Current understanding of antibiotic-associated dysbiosis and approaches for its management

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Abstract: Increased exposure to antibiotics during early childhood increases the risk of antibiotic-associated dysbiosis, which is associated with reduced diversity of gut microbial species and abundance of certain taxa, disruption of host immunity, and the emergence of antibiotic-resistant microbes. The disruption of gut microbiota and host immunity in early life is linked to the development of immune-related and metabolic disorders later in life. Antibiotic administration in populations predisposed to gut microbiota dysbiosis, such as newborns, obese children, and children with allergic rhinitis and recurrent infections; changes microbial composition and diversity; exacerbating dysbiosis and resulting in negative health outcomes. Antibiotic-associated diarrhea (AAD), *Clostridiodes difficile*-associated diarrhea (CDAD), and *Helicobacter pylori* infection are all short-term consequences of antibiotic treatment that persist from a few weeks to months. Changes in gut microbiota, which persist even 2 years after antibiotic exposure, and the development of obesity, allergies, and asthma are among the long-term consequences. Probiotic bacteria and dietary supplements can potentially prevent or reverse antibiotic-associated gut microbiota dysbiosis. Probiotics have been demonstrated in clinical studies to help prevent AAD and, to a lesser extent, CDAD, as well as to improve *H pylori* eradication rates. In the Indian setting, probiotics (*Saccharomyces boulardii* and *Bacillus clausii*) have been shown to reduce the duration and frequency of acute diarrhea in children. Antibiotics may exaggerate the consequences of gut microbiota dysbiosis in vulnerable populations already affected by the condition. Therefore, prudent use of antibiotics among neonates and young children is critical to prevent the detrimental effects on gut health.

Keywords: antibiotic-associated diarrhea, antibiotic-associated dysbiosis, antibiotic resistance genes, *Clostridiodes difficile*-associated diarrhea, gut microbiota, gut microbiota dysbiosis, *Helicobacter pylori* infection, probiotics

Introduction

The human gut microbiota (GM) refers to a colony of bacteria, fungi, viruses, and protozoa that dwell in the gastrointestinal (GI) tract of humans.[1,2] The human GM is an intricate ecosystem, wherein the resident microorganisms interact among themselves and with the human host.[3] The human GM comprises a massive microbial population that plays a crucial role in numerous aspects of human health and survival such as maintenance of host intestinal homeostasis and energy homeostasis, development and modulation of the immune system, metabolic functions, and protection against pathogen colonization in the gut.[3,4]

Given the significance of GM in health and disease, this review examines antibiotic-associated dysbiosis and its evidence-based role in the most vulnerable populations, which include neonates and children with obesity, allergic rhinitis, or recurrent infections. It also provides a brief

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overview of the short- and long-term effects of antibiotic-induced microbiota changes, as well as their economic impact. Furthermore, the management of antibiotic-associated dysbiosis has been discussed with a special focus on the role of probiotics in gut dysbiosis and related conditions.

GM dysbiosis

Disturbances in the symbiotic balance between the host and gut microbiota impair intestinal homeostasis and cause GM dysbiosis.[1,2,4,5] In this context, GM dysbiosis is defined as a change in the diversity, composition, and function of the gut microbiota.[1,2,4] These alterations in the microbiota can be caused by factors related to the host and/or environment and include unbalanced diet, exposure to pathogens and toxins, long-term use of proton pump inhibitors (PPIs), exposure to antibiotics, excessive alcohol consumption, increased sugar or protein intake, pesticide exposure, poor dental hygiene, and long-term stress.[6] The gut microorganisms also communicate with the central nervous system through the brain-gut-microbiota axis. Although the exact mechanisms are not clear, endocrine, neural, and metabolic pathways have been suggested. These interactions are considered important and can impact the intestinal homeostasis.[7] Disturbances in GM have been linked to the development of several diseases, including metabolic diseases (obesity, diabetes, and metabolic syndrome), atopic diseases (allergies, allergic rhinitis, and asthma), inflammatory and autoimmune diseases [necrotizing enterocolitis, Crohn's disease, inflammatory bowel disease (IBD), and irritable bowel syndrome].[3,8,9] A meta-analysis revealed disease-associated changes in the human gut microbiome with distinct shift patterns.[10] In addition, people with inflammatory and metabolic disorders have been found to have less diversity of bacteria than healthy controls.[11]

Antibiotic-associated dysbiosis

The most frequently prescribed drugs for infectious diseases are antibiotics.[5] While primarily targeting disease-causing bacteria, antibiotics also attack beneficial gut microbes, resulting in altered microbiota composition.[12] The GI tract is the organ most sensitive to antibiotics taken orally.[6] The intestine has three barriers: a physical barrier made up of intestinal epithelial cells (IEC) connected by interepithelial tight junctions, a secretory barrier composed of mucus and antimicrobial peptides (AMP), and an immunological barrier composed of different immune cell types and biomolecules. In addition to affecting the gut microbiota, antibiotic treatment damages the three intestinal barriers. Antibiotic-induced changes in the composition of the gut microbiota alter the production of mucin, cytokines, and AMP, weakening the IEC barrier.[6]

