

The Effect of Bifidobacterium on Antibiotics and Its Impact on Infant Intestines

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Abstract. This study presents the benefits of *Bifidobacterium longum* in countering the negative effects of antibiotics, caesarean delivery, and formula feeding on infant gut microbiota. Antibiotics, often used post-caesarean to prevent infections, can impede the development of neonatal microbiota, reducing bacterial diversity and altering gut structure. The microbiota of caesarean-delivered infants exhibits less diversity, a problem that can be mitigated by probiotic supplementation. Breastfeeding, rich in human milk oligosaccharides (HMO), is shown to be critical for early gut flora compared to formula feeding, which lacks these beneficial components and delays microbiota maturation. *Bifidobacterium longum*, essential for infant gut health, adapts genetically to metabolize HMOs, promoting gut development and microbial cross-feeding, essential for producing health-promoting short-chain fatty acids (SCFAs). It repairs antibiotic-induced intestinal damage and helps maintain a balanced gut microbiota. Additionally, *B. longum* offers therapeutic potential for treating colitis and functional constipation in infants and may be an effective treatment for inflammatory bowel disease (IBD), fostering immune homeostasis and intestinal health recovery. The probiotic role of *B. longum* in early life could have lasting health implications.

Keywords: Bifidobacterium; Antibiotics; gut microbiota; Breastfeeding.

1. Introduction

The most common surgical approach in obstetric care is cesarean section, it has become a successful way to preserve the lives of women and perinatal children [1]. Infection is one of the most common consequences of cesarean section surgery. Cesarean section surgery is not a polluting process, but it is also performed in a sterile atmosphere. However, pregnant women are affected by surgical trauma, blood loss, and other events that causes infection to arise during cesarean section, resulting in a high infection rate [2]. In order to save the mother from bacterial infection, the use of antibiotics is almost a necessary measure. At the same time, cesarean section prevents the fetus from contacting the bacterial flora in the vagina and cervix, leading the problem of bacterial flora imbalance in newborns.

The use of antibiotics can have an impact on the fetus, especially on the establishment of the neonatal microbiota. The misuse of antibiotics may lead to unnecessary intake of antibiotics in infants, and the lethality of antibiotics will affect a variety of important intestinal microorganisms. At the same time, the proportion of formula milk replacing breastfeeding continues to increase, and human milk oligosaccharides (HMO) are of great significance for the establishment of early intestinal flora in infants. Its absence in formula milk also has a negative impact on the establishment of the infant's intestinal flora.

Early infancy is crucial for the establishment and development of both the microbiome and the host. Antibiotic exposure in childhood, caesarean delivery, and formula feeding may disturb microbiome formation and negatively impact health later in life, inducing various diseases [3]. One of the most common aspects of these disorders is changes in the quantity and makeup of microbiome populations [4]. With the widespread use of antibiotics and the necessity of caesarean section, together with the rising antibiotic resistance documented in recent years, has sparked interest in the use of helpful bacteria, or probiotics, to aid in the recovery of illnesses by restoring intestinal homeostasis [5]. *Bifidobacterium longum* is a symbiotic bacterium that is good to the intestines and is directly associated to newborn and early child intestinal health. This article explores the role of bifidobacteria in gut microbiota restoration and early infant health.

2. The Effect of Antibiotics on the Intestine

2.1. Impact on gut microbiota composition

Lisa Maier et al. found that the selective bactericidal action of macrolides and tetracyclines may explain their significant influence on gut microbiota makeup. Microbes that are killed by the antibiotic are more likely to be accidentally lost from the population, but those that are inhibited can recover more quickly if treatment is stopped [6].

Marta Reyman et al. found that, *Bifidobacterium* spp., were less numerous in antibiotic-treated newborns compared to controls, even after controlling for method of delivery, and similarly in *Escherichia* and *Staphylococcus* spp [7].

