IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 18, Issue 6 Ser. 2 (Nov. – Dec. 2023), PP 10-13
www.Iosrjournals.Org

Tiny Allies, Big Impact: A Comprehensive Exploration Of Infant Gut Microbiome And Its Lifelong Health Implications

Pooja Katira[1], Ritvik Patel[2], Gopinath G Gangadharan[3], Sai Vikas Pathakota[4], Gabriela Fernandes[5,6]

[1] *Henry M. Goldman School of Dental Medicine, Boston University, Massachusetts, USA*
[2] *Krishna Vishwa Vidhyapeeth, School of dental sciences, Karad, Maharashtra, India*
[3] *Clinical Education Fellow, George Elliot Teaching and Education Centre, College Street, Nuneaton, United Kingdom*
[4] *Department of Orthopaedics, Manipal Hospital Yeshwanthpur, Bengaluru, Karnataka, India.*
[5] *Department of Periodontics and Endodontics, University at Buffalo, SUNY Buffalo, New York, USA*
[6] *Department of Oral Biology, University at Buffalo, SUNY Buffalo, New York, USA*

Abstract:
The escalating recognition of the gut microbiome's substantive implications for infantile health has become increasingly pronounced and is poised to persist in this trajectory. The gastrointestinal microbial milieu undergoes formative processes during infancy, intricately entwined with immune system maturation and marked by considerable inter-individual variability. Consequently, the nascent years constitute a pivotal phase conducive to the establishment of a salubrious microbiome, subject to environmental influencers such as delivery mode, gestational age, and, notably, early-life nutritional interventions. This chapter undertakes a comprehensive synthesis of the current comprehension surrounding the ontogeny of the pediatric gut microbiome, its integral involvement in infant immune ontogeny, the assorted determinants governing microbial colonization, and the empirically grounded health advantages conferred by prebiotics and probiotics in fortifying pediatric gut well-being. The overarching tenet posits that the human gut microbiome assumes a pivotal role in the continuum of health and malady, commencing from the prenatal epoch and extending throughout childhood.

Date of Submission: 12-11-2023 Date of Acceptance: 22-11-2023

I. Background

The first 1000 days- right from the time of conception to 2 years of age – lay down the foundation of child's future health. During this critical period, the paediatric gastrointestinal tract undergoes series of changes, including the establishment of the gut microbiota for normal growth and development. The human gastrointestinal tract is a complex and dynamic environment harbouring trillions of microbial cells which form a symbiotic relationship with the host and play a vital role in both health and disease. This population of microbes living in the gut (and the collection of genes represented by them, known as the gut microbiome) has been referred by some scientists as "forgotten organ". The specific microbial composition may differ among healthy individuals, but the functional repertoire of the microbiome remains constant. These microbes play important roles in mammalian homeostasis, including providing essential nutrients, metabolizing dietary fibre into short chain fatty acids, and ensuring proper development of the immune system. Therefore, the intestinal microbiota is considered as a crucial factor for normal early life development and lifelong health. Since it is established in early years of life, it is of particular importance to support a child's gut microbiome to thrive while they're growing. It is believed that up to the age of four or five, children's microbiome remains pliable, making this an appropriate time to build a strong and healthy gut. While some researchers suggest that the paediatric microbiome reaches a relatively stable, adult-like configuration within the first 3 years of life, other studies have demonstrated continued development through childhood into the teenage years. Once the microbiome becomes well established, it is harder to change.

Establishment of early life gut microbiome

Until recently, it was believed that children were born with a sterile gut, with infant gut colonization beginning at the time of delivery, when the neonate is exposed to an avalanche of microbes, starting with those from mother's vaginal and faecal microbiotas. However, recent work demonstrating the presence of a microbial community in the meconium, a new-born's first intestinal discharge, has challenged this notion. While still controversial, it is now clear that microbial colonization of the infant gut may begin in utero as additional evidence suggests microbial colonization of the placenta, amniotic fluid and the umbilical cord.

Following birth, many factors have an effect on the development of the neonate's gut microbiome, including type of delivery, exposure to antibiotics, and breastfeeding status. The gut microbial composition changes over a period of time, in response to the infant's external environment and nutrition. The very first microbes to colonise the gut soon after birth are bacteria such as *E. coli* and *Streptococci* sp. Next, *Staphylococcus*, *Enterococcus* and *Lactobacillus*-like species take over. However, within the first week of life, the gut develops a very uneven bacterial community, often largely dominated by one or a few taxa, usually belonging to the genera *Escherichia*, *Clostridium*, *Bacteroides* or *Bifidobacterium.* The introduction of solid food at around 4-6 months is associated with a shift in the infant microbiome to more closely resemble adult profiles, however, the paediatric microbiome remains flexible for at least the first 3 years of life. This suggests a period of relatively malleability and implies that diet in early childhood may have a huge impact on lifetime microbiome composition and associated health impacts.