Different levels of evidence confirm that the administration of antibiotics results in gut microbiota dysbiosis, which mainly involves a reduction in the diversity of gut microbiota, alterations in the abundance of certain taxa, alterations in gene expression, protein activity, and gut metabolome, compromised colonization resistance to invading harmful bacteria, and the emergence of antibiotic-resistant microbes (Figure 1).[1,4,8,12] Furthermore, antibiotic-induced changes in the gut microbiota disrupt host–microbial interactions, resulting in increased infectivity and acute gut infections.[6,12]

Antibiotics with a broad spectrum of activity that target several bacteria are widely used. Macrolides, penicillins, and vancomycin are examples of such antibiotics. Notably, not all antibiotics affect the microbiome in the same way. Various antibiotics have different modes of action, thus they may wipe out certain subpopulations of microbiota.[4] Different antibiotic classes have distinct effects on the GM depending on the drug's spectrum, delivery route, dosage, and administration duration, as well as the host's attributes and condition.[6,13,14]

Compared with adults, infants are more prone to bacterial infections and sepsis, especially premature infants. Antibiotic exposure during infancy causes dysbiosis, which can have detrimental health outcomes in later life.[2,4,15–19] Children with obesity, recurrent infections, and allergic rhinitis require multiple doses of antibiotics to combat infections. Repeated exposure to antibiotics alters microbial composition and diversity, which exacerbates dysbiosis and results in substantial health consequences.[2] Populations most vulnerable to antibiotic-associated dysbiosis include neonates (first 1000 days of life), children with obesity, children with allergic rhinitis, and children with recurrent infections.
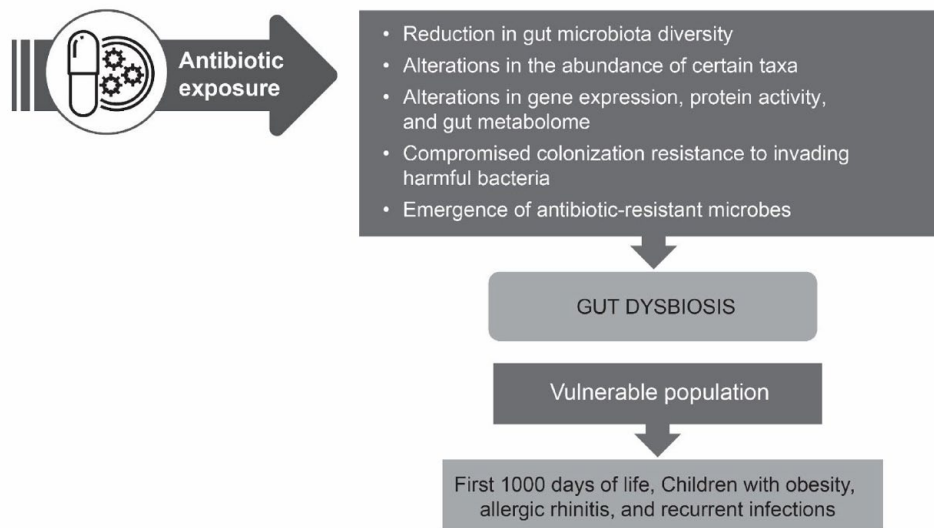
Figure 1. Gut dysbiosis pathology and vulnerable population.

Evidence-based impact of antibiotic administration on gut microbiota in vulnerable populations

Neonates first 1000 days of life

The GM in infants is acquired during birth and subsequently plays a crucial role in the establishment of gut immunity.[20] Neonates, especially underweight and premature infants, are susceptible to bacterial infections, and these infections are treated using antibiotics.[4,21] Antibiotics are the most often prescribed drugs in critical care units for neonates.[22] Antibiotic exposure in early life has been shown to have negative effects on the microbiota and immune system of infants, making them vulnerable to a variety of disorders, including infections, in later life.[4,23] The nature of the effects depends upon the class of antibiotics, dosage, route of administration, duration of treatment, and bioavailability.[13,14]

The development of the GM is influenced by early antibiotic exposure. Delayed microbiota development after antibiotic usage was most noticeable between the ages of 6 and 12 months in a study involving 2-year-old children.[24] Evidence from epidemiological studies indicates that early antibiotic exposure in neonates and infants is associated with changes in gut microbiota composition and metabolic activities.[18,25,26] Several studies regarding species diversity revealed a substantial link between antibiotic use

and a decrease in gut microbiota diversity in neonates, infants, and children.[25,27–31] A systematic review including 48 studies evaluated the effects of antibiotic treatment on the infant microbiome and concluded that exposure to antibiotics was linked to decreased microbial diversity and decreased rates of colonization of beneficial bacteria in the gut.[32] Of note, penicillin does not exert the same effect on microbiome composition of children as there were no apparent taxonomic changes in the microbiome of untreated and penicillin-treated infants.[25]

Antibiotic exposure to premature infants can affect their gut flora.[20] According to studies, preterm infants who underwent lengthy antibiotic therapy exhibited reduced gut bacterial diversity and species abundance, as well as an upregulation in the genes for antibiotic resistance.[33–35] Prolonged treatment with antibiotics in premature infants can increase the risk of acquiring serious infections, and even death.[36]