2.2. Impact on intestinal structure

Yu Qiangqing et al. discovered that, there were substantial variations in colon length and total intestinal transit time when G+ and G-antibiotics were inhibited. Among them, the antibiotic treatment group and broad-spectrum antibiotic treatment group that suppressed G-bacteria considerably increased colon length in mice ($P < 0.001$) and significantly lengthened total intestinal transit time in mice ($P < 0.05$). Ampicillin, a G+ bacteria inhibitor, has essentially little influence on colon length or total intestinal transit time. Different antibiotic treatments can result in variable degrees of cecal hypertrophy. The group given gentamicin, which inhibits G-bacteria, significantly expanded the cecum ($P < 0.001$), followed by the group given ampicillin, which also inhibits G-bacteria, and the group given broad-spectrum antibiotics. These findings are consistent with previous research, and it is speculated that antibiotics may cause an imbalance in the intestinal microbiota, particularly the significant impact on the abundance of bacteria that maintain intestinal water transport function, resulting in a large amount of water retention in the cecum and eventually leading to cecal enlargement. Simultaneously, the ampicillin treatment group and broad-spectrum antibiotic treatment group that inhibited G+ bacteria significantly increased the fecal water content of mice, whereas the gentamicin treatment group that inhibited G+ bacteria showed no significant difference in fecal water content when compared to the control group.

Whilst, they also found that the antibiotic treatment group that inhibited G-bacteria had a significantly greater impact on the intestinal nervous system than the broad-spectrum antibiotic group and the antibiotic group that inhibited G+ bacteria. Based on the effects of various antibiotics on the structure, function, and nervous system of mice's intestines, it is possible to conclude that antibiotics that inhibit G-bacteria have dramatic impacts on the host's intestinal physiology and function [7].

3. Differences in gut microbiota between natural and cesarean delivery infants

When the baby is born via caesarean section or receives antibiotics, the natural bacterial colonization and development process is hampered [8-12]. The topic of early-life microbiome alteration is a substantial public health concern because both early exposure to antibiotics and caesarean birth are relatively widespread practices, impacting more than 50% of infants in some cultures [13, 14].

Through their research, Nicholas A. Bokulich et al. discovered that the use of antibiotics during caesarean delivery led to considerably ($P < 0.05$) higher baseline levels of phylogenetic variety, richness, and evenness in caesarean-delivered infants than in vaginally born infants. Cesarean-born kids, on the other hand, caesarean-born infants had a significant decline in these within the initial month of birth as well as caesarean-born infants thereafter showed reduced variety and depth up until the age two, particularly 8 months later. These effects were not brought on by variations in the absolute number of bacteria [4]. Among these were *Bacteroides* (96% decline, $p < 0.0001$, GLM) and *Bifidobacterium* (75% decline, $p = 0.01$, GLS). The percentage decrease in bifidobacteria caused by caesarean delivery and antibiotic use was the most obvious consequence, but it was reversed by probiotic supplementation [15].

Modern procedures, like as C-sections and perinatal antibiotics, have interfered with the mother-to-baby transmission of *B. infantis* at delivery, resulting in the loss of this essential component of the infant gut microbiota, which has caused an elevation in the pH of the infants' stool [16].

4. Formula feeding and the development of neonatal gut microbiota

Nicholas A. Bokulich et al. discovered that infants who were predominantly breast-fed (>50% of feedings) or exclusively fed formula during the initial three months. Growth rates of genealogical variety as well as microbiological diversity in fed formula children aged between the ages of 12 and 24 were significantly lower ($P < 0.05$). During the first 12 to 24 months of infancy, formula feeding changed β -diversity and lowered microbiota maturation. *Lactobacillus*, *Staphylococcus*, *Megasphaera*, as well as *Actinobacteria* proved to be more numerous in breast-fed infants throughout this time period, but other *Clostridiales* and *Proteobacteria* species were less common in fed formula kids [4]. This difference is likely due to the influence of HMO in breast milk. Human milk oligosaccharides have been found to affect the abundance of probiotic bacteria such as *Bifidobacteria*.

5. Physiological characteristics of *Bifidobacterium* and its genetic adaptation to human intestines

Bifidobacteria were shown to be vertically inherited from the mother to her infant in primates and some mammals, performing strong bile tolerance [17]. *Bifidobacteria* play a dominant role in customizing infant gut patterns. *B. longum* subtype metabolizes HMOs and other complex carbohydrate oligosaccharides using several types of enzymes, producing milk-N-disaccharide and galactose-N-disaccharide to build body tissue. *B. longum* subspecies can also collaborate with other strains to digest oligosaccharides and cross-feed to increase gut microbiota development. In terms of colonization ability, investigations have demonstrated that *B. longum* ssp. *Longum* 44Mub can be colonized in the intestines of the same people for more than 6 years from early infancy and can coexist with other *bifidobacteria* to create positive longitudinal effects [18].

