

Conclusions. A diverse and stable microbial community, the intestinal microbiota's intimate ties to the host are essential for preserving intestinal homeostasis and pathogen-resistant colonization. When this delicate equilibrium is upset, disease manifestation will increase. Due to a lack of precise methods and concrete proof, the fundamental mechanisms by which the

intestinal microbiota prevents the pathogen from colonizing the intestines are still up for debate. To uncover pathogenic and pathophysiological elements of illnesses and to create a more effective treatment agent, a deeper comprehension of commensal microbiota interactions with the host is required. Numerous symptomatic disorders can be treated with FMT therapy, which returns the altered gut microbiota to a healthy state.

The contribution of dysbiosis to the form of the disease is a critical factor in determining the efficacy of microbiome-based therapy. Although FMT is safe, the possibility of spreading virulent or antibiotic-resistant genes among microbiomes makes it unreliable in the long run. While there haven't been any reports of serious systemic adverse effects with FMT therapy, minor gastrointestinal discomfort like nausea, vomiting, and stomach pain are frequent.

Therefore, it is highly recommended that the treatment plan, mode of administration, and efficient patient communication be improved. In summary, there are a number of early but encouraging studies on the modulatory role of the intestinal microbiome in host health and illnesses, and the area of microbiome research is still relatively young but growing quickly. Future research projects in the areas of microbiome-based disease diagnosis, prognosis monitoring, prophylaxis, and treatments have the potential to revolutionize current disease prevention and treatment measures.

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