Furthermore, the effects of antibiotic-associated dysbiosis might persist for several years. Several observational studies have demonstrated a link between early or repeated exposure to antibiotics during infancy and a higher risk of obesity,[15,19,37–44] allergy, and asthma[16,17,45] later in childhood. A recent systematic review and meta-analysis advocated that the risk for developing obesity is 20% higher in children who are exposed to antibiotics.[46]

Several meta-analyses have found that antibiotic use throughout childhood is linked to an increased risk of childhood obesity in a dose-response manner.[47,48] Children with earlier postnatal or recurrent exposures to multiple and broad-spectrum antibiotics during the first years of life had a higher risk of childhood obesity.[43,46,49,50]

Antibiotic usage during late pregnancy increases the abundance of antibiotic-resistant bacteria with increased expression of antibiotic resistance genes (ARGs) in the gut of pregnant women. During delivery, there is transmission of ARGs from the mother to the newborn.[1] Exposure to antibiotics within months of birth results in the growth of antibiotic-resistant microbes and spread of antibiotic resistance in the infant gut microbiome.[4] According to a study, the incidence of ARGs in the infant GM rises with age and is much higher in infants born by cesarean section.[51] Furthermore, ARGs were found on movable genetic elements in infants even after treatment was stopped.[31]

Overall, infants with antibiotic-driven dysbiosis have altered GM in terms of microbial diversity and abundance, lower resistance to opportunistic pathogens, and increased antibiotic resistance.[4,5,8,44]

Children with obesity
Antibiotic-associated gut dysbiosis is common in obese people as seen by a decline in the variety and abundance of their gut microbiome.[52,53] Generally, the biodiversity depleted due to antibiotic treatment recovers following treatment cessation with significant changes in species composition.[2] However, in obese individuals, the microbiome becomes more adept at obtaining energy from various sources as a result of these compositional changes, which affect metabolism and sensitize the host to obesity.[3,52]

The interplay between gut microbes and obesity is influenced by several metabolic, genetic, and inflammatory mechanisms. The reduced microbial diversity in obese people results in altered levels of metabolites such as succinate and short-chain fatty acids (SCFAs) released from GM-assisted fermentation of indigestible carbohydrates. These metabolites prevent obesity by decreasing appetite and increasing energy consumption.[3,54] A study on 42 school children in Malaysia revealed that the total composition of bacterial species was lower in overweight children than in normal-weight children and that there were significant differences in total SCFAs among the two groups.[55] *Bifidobacteria* population during infancy was lower in children becoming overweight, compared with children remaining at a normal weight. It was accordingly suggested that risk of being overweight may be influenced by differences in gut microbiota.[56]

Studies on children who were exposed to antibiotics during fetal life revealed that obesity and being overweight were linked to early antibiotic administration and were likely to last into adolescent and school-age years even when antibiotics were no longer provided.[57] The findings of a study by Schwartz *et al.*[58] suggested that antibiotic administration significantly impacted weight gain irrespective of the age (early or later) at which they are prescribed. Among the different antibiotics, a positive correlation was shown between broad-spectrum antibiotics, such as macrolides, which are active against both aerobic and anaerobic bacteria, and increased body weight.[2,59]

Children with allergic rhinitis
Allergic rhinitis (AR) is the most common allergic disease that greatly impacts the health of children.[60] There are few studies that specifically address the role of gut microbiota in the onset of AR. A cross-sectional study demonstrated a relationship between dysbiosis of specific subgroups of gut microbiota and IgE-mediated reactions to allergens in children aged 4 to 7 years with AR. This could play a role in vulnerability to allergic rhinitis during early childhood.[61] A longitudinal prospective study evaluating the changes in gut microbiota composition from early childhood to school age among children diagnosed with IgE-associated allergic diseases (including AR) revealed that *Bifidobacterium* was abundant, while *Lactobacillus, Enterococcus*, and *Lachnospira* were depleted compared with children without IgE-associated allergic diseases.[62]

As most people with asthma also have AR, the two conditions are commonly linked. The presence of AR increases the probability of developing asthma.[63] A systematic literature review reported that the composition of the human GM during the first few months of life was linked to the later development of allergic disease.[14] Antibiotic use

during the first few days of life has been demonstrated to increase the risk of AR during later stages of childhood.[16] A study reported favorable and dose-dependent relationships between early antibiotic exposure (during the first year of life) and the beginning of asthma, and between lifetime antibiotic use and the emergence of AR.[17] The findings of this study suggested that while the gut microbiota may become stable and mature within 1 year of birth, it may still be susceptible to insult as the child grows older. Antibiotic insult(s) to the gut microbiota may add up, meaning that the more an infant gets exposed to antibiotics, the more likely he or she will contract the disease (AR and/or asthma) as a child. This suggests that using antibiotics repeatedly can worsen gut dysbiosis.[23,64]

A Taiwan-based study involving AR patients with and without asthma reported that antibiotic use before the age of three was not linked to the emergence of asthma. However, a 5-year exposure to antibiotics increased the likelihood of developing asthma in a dose-dependent manner. Among children with AR diagnosed with asthma before the age of 12 years, previous 5-year exposure to penicillin and macrolide (but not cephalosporin), markedly increased the likelihood of asthma. However, this was statistically insignificant when asthma was detected after the age of 12 years. In this study, macrolides and penicillin groups were linked to an increased risk of developing asthma among younger children with AR.[65]