Immunity through the gut

Undoubtedly, one of the main routes through which the early microbial colonization of the gut will shape the health of an individual is because of its close interaction with the immune system. Around 70-80% of the immune cells are located in the gut – specifically, within the inside lining of the intestines, in a single layer of cells known as the "epithelium". Because the intestines are long, and the lining is highly folded, the gut epithelium represents the body's largest and most important interface with the outside world. By acting as a physical barrier, and by hosting many of the body's immune cells and tissues, the gut epithelium is part of the first line of defence against potentially harmful substances.

A healthy gut microbiota and gut is essential for a healthy immune system. A diverse gut flora is the healthiest. A healthy microbiota – characterised by a diverse and well-balanced array of microbes – can directly protect against intestinal pathogens. Furthermore, a healthy gut microbiota is necessary for the development of a resilient and well-functioning immune system.

It's not surprising that the alterations in gut microbiota have an impact on the developing immune health since the bacteria interact with the immune system in a number of ways and modulate its activity. Innate immunity, the very first line of defence against microbes, is most developed in the intestinal tract, where a range of immune and epithelial cells encode receptor molecules for ligands of microbial origin. In response to such ligands, cytokines are produced that shape the differentiation of the naïve T cells of the adaptive immune system, which can differentiate into regulatory cells (Tregs) or into different types of helper cells (Th), mostly Th1, Th2 and Th17. An inadequate microbial colonization of the gut causes an imbalance between regulatory cells and their effector targets, the different Th cells, and the subsequent deregulation of immune responses can promote a variety of diseased outcomes. An unbalanced bacterial flora with too many opportunistic pathogens can shift the immune system to an increased inflammatory state with a so-called "leaky gut".

Determinants of gut microbiome colonization in neonates

A new-born's first gift from mother is the transfer of healthy microbes. Some are transferred through the process of breastfeeding and skin-to-skin contact, but quite a lot of microbes are attained during passage through the birth canal. This means that if the baby is delivered by caesarean section, they might miss out on a valuable bacterial starter kit because of the lower microbial diversity observed in infants born by caesarean section. Because a child's earliest years form the basis of gut community that will persist throughout adulthood, the resulting disturbances can have serious health consequences in long term. Microbiotas of babies born by vaginal delivery resemble their own mother's vaginal microbiota, which is dominated by *Lactobacillus*, *Prevotella*, or *Sneathia*. However, in infants born by C-section, microbiota is mostly similar to that of the skin which is dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*. Also, preterm infants may show disturbed development of healthy host–microbiota relationships early in life due to underdeveloped intestines. These infants have been shown to have differences in microbiome diversity, dependent on gestational age. Dysbiosis in the preterm infant gut has been linked to delivery method, steroid use, and antibiotic use, all of which affect intestinal microbiome development.

After birth, the new-born receives immunity shot in the form of colostrum (mother's first milk produced immediately after birth) and followed by mature breast milk. Breast milk plays a major role in shaping the intestinal microbiota and the immune system of the infant. An important difference between breast milk and infant formula is the presence of prebiotics, oligosaccharides, and antibodies, which can selectively modulate bacterial abundance. Breast milk may contribute directly to the infant gut microbiome as it contains *Bifidobacterium*, *Streptococcus*, and *Lactobacillus* species. However, the composition of human breast milk is largely modulated by maternal health status. The oligosaccharides of human milk (HMO), one of the main immune-nourishing components of breast milk, are only partially digested in the small intestine and are mostly fermented by the colon, mainly by *Bifidobacterium*, to produce short-chain fatty acids that feed the beneficial gut microbiota. Therefore, HMOs function clearly as prebiotics by providing selective substrates for development of a *Bifidobacterium*-rich microbiota. Microbiotas of breast-fed and formula-fed infants report significant differences, with breast-fed infants showing increased colonization of *bifidobacteria* and *lactobacilli.*

Maternal diet is an important factor affecting the composition of breast milk and can have an impact on the levels of the immune factors that it carries. It also influences the development of the infant's immune cells. The fatty acids (FA) present in the maternal diet, reflected in breast milk, carry special relevance for the development of immune system of the infant and his/her susceptibility to immune disease.

Now that we know the role of gut microbiota in immune homeostasis, it follows that antibiotic administration brings along with it the risk of altering the basic equilibrium by affecting microbiota composition. Thus widespread use of antibiotics in initial years is a serious concern as it may have unintended long-term health consequences. Studies suggest that early and frequent use of antibiotics and potentially other medications during childhood is an essential determinant of microbiome composition, which may impact future disease risk. Antibiotics usage causes a decline in microbiome diversity and lessens resident beneficial commensals in the gut.

Due to the important role the gut microbiome plays in the development of the immune system, it has been hypothesized that the gut flora may influence the host response to vaccines. In literature, there are very few studies investigating microbiome composition and vaccination, the data suggests that microbiota play a role in vaccine response. It is yet to be determined if vaccination induces any changes in the microbiome.