The *Bifidobacterium adolescentis* organisms, which can use certain dietary polymers of carbohydrates including resistant starch to survive, is a noteworthy example of *bifidobacteria* being genetically adapted to the human colon. Numerous *bifidobacterial* species, particularly *B. breve* and *B. adolescentis*, have been shown in the past to use similarities in structure glycans involving starch, amylopectin, and the pullulan [19]. Specifically, no genes implicated in the cellular breakdown of host-derived carbohydrates are found in any of the aforementioned *B. adolescentis* chromosomes. All things considered, the results point to *B. adolescentis*'s adaptation for the adult digestive system, where dietary starch makes up an important part of the glycoprotein composition. While the adult-associated *Bifidobacterium adolescentis* taxon is predicted to colonize an environment rich in certain dietary derived from plant glycans, infant-associated *Bifidobacterium* organisms, including *B. bifidum* and *B. longum*, both of which are subsp. *infantis*, have evolved to thrive in environments rich in host-polysaccharides, which means as mucin and HMOs [19].

6. Microbial cross feeding activities affect the intestines

All *B. brevity* strain appear to have metabolic skills that allow them to survive on at least three distinct HMOs. The HMOs having a low polymer level, on the other hand, can be degraded by *B. brevity* and *B. longum*, both subsec. *longum*. To survive in the competitive neonatal gut environment, they rely mostly on cross-feeding situations in which other HMO-degrading *bifidobacterial* organisms dismantle bigger HMOs in order to obtain access to these simpler host-derived carbohydrates [20].

Carbohydrate metabolism by gut commensals results in the synthesis of short chain fatty acids (SCFA), in the intestines of humans, the most significant of these are acetate, propionate, and butyrate. These SCFAs have important roles in the body, including increasing calcium and magnesium intake, delivering nutrients to colonocytes, and activating the host's defenses. Butyrate, one of the SCFAs

generated in the colon, is a molecule of significant relevance and influence on the gut. In reality, it provides energy to the intestinal mucosa cells, promoting their reproduction. Because bifidobacteria cannot synthesize butyrate directly, they rely on a mutually beneficial cross-feeding connection to butyrogenic intestinal components including fecal bacteria *prausnitzii*. Bifidobacteria in this environment digest complex sugars to produce acetate, which in turn serves as a supply of power to feed supplementary degraders who utilize acetate to produce butyrate, an advantageous communication because both species profit from the presence of the other by metabolite metabolism, enabling them to thrive in the same biological niche. Bifidobacteria interact trophically with one another and with other intestinal components [21].

7. The Effect of Bifidobacterium on antibiotics damage

It is critical to emphasize that there is no conclusive evidence linking lower bifidobacterial numbers or changed species composition to illness. The most commonly reported microbiota alteration in the gut, however, is an abnormal bifidobacterial abundance or structure, which has been linked to a variety of illnesses. This reveals how the bifidobacteria abundance is crucial for intestinal homeostasis. The bifidobacteria signature, on the other hand, has the potential to be employed as a biomarker to more reliably determine gastrointestinal health, signaling a potential dysbiosis. Raising bifidobacterial numbers in the gastrointestinal tract, on the contrary hand, could possibly be viewed as an achievable goal for avoiding and/or treating microbiota-related diseases. Certain strains of this species have been scientifically linked to a number of health-promoting qualities. Dietetic treatments for gastrointestinal dysbiosis rely on the application of nutritional food for the ingestion of beneficial bifidobacteria (probiotics), either by themselves or in conjunction with materials (prebiotics) that promote the development of beneficial bacteria in the gut [22].