Children with recurrent infections

Infants have an immature microbiome immune system, which increases their risk of recurrent respiratory tract infections (rRTIs).[4] Annually, four to eight episodes of rRTIs may be noted in children.[66] These infections are treated effectively with the use of antibiotics.[67] Antibiotic exposure to infants causes gut microbiota dysbiosis, which in turn alters the innate and adaptive immune responses to pathogens and induces infections associated with a dysfunctional immune system.[2,4,13] Antibiotic use during childhood has been linked to a higher incidence of allergies and various infections.[68] The use of antibiotics disrupts the communication between the immune system and the microbiota and consequently increases the risk of recurrent infections and allergies.[4] A cohort study that investigated the link between an infant's exposure to antibiotics in the first 6 months of life and the development of eczema, wheezing, and allergic sensitization at 2 years of age found that direct antibiotic exposure increased the likelihood of frequent and persistent wheezing but not of allergic sensitization or eczema.[69]

Early in life, gut dysbiosis is defined by delayed colonization by anaerobic microbes and increased colonization by opportunistic pathogenic bacteria, especially enterococci and members of the Enterobacteriaceae family.[70] In a brief study on children with rRTIs, Li et al.[71] found that while the richness of *Faecalibacterium, Eubacterium*, and *Bifidobacterium* was much lower in the rRTIs group, *Enterococcus* was significantly more abundant in this group. In comparison to children who had less than two RTIs in a year, Bosch et al. found that children who had more RTIs in their first year of life had an abnormal pattern of microbial development beginning in the first month of life. These patients had an early abundance of *Moraxella*, a protracted reduction of *Dolosigranulum* and *Corynebacterium*, and reduced stability of the bacterial population.[72] Robinson et al.[73] reported that *Moraxella catarrhalis, Haemophilus influenza, Streptococcus pneumoniae*, and *Staphylococcus aureus* were the most frequently isolated bacteria in children with wheezing.

Short-term and long-term consequences of antibiotic-induced changes in the microbiota of infants and adults. Antibiotics are known to have a negative impact on the composition and diversity of the gut microbiota in adults and children. These effects can be for a short duration or extended periods.[1,4,13]

Short-term consequences

The effects of antibiotics on gut microbiota composition and diversity can last from weeks to months.[4] Antibiotic use throughout childhood leads to a decrease in the diversity and quantity of some microbial species in the gut, particularly *Bifidobacterium*, as well as low susceptibility to opportunistic infections and increased antibiotic resistance.[5] Korpela et al. analyzed feces samples from infants after a course of antibiotics in a recent longitudinal study. They discovered that after a single course of antibiotics, infant gut microbiomes exhibited varying abundances of bifidobacteria, enterobacteria, and clostridia,

which lasted for several months. Bifidobacteria levels varied the most in the infant.[26] Short-term effects also include antibiotic-associated diarrhea (AAD), *Clostridiodes difficile*–associated diarrhea (CDAD), and *Helicobacter pylori* infections.[1]

Antibiotic-associated diarrhea. Antibiotic-associated diarrhea is a condition caused due to disturbed gut microbiota and stimulated overgrowth of pathogenic or opportunistic strains following administration of antibiotics.[74] These organisms mostly include *Klebsiella pneumoniae, Staphylococcus aureus*, and *C difficile*.[8] The incidence of AAD among children ranges between 11% (outpatient setting) to 21% (inpatients).[75] Among adults, it varies between 5% and 70%.[76] The prevalence of AAD among hospitalized patients on antibiotics was 9.6%.[77] The underlying mechanism of AAD involves antibiotic exposure-driven eradication of gut microbiota and consequent reduction of antimicrobial peptides that control the numbers of intestinal bacteria. Some antibiotics target the mucus layer and tight junctions in the intestinal epithelium, exposing it to more damage. In addition, functions of the mucosal barrier may be affected by alterations in microbial proteases.[78] Antibiotics, such as cephalosporins, aminopenicillins without/with clavulanate, clindamycin, and anti-anaerobic antimicrobial agents, whether used orally or intravenously, pose a high risk of causing AAD.[79]

C difficile–associated diarrhea. In some cases, AAD can be caused by an overgrowth of *C difficile*, referred to as CDAD.[80] It can present as long-term recurrent infections and fatal pseudomembranous colitis.[81] Antibiotic use is the main cause of CDAD, and the antibiotics most frequently linked to CDAD are amoxicillin, fluoroquinolones, ampicillin, clindamycin, and cephalosporin.[1] Clindamycin has been demonstrated to have a significant unfavorable influence on intestinal microbiota, resulting in decreased resistance to pathogen colonization and an elevated risk of pseudomembranous colitis due to *C difficile* multiplication.[74]

H pylori infection. H pylori is a pathogen that inhabits the gastric mucosa. The gastric mucosa becomes inflamed as a result of *H pylori* infection.[1] This reaction is mild and asymptomatic in the majority of instances; however, in some people, it is the primary cause of peptic ulcers and chronic gastritis.[1] *H pylori* infection alters the gastric microbiota, resulting in the development of gastric dysbiosis. These changes are driven by altered pH-gradient across the mucosal surface, leading to the invasion of the gastric mucosa. Mucosal damage leads to increased adhesion and migration of immune cells, which produce inflammatory mediators that cause gastric damage and stop other microorganisms from surviving.[82,83] There is a reduction in bacterial diversity in *H pylori*-infected subjects, with *Proteobacteria, Firmicutes, Bacteroidetes*, and *Actinobacteria* being the most prevalent phyla. However, in healthy individuals, gastric microbiota is more diverse and mainly comprises of phyla *Bacteroidetes, Firmicutes, Actinobacteria*, and *Proteobacteria*.[84]