Early exposure to pets has been associated with increased bacterial richness and diversity in the infant gut microbiome, which may protect against obesity and allergies. The presence of siblings in the household has been associated with both increased diversity, as well as with reduced diversity and richness, and with differences in specific bacteria. Consistent with the hygiene hypothesis, it is likely that exposure to microbiota from pets and other children can contribute to development of a healthy microbiome. Thus developing and maintaining a balance between the intestinal microbiota and the immune system is an essential and dynamic process during the first 1000 days and beyond, influencing lifelong health.

Health benefits of probiotics and prebiotics in infants and young children

Probiotics are live microorganisms that when being administered in appropriate dose, they confer benefit of health to the receiver. They can be found in natural sources, such as fermented and cultured foods (e.g., yogurt, kefir, buttermilk), or supplemental forms such as liquids, powders and capsules. Although many different types of bacteria can be classified as probiotics, the majority fall into one of two broad groups: *lactobacillus* and *bifidobacterium.* Well-researched strains that appear to be safe for most children include *Lactobacillus rhamnosus GG* (LGG), *Bifdobacterium lacti,* and *Lactobacillus reuteri.* Probiotics help maintain a healthy gut microbiome possibly by increasing the number of healthy microbes in the gut, stimulating immune function, and inhibiting the colonization of potential pathogens (i.e., harmful bacteria, yeasts, and protozoa). A growing amount of literature finds that probiotics represent a safe and effective way to support a healthy gut microbiota during early development. Incorporating probiotic foods or supplements into a child's diet can:

- Decrease the need for antibiotic treatments in children attending day-care.
- Promote a healthy immune response in babies delivered via caesarean section
- Ameliorate symptoms of antibiotic-associated gastrointestinal distress
- Support the immune health of infants at "high risk" for allergies and skin dysfunctions
- Promote overall gastrointestinal health and function

Literature on probiotics states that both foods and supplements can provide effective support for children's gut health. Whether one delivery method is preferable to the other will likely depend on the child. Studies show that probiotics are generally safe for most children, with several possible exceptions including preterm infants, children with compromised immune systems, and children using intravenous medical devices. Although cases of serious side effects are extremely rare, it is advisable to speak to child's paediatrician about whether they are a suitable candidate for probiotics before exposing them to either foods or supplements.

Prebiotics are non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon. It helps in digestion, increasing the number of healthy gut commensals and enhances valuable vitamins production. Good bacteria prevent growth and development of disease-causing bacteria, thus forming a crucial role in regulating the immune system. From infants to adults, prebiotic intake is a must. For new-born babies it is not easy to eat natural sources of prebiotics like onions, garlic or banana, and hence breast milk is essential for them. After knowing and understanding the positive effects of oligosaccharides on paediatric gut health, researchers have developed a non-human milk oligosaccharide as a substitute. Most common prebiotics developed for infants include galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), polydextrose, inulin and their mixtures. Among these the most studied prebiotic is a combination of Galacto-oligosaccharides and Fructo-oligosaccharides (GOS and FOS)

In cases of insufficient breast feeding, infant formula containing GOS/ FOS (oligosaccharides) should be considered. Lack of beneficial bacteria in infants makes them susceptible to common gut infections. Literature shows clinical benefits of prebiotics in terms of reduced incidence of diarrhoea, upper respiratory tract infections, lesser use of antibiotics, lesser allergies and softer stools. Moreover, US FDA and European Food Safety Authority (EFSA) considered prebiotics as safe for both preterm and full-term infants and no side effects have been reported. Ultimately, prebiotics serve as a useful tool in making every child a healthy child by sticking to the golden old rule- "Prevention is better than Cure" And as it is said, a healthy gut is a key to a healthy child!

References:

[1]. Agrawal, S., S. Rao And S. Patole. "Probiotic Supplementation For Preventing Invasive Fungal Infections In Preterm Neonates--A Systematic Review And Meta-Analysis." Mycoses 58, No. 11 (2015): 642-51.

[2]. Davis, E. C., A. M. Dinsmoor, M. Wang And S. M. Donovan. "Microbiome Composition In Pediatric Populations From Birth To Adolescence: Impact Of Diet And Prebiotic And Probiotic Interventions." Dig Dis Sci 65, No. 3 (2020): 706-722.

[3]. Gao, J., H. Wu And J. Liu. "Importance Of Gut Microbiota In Health And Diseases Of New Born Infants." Exp Ther Med 12, No. 1 (2016): 28-32.

[4]. Ihekweazu, F. D. And J. Versalovic. "Development Of The Pediatric Gut Microbiome: Impact On Health And Disease." Am J Med Sci 356, No. 5 (2018): 413-423.

[5]. Shankar, V., R. Agans, B. Holmes, M. Raymer And O. Paliy. "Do Gut Microbial Communities Differ In Pediatric Ibs And Health?" Gut Microbes 4, No. 4 (2013): 347-52.

[6]. Videhult, F. K. And C. E. West. "Nutrition, Gut Microbiota And Child Health Outcomes." Curr Opin Clin Nutr Metab Care 19, No. 3 (2016): 208-13.

[7]. Yamashiro, Y. "Gut Microbiota In Health And Disease." Ann Nutr Metab 71, No. 3-4 (2017): 242-246.