7.1. The effect of bifidobacterium on the structure and function of intestine

Yu Qiangqing et al. discovered that giving mice broad-spectrum antibiotics for 14 days to build a model of intestinal function and nerve injury resulted in significant differences in cecal weight, fecal water content, overall intestinal transport time, and colon length compared to the control group. The abnormalities in intestinal structure and function produced by antibiotics were restored to varied degrees by *Bifidobacterium 45M3*, and the cecal weight, total intestinal transit time, and colon length of the treatment group reverted to normal levels ($P < 0.05$). This suggests that *Bifidobacterium 45M3* can heal the structural and functional damage caused by broad-spectrum antibiotics in the intestine.

7.2. The effect of bifidobacteria on the diversity of gut microbiota

The organization of the intestinal microbiota in mice changed significantly after broad-spectrum antibiotic therapy, as evidenced by a substantial drop in the number of detected species and the Shannon index. This implies that there was no difference in "attacking" the intestinal microbiota in mice following antibiotic therapy, resulting in a drop in the quantity of microbial bacteria in the intestine. The microbiota diversity is also considerably different between the normal and probiotic-treated groups, which helps to understand how antibiotics affect the host gut microbiota. The following are the distinct manifestations: The relative abundance of Bacteroidetes, Firmicutes, and Verrucomimicrobia was dramatically decreased after antibiotic treatment, but Proteobacteria was significantly increased. Proteobacteria, the biggest phylum of bacteria, is known to be a G- bacterium that includes numerous dangerous bacteria. The considerable increase in Proteobacteria abundance following antibiotic therapy also highlights the disadvantages of antibiotics. The number of gut microbiota species in mice increased after treatment with various bifidobacteria, and their gut microbiota structure tended to be normal. This suggests that alterations in gut microbiota induced by antibiotics will be reversed to variable degrees after intervention with different bifidobacteria [7].

7.3. Effect of Bifidobacterium on SCFAs

The concentration of SCFAs in the cecal contents dropped considerably after treatment with several antibiotics. Antibiotic treatment significantly reduces the number of gut microbiota species in mice, resulting in gut microbiota disorder and the loss of some bacteria related to carbohydrate catabolism, which prevents the normal fermentation of complex carbohydrates from dietary sources and the production of SCFAs. All SCFAs, with the exception of valeric acid, were able to return to levels that were comparable to the blank group when treated with various bifidobacteria or after being restored for seven days. These findings suggest that adding bifidobacteria to a diet after taking antibiotics can help to rebuild the intestinal biological barrier. Combining the effects of various bifidobacteria on the intestinal structure and function of mice following antibiotic treatment, however, reveals that the 45M3 bifidobacteria have a better effect [7].

7.4. The relationship between bifidobacteria and intestinal health in infants and young children

B. infantis likes smaller HMOs and milk samples with high concentrations of these HMOs. *B. infantis* HMO decomposition creates SCFAs which include acetate, which is crucial in nutrition, intestine and immunological development, and promotes anti-inflammatory/inhibits pro-inflammatory cytokines to be produced by intestinal cells. In vivo, bacterial acetate stimulates the immune system activity of host epithelial cells. Additionally, *B. infantis*' acetate acts as a source of carbon, boosting the growth and operation of the bacteria that produce butyrate. By cross-feeding, HMO enhances the proliferation of bifidobacteria and boosts the production of butyrate, a preferred source of energy for colonocytes [22].

8. The regulatory of Bifidobacterium on other intestinal problems

8.1. Immune-related disorders

Autoimmune illnesses are those in which the body responds to its own antigens, causing tissue damage. *Bifidobacterium longum* regulates intestinal immunity and alleviates immune-related disorders by using metabolites such as extracellular polysaccharides, structural components such as peptidoglycans, and lipoteichoic acid. As a polysaccharide that can be discharged into cell osmotic culture media, extracellular polysaccharides (EPS) from *Bifidobacterium longum* play a significant influence in host immune control and are a class of efficient immune modulators.

Furthermore, whole peptidoglycan (WPG), the primary constituent of the cell wall of *Bifidobacterium longum*, is a bag-like polysaccharide and peptidoglycan polymer that maintains the bacterial cell wall's integrity and has immune activity. Intact peptidoglycan stimulates lymphocyte transformation, boosts Bcl-2 positive expression, lowers Bax gene expression, and improves tumor inhibition rate.