Potential long-term consequences

Antibiotic-induced effects on microbial composition may often last for as long as 2 years after antibiotic exposure. These modifications in the microbiota may result in the development of long-term antibiotic resistance, as well as physiological changes related to the immune system or metabolic function, which remain for years after antibiotic exposure.[4] A study analyzed the impact of 7 days of clindamycin treatment on the microbial composition of feces samples and found substantial alterations even 2 years after exposure. Specifically, *Bacteroides* diversity was lost, abundance of specific taxa was altered, and ARGs were upregulated. These findings show that after short-term exposure to clindamycin, the effects on the composition of the intestinal microbiota may continue for up to 2 years after antibiotic exposure.[85] Another study reported that in comparison to the control group that had not been treated with clindamycin, an increased abundance of resistant *Bacteroides* strains was reported up to 2 years after clindamycin exposure.[86] The long-term upregulation of ARG in the human gut is a concerning side-effect of antibiotic treatment.[13] Antibiotic exposure during infancy has been linked to a higher chance of acquiring obesity,[15,19,37–44] allergies, asthma,[16,17,45] and IBD[8] later in life.

Economic impact of antibiotic-associated dysbiosis

Antibiotic-associated dysbiosis increases the risk of antibiotic resistance. Resistant bacterial infections increase mortality and morbidity as well as healthcare cost. Antibiotic resistance, according

to the Centers for Disease Control and Prevention (CDC), may add nearly US$1400 to hospital bills for treating patients with bacterial infections in the United States alone. This increased expense could rise to more than US$2 billion per year in the future.[87] Several studies have shown that antibiotic-associated dysbiosis can be treated with probiotics. However, neither federal medical aid programs nor insurance companies offer coverage for probiotics.[88] Antibiotic-associated diarrhea results in higher morbidity, longer stays in the hospital, and greater use of healthcare resources. The increased duration of intensive care unit (ICU) stays and readmission rates result in an additional lifetime cost of £13,272.53 per AAD patient in the United Kingdom. The use of probiotics as a part of a regular perioperative regimen can result in significant cost savings.[89] Due to extended and frequent hospitalizations, requirements of medicines, and laboratory tests, CDAD also raises healthcare costs for patients. Healthcare expenses associated with primary CDAD and recurrent CDAD were US$24,205 and US$10,580, respectively, in 2014 in the United States.[90] In a prospective study of children aged between 6 and 12 years with acute diarrhea, the direct cost of treatment was INR 779 and INR 944, while the indirect cost was INR 937 and INR 1409 in Group 1 (which received oral rehydration therapy + zinc + *Bacillus Clausii* as probiotic) and Group 2 (which received oral rehydration therapy + zinc), respectively. The findings indicated that addition of *Bacillus Clausii* as probiotic helped reduce the duration and frequency of diarrhea, as well as the length of hospital stay, hence lowering the treatment and indirect costs.[91]

Management of antibiotic-associated dysbiosis

Clinicians should be aware of the potential interaction between gut dysbiosis and metabolic, gastrointestinal, and immunological disorders among children. This can help in ensuring an appropriate treatment approach and also initiating adequate preventive measures. Digestive problems are the main indications of dysbiosis. People with dysbiosis may frequently feel gassy or bloated.[92] Dysbiosis is suspected based on clinical symptoms, medical history, physical examination, diagnostic testing (organic acid tests, comprehensive digestive stool analysis, hydrogen breath test, and biopsy), and culture-independent approaches, including next-generation sequencing.[93–95]

Prebiotics and probiotics may be utilized to treat antibiotic-associated dysbiosis to reduce symptoms and reestablish microbial balance in light of the proven effects of antibiotics on the microbiota.[6]

Diet supplementation/prebiotics

Diet can quickly and significantly alter the composition of the GM, which will have an impact on the intestinal barrier.[96] The GM structure can be modified by a combination of different herbs and vegetables, such as the traditional Chinese herbal medication Shen Ling Bai Zhu San, while receiving antibiotic therapy. It may be beneficial in reducing the presence of harmful bacteria (e.g. *Sutterella* spp.) while increasing the number of beneficial bacteria (e.g. *Bacteroides* spp.).[97] It was demonstrated in a mouse model that prebiotic fructo-oligosaccharides might undo alterations induced by cefixime in the GM, such as a rise in the number of *Akkermansia* spp.[98] Prebiotics, such as galacto- and short-chain fructo-oligosaccharides, are nondigestible dietary items that stimulate the growth and activity of bacteria, such as *Lactobacillus* and *Bifidobacterium*, and restore healthy microbiota following antibiotic exposure.[4,99] A 6-g prebiotic supplement containing an inulin-type fructan taken daily prevented antibiotic-induced alterations in the composition of GM by increasing the abundance of *Bifidobacterium*.[100]

In a single-center, double-blind, placebo-controlled trial involving overweight/obese children between the ages of 7 and 12, prebiotic oligofructose-enriched inulin (OI) was found to selectively modify the intestinal microbiota and significantly reduce body fat in overweight/obese children.[101] Similarly, in a randomized, double-blind, placebo-controlled trial, prebiotic OI supplementation in 7- to 12-year-old obese or overweight children improved appetite control.[102] Furthermore, when prebiotics were given to infants in formula-based milk together with antibiotics, the amount of bifidobacteria in their feces was higher than when the children had only received antibiotics.[103]

Probiotic supplementation

Probiotics are dietary supplements with live microorganisms that have health benefits.[4] The microorganisms that are commonly used as probiotics include *Lactobacillus* species, *Bifidobacterium* species, *Saccharomyces* species, and

Table 1. Commonly used species as probiotics and their key features.

Probiotic species	Key features
Lactobacillus spp.[104]	• A group of lactic acid-producing, nonspore-forming anaerobes • Considered as 'friendly' bacteria taken to recolonize parts of the body to deliver nutritional benefits • Members include *Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus casei, and many more*
Bifidobacterium spp.[104]	• A group of lactic acid– and acetic acid–producing nonspore-forming anaerobes • Used as probiotics in combination with other species • Members include *Bifidobacterium brevis, Bifidobacterium infantis*, and *Bifidobacterium bifidum* amongst others
Saccharomyces spp.[104]	• A nonpathogenic yeast strain that has been used to treat and prevent diarrhea caused by a variety of sources • Includes *Saccharomyces cerevisiae* often known as *Saccharomyces Boulardii*

Bacillus spp.[105–107]	• A group of spore-forming bacteria
	• Used as probiotics for many decades
	• Members include *Bacillus clausii, Bacillus subtilis*, and *Bacillus coagulans*
	• Spore-forming bacteria have an advantage over nonspore-forming bacteria such as *Lactobacillus* spp:
	  ○ *B clausii* spores are resistant to heat and high temperatures so they can be stored at room temperature with no alterations in their viability.
	  ○ They are also resistant to acidic pH (pH < 7.0) in the stomach and intestine, allowing them to survive passage to the intestine. Of note, *B clausii* (O/C, SIN, N/R, T) was found alive in the feces for up to 12 days after a single-dose administration of *B clausii* spores
	  ○ *B clausii* strains O/C, N/R, SIN, T have been shown to be resistant to at least 14 antibiotics

Bacillus species[104–107] (Table 1). The probiotic bacteria can modulate intestinal microbiota and can help regulate immune response disorder by stimulating immune cells. The antimicrobial effects of *Lactobacilli* and *Bifidobacteria* are attributed to their influence on both local and systemic immunity. Furthermore, they compete with pathogens for nutrients and hence prevent their proliferation. They can also stimulate the release of antimicrobial substances (such as mucin) and prevents adherence of the pathogens to the epithelial barrier.[108]

Probiotics are shown to alleviate gut dysbiosis and antibiotic-associated side-effects such as diarrhea.[109,110] While most studies confirm that probiotics can be effective against gut dysbiosis, more data are needed to ascertain which probiotics are ideal for a specific group of patients, particularly given the wide variations in gut microbiota composition across individuals. Even within a single species, the health advantages of one probiotic strain may not necessarily apply to another.[111] Therefore, it is essential to devise new, individualized probiotic supplementation strategies.[6] Few next-generation technologies are being evaluated for developing microbiota-related personalized dietary recommendations and the outcomes are promising.[112]

Role of probiotics

Gut dysbiosis

Probiotics have been shown to confer protection against gut dysbiosis caused by antibiotic treatment. *B clausii* is the most popular probiotic species that can modify gut microflora and is effective against antibiotic-associated dysbiosis.[113] Prolonged supplementation with *Lactobacillus rhamnosus GG* was reported to alter the intestinal microbiota of children, resulting in a rise in *Ruminococcus, Lactococcus*, and *Prevotella* and a decline in *Escherichia*.[114] According to studies, only a few of the species belonging to the genera *Bifidobacterium* and *Lactobacillus* are beneficial in terms of their effects on body weight and metabolism.[115] A

meta-analysis revealed that the use of probiotics appears to be a practical method to reduce the prevalence of RTIs in children.[116] According to a randomized trial, younger children who experience recurring respiratory infections over the winter would benefit the most from the use of *Lactobacillus* GG (LGG).[117]