8.2. Colitis relief

Colitis is an inflammatory bowel illness that mostly affects the rectum, colon mucosa, and submucosa. Probiotics can help by suppressing inflammation by modulating immunological responses, improving the intestinal mucosal barrier, and controlling oxidative stress responses. By modulating immunity, *Bifidobacterium longum* can successfully treat colitis. Schiavi et al. discovered that the *B. longum*35624 sEPS-neg strain (an EPS negative mutant) may stimulate IL-12p70 and IFN production in human peripheral blood mononuclear cells in vitro. *B. longum* 35624 can inhibit T cell metastatic colitis and enhance IL-17+ lymphocyte proliferation in the gut. Srutkova et al. discovered that strain *B. longum* 7952 lowers TNF and IFN release by mesenteric lymph node cells while increasing zonulin-1 and occlusive factor in the colon to ameliorate acute colitis.

8.3. Bifidobacterium longum and functional constipation in infants and young children

The mechanism of action of *Bifidobacterium longum* in the therapy for functional constipation is primarily focused on two elements: First, in the colon, it ferments complex carbohydrates, creating metabolites such as SCFAs and BAs. SCFAs lower intestinal pH, raise osmotic pressure, increase water secretion, improve smooth muscle peristalsis and contraction, decrease food residue retention in the colon, and increase bowel frequency. Meanwhile, SCFAs promote the expression of TPH1 and the production of 5-HT, thereby stimulating the response of mucosal mast cells, inducing excitability of colonic motility, and promoting defecation via fatty acid receptors FFA 2 and FFA 3. The second is that *Bifidobacterium longum* can fight gut infections, and its distinct gene sequence creates antibacterial chemicals that are unique. It can inhibit many Grams negative and positive bacterial pathogens after being mediated by organic acids such as lactic acid and acetic acid, enhancing intestinal peristalsis and improving fecal characteristics [18].

8.4. Bifidobacterium longum and childhood inflammatory bowel illness

IBD is a non-specific immune disorder a section of the digestive system ulcerative colitis (UC) and Crohn's disease (CD). In recent years, research has discovered that treating IBD in babies and young children with *Bifidobacterium longum* is a safe, acceptable, and clinically effective medication.

Bifidobacterium longum mediating the microbiota intestinal epithelial cell intestinal immune interaction, stimulating B cell differentiation to produce IgA, initiating Tregs, secreting immune cells Th 1, Th 17, and ILC 3 s to maintain immune homeostasis, thereby inhibiting IBS. Additionally, *bifidobacterium longum* is involved in the fermentation of dietary fiber to generate SCFAs. GPR 41 and GPR 43 identify, destroy, and remove mutated cells in the body by activating the G protein coupled receptor signaling pathway. GPR 109 A inhibits the activation of the NF- κ B signaling pathway, which is mediated by immune cells and intestinal epithelial cells, assisting in the repair of damaged intestinal epithelium, improving intestinal permeability, achieving anti-inflammatory and anti-inflammatory effects, alleviating diarrhea, and improving fecal characteristics, and thus promoting the recovery of children's intestinal health [18].

9. Conclusion

Cesarean section has grown more prevalent in the birth of pregnant women as surgical procedures have matured. However, medicines are still required to treat infection concerns associated with cesarean section. Whether it is the use of antibiotics during delivery or the ingestion of antibiotics for various reasons after birth, it can have a significant impact on the baby. The harm of unnecessary ingestion of antibiotics in neonates is considerable, mainly focusing on the impairment of microbiota structure and abundance, especially in non-breastfed infants born by caesarean section. This caused varying degrees of damage to their intestinal structure and function. Taking *Bifidobacterium* can reverse the damage caused by antibiotics. Although studies have shown that cross-feeding with *Bifidobacterium* can help infants achieve a higher level of HMO utilization, and that *Bifidobacterium* regulates the intestinal biological barrier to improve antibiotic-induced intestinal motility and structural damage, there are still irreversible issues, such as *Bifidobacterium* only repairing intestinal structure and function damage caused by broad-spectrum antibiotics, which has not yet been fully proven. Other scholars must continue to investigate these topics.

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