Antibiotic-associated diarrhea

There is mounting evidence that probiotic administration can aid in the treatment of AAD as well as the prevention or reduction of the risk of AAD. A multicenter, randomized, open-label, clinical trial that investigated the ability of *B clausii* to prevent AAD in Filipino infants and children who were given *B clausii* while receiving antibiotic therapy found that the *B clausii*-treated group had a decreased incidence of AAD.[118] In a longitudinal, multicenter, observational study conducted in Lebanon, an extra course of probiotics to prevent any AAD was given to 118 (48%) of the 246 recruited pediatric participants who were assigned an antibiotic treatment regimen. *B clausii* was the most commonly recommended probiotic (81.4%; n = 96). Among high-risk patients, the prevalence of diarrhea was twice in the group without probiotics compared with the probiotic group (50% *versus* 21.9%; *versus* 50.0% *p* = 0.182).[119] A meta-analysis assessing the effectiveness of probiotics for the prevention of pediatric AAD was undertaken from 1985 to 2013. Overall, probiotics lowered the prevalence of AAD (RR = 0.42, 95% CI: 0.33–0.53) in children (pooled from 22 trials).[120] Another meta-analysis of 63 studies showed a statistically significant correlation between probiotic administration and a decline in AAD ($p < .001$).[109] Several studies have shown that the consumption of probiotic combinations orally, including *L rhamnosus, Lactobacillus casei, Lactobacillus acidophilus*, and *Bifidobacterium*, lowers the risk of AAD. This effect may be caused by controlling the GM, improving the function of the gut barrier, and modifying immune responses.[121–124]

Individual or combined strains of *Lactobacillus, Bacillus, Lactococcus, Saccharomyces, Bifidobacterium, Leuconostoc cremoris*, or *Streptococcus* spp. have been shown to protect against AAD.[125] *Clostridium butyricum, Bacillus* spp., *Lactobacilli* spp., *Bifidobacterium* spp., *Lactococcus* spp., *Saccharomyces* spp., *L cremoris*, or *Streptococcus* spp., alone or in combination, were evaluated in the Cochrane comprehensive review that included 33 studies involving 6352 subjects. It was concluded that AAD is reduced by probiotics [number needed to treat to benefit (NNTB) 9; 95% CI, 7–13], with large dosages (five billion CFU per day) being preferred.[126] According to meta-analyses, certain probiotic strains may help prevent AAD. Therapy with probiotics containing *L rhamnosus* GG[127] or *Saccharomyces boulardii*[128] significantly decreased the risk of AAD in children and adults receiving antibiotics compared with placebo or no therapy. Furthermore, according to the Asian experts' guidelines on the use of probiotics and *B clausii* in the management of diarrhea in infants and children, *B clausii* may be taken into consideration to prevent AAD.[129]

C difficile–associated diarrhea. Probiotic administration has also been shown to help in the treatment of CDAD as well as the prevention or reduction of the risk of CDAD. A meta-analysis of 20 trials involving 3818 adult or pediatric patients showed that probiotics reduced the incidence of CDAD by 66%.[110] A systematic review and meta-analysis of 31 randomized, controlled trials suggested that probiotics can be used to prevent CDAD.[130] Furthermore, *Saccharomyces boulardii* administration decreased the likelihood of CDAD in children (RR, 0.25; 95% CI, 0.08–0.73).[131] A meta-analysis of clinical studies assessing probiotics for the prevention of pediatric *Clostridiodes difficile* infections (CDI) was undertaken from 1985 to 2013. In conclusion, probiotics dramatically decreased CDI in children (pooled from 22 trials).[120] In addition, according to the Asian experts' guidelines on the use of probiotics and *B clausii* in the management of diarrhea in infants and children, *B clausii* may be taken into consideration to prevent CDAD.[129]

H pylori infection. Probiotic strains can potentially increase *H pylori* eradication rate by 5–10% and are useful in the reduction of related side-effects.[132] In a randomized, double-blind, placebo-controlled trial, treatment with *B clausii* was observed to lessen the frequency of the most prevalent adverse effects (epigastric pain, diarrhea, and nausea) associated with anti-*H pylori* antibiotic treatment.[113] In comparison to the placebo, *B clausii* capsules reduced the frequency and duration of diarrhea in patients who had *H pylori* elimination therapy in a randomized, double-blind, placebo-controlled trial. In week 1, the *B clausii* group had 29% diarrhea and the placebo group had 48% ($p < 0.05$). In week 2, as compared with placebo, the incidence of diarrhea was still lower with *B clausii* (20% *versus* 7.7%) ($p < 0.05$).

From week 1 to week 2, the frequency of days with diarrhea decreased significantly in both groups ($p < 0.0001$).[133] A placebo-controlled, double-blind study found *Lactobacillus johnsonii* La1 and *S boulardii* to be effective at reducing *H pylori* burden.[134] Supplementation with *L gasseri, L casei* DN-114001, *L acidophilus*, and *Bifidobacterium infantis* 2036 was linked to significantly greater eradication rates when compared with controls in a meta-analysis of studies in which patients received antibiotic therapy for the eradication of *H pylori*.[135]

In addition, the Asian experts' guidelines on the use of probiotics and *B clausii* in the management of diarrhea in children suggested that *B clausii* may be used in conjunction with *H pylori* abolition therapy.[129] According to recent World Gastroenterology Organization (WGO) global guidelines related to *H pylori* infection, probiotic supplementation may be used to reduce antibiotic-related adverse events.[136]

Indian perspective on probiotics

It is reported that antibiotics are frequently prescribed to children in India. A study conducted in Bhopal revealed that antimicrobial agents were given to 64% of children under the age of five who were diagnosed with acute gastroenteritis in outpatient facilities.[137] Another study conducted in a tertiary referral hospital in Eastern India revealed that 535 antimicrobial drugs were given to 80% of children. In the majority of children (85.6%), antimicrobial therapy was empirical and dependent on clinical judgment.[138] Children frequently treated with antibiotics are more vulnerable to gastrointestinal problems, and thus have a special need for probiotic supplementation to maintain a healthy gut flora and a strong immune system. Acute diarrhea is a leading cause of infant and child mortality.[139] The studies summarized in Table 2 highlight the use of probiotics in the Indian setting to treat diarrhea in children.

Table 2. Studies regarding the use of probiotics in the Indian setting to treat diarrhea in children.

First author/ year	Study type	Study population	Findings
Sudha *et al.*[139]	Double-blind, randomized, placebo-controlled, multicenter study	$N = 119$ Children aged 6 months to 5 years with acute diarrhea	Compared with placebo, *B clausii* UBBC-07 significantly reduced diarrhea duration (75.66 ± 13.23 *versus* 81.6 ± 15.43 hours; $p < 0.05$) and frequency (3.46 ± 0.66 *versus* 4.57 ± 1.59; $p < 0.01$), suggesting that the strain is effective in the treatment of pediatric acute diarrhea
Bhat *et al.*[140]	Open-label randomized controlled trial	$N = 120$ Children aged 6 months to 5 years with acute diarrhea	Duration of diarrhea and hospital stay were reduced in children with acute diarrhea who received *Saccharomyces boulardii along with* ORT + zinc compared with children who received *B clausii* + ORT + zinc and ORT + zinc alone
Vidjeadevan *et al.*[141]	Three-armed randomized controlled trial	$N = 105$ Children aged 6 months to 3 years with acute diarrhea	Adding probiotics such as *Saccharomyces boulardii* and *Bacillus clausii* to ORT and zinc helped to shorten the duration of diarrhea
Das *et al.*[142]	Double-blind randomized controlled trial	$N = 60$ Children aged 3 months to 5 years with acute rotavirus diarrhea	*Saccharomyces boulardii* was shown to be safe and efficacious in children with acute rotavirus diarrhea by reducing the duration of diarrhea as well as duration of hospitalization
Lahiri *et al.*[91]	Prospective study	$N = 131$ Children aged 6 months to 12 years with acute diarrhea	*Bacillus clausii* used as a probiotic along with ORT and zinc reduced the duration (22.64 *versus* 47.05 hours; $p < 0.01$), frequency ($p < 0.01$), and hospital stay (2.78 *versus* 4.30 days) of diarrhea
Lahiri *et al.*[143]	Prospective study	$N = 160$ Children aged 6 months to 6 years with acute diarrhea	*Bacillus clausii* was found to be safe and efficacious with a significant reduction in the duration (22.26 hours *versus* 34.16 hours; $p < 0.05$) and frequency of acute diarrhea in children who received probiotic (*B clausii*) along with ORS + zinc compared with children who received ORS + zinc alone

ORS, oral rehydration solution; ORT, oral rehydration therapy.

Since the past decade, probiotics have received a lot of attention in India. The introduction of probiotic supplements has coincided with a surge in public awareness primarily in urban areas.[144] According to a survey, rising health concerns, increasing stress, changing food habits, and an increase in diabetes, cardiovascular diseases, and lifestyle-related diseases are boosting probiotic demand in India.[145] People with special requirements, such as pediatric patients, make up a large portion of India's probiotic market, and big pharmaceutical companies have been developing probiotic-based nutritional supplements for them.[146] The content and analytical validity of probiotics sold commercially in India were rigorously reviewed in a study by Kesavelu *et al*. There were notable differences in the quantity and quality of probiotics in terms of viable cell count and genus and species content among brand formulations and results of next-generation sequencing.[147]

Conclusion

Antibiotics can alter the composition and diversity of the gut microbiota in neonates, children, and adults, and may result in antibiotic-associated dysbiosis and intestinal barrier disruption. The disruption of gut microbiota and host immunity in early life, during which the microbiota and immune system are still developing, is linked to the development of immune-mediated and metabolic diseases later in life. Neonates, obese children, and children with allergic rhinitis and recurrent infections comprise the vulnerable populations for antibiotic-associated dysbiosis. The short-term effects of antibiotic use, which last from a few weeks to months, include AAD, CDAD, and *H pylori* infection. The long-term consequences include changes in gut microbiota, which remain even 2 years after antibiotic exposure, and the development of obesity, allergies, asthma, and IBD. Probiotic bacteria and dietary supplements are highly promising in preventing or restoring the equilibrium disturbed by antibiotics in the gut microbiota. Clinical trials have shown that probiotics can help prevent AAD and, to some extent, CDAD. Probiotics have also been shown to improve *H pylori* eradication rates. Prescribing antibiotics in vulnerable populations who already present with gut dysbiosis may further exaggerate the effects of dysbiosis. Therefore, it is important to consider the deleterious effects of antibiotics on gut health before prescribing antibiotics to neonates and young children. Prudent use of antimicrobials by following antimicrobial stewardship approaches is the need of the hour and can help prevent gut microbiota dysbiosis to a great extent.

Declarations

Ethics approval and consent to participate
Not applicable. This article is based on previously conducted studies and does not contain any new data collected from human participants or animals.

Consent for publication
Not applicable.

Author contributions
Dhanasekhar Kesavelu: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Supervision; Validation; Visualization; Writing – review & editing.

Pramod Jog: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Supervision; Validation; Visualization; Writing – review & editing.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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