LUMEN ET VIRTUS

Microbiome and its relevance in the various pediatric pathologies: A systematic review

https://doi.org/10.56238/levv15n40-029

Isabela Malafaya Rosa[1], Maria Eduarda Ferreira Paiva Carvalho[2], Túlio Vilela Oliveira[3], Raira Delalata de Castro Meira[4], Maria Eugênia Alves Martins de Araújo Tristão[5].

ABSTRACT

Objective: To analyze the scientific evidence on the role of the gut microbiome in pediatric pathologies, identifying clinical manifestations and treatment methods. Methodology: Systematic review guided by the question: "What is the biological and immunological mechanism regarding the interaction between the microbiome in susceptibility and in the development of different pathologies in pediatric patients?". Searches were performed in the PubMed Central (PMC) database using the descriptors: Intestinal Microbiome, Dysbiosis and Children. A total of 210 articles were found, of which 31 were selected after applying the inclusion and exclusion criteria, and 14 articles were chosen to compose the collection. Results: The gut microbiome is crucial in the development of pediatric pathologies such as inflammatory bowel diseases, allergies, and metabolic disorders. Clinical manifestations range from gastrointestinal symptoms to systemic complications. Treatments include dietary interventions, probiotics, and fecal microbiota transplantation. The prevention and management of these conditions require a multidisciplinary approach. Conclusion: The interaction between the gut microbiota and the development of health conditions, such as allergic, respiratory, metabolic, neurodevelopmental, and psychiatric diseases, evidences its central role in immune, metabolic, and cognitive regulation since childhood. Dysbiosis is associated with diseases such as asthma, cystic fibrosis, obesity, metabolic syndrome, autism, and depression. Early interventions, such as balanced diets, hold promise for prevention and management. Future studies should focus on targeted microbiological therapies to prevent and treat pathologies associated with dysbiosis.

Keywords: Gut microbiome, Dysbiosis, Pediatric pathologies.

[1] Graduated in medicine from the University of Franca (UNIFRAN), Franca - SP and resident in pediatrics at Santa Casa da Misericórdia de Franca
Email: isabelamalafayar@hotmail.com
[2] Medical student at the University of Franca (UNIFRAN), Franca – SP
[3] Medical student at the University of Franca (UNIFRAN), Franca – SP
[4] Medical student at the University of Franca (UNIFRAN), Franca – SP
[5] Medical Degree from the University of Franca (UNIFRAN), Franca - SP
Pediatrician specialized in pediatric palliative care, pediatric and neonatal ICU and pediatric nutrition

INTRODUCTION

Human beings maintain a deep symbiotic relationship with microorganisms. The human body is home to 10 to 100 trillion microbial cells. Most of these microorganisms reside in the gut, which provides a warm, stable, and nutrient-rich environment. There is significant variation in microbial composition in different areas of the body, with a notable distinction between health and disease states. Although the term microbiota is occasionally used interchangeably with microbiome, microbiota refers to organisms that live in a specific environment, while microbiome refers to microorganisms and their genes present in a given environment. The microbiome contains about 3.3 million active genes, compared to 22,000 human genes. The gut microbiota consists of organisms that live in the gut, accounting for about 60% of the dry weight of feces; 99% are anaerobic bacteria. Although bacteria form the majority of the microbiome, viruses, archaea, and eukaryotes are present in smaller numbers, but we should not ignore their presence (SAEED et al., 2022).

Microbial colonization, with more than 1000 different species, plays a crucial role in the development and maturation of the gut. There is evidence that this colonization begins in the womb, with the presence of bacteria blocked in the meconium, amniotic fluid, and placenta of healthy full-term babies. After birth, the microbiota of newborns from vaginal delivery resembles the mother's vagina, while in those born by cesarean section, the microbiota resembles the maternal skin. Over time, the infant microbiota undergoes changes as the diet evolves, from a simple neonatal microbiota dominated by facultative anaerobic bacteria, such as Enterobacteria, Enterococci and Streptococci, to a more complex microbiota, characteristic of adults, in the first years of life, with greater diversity and ability to synthesize vitamins and digest polysaccharides. However, the infant microbiota continues to develop during childhood and adolescence. Although it is similar to the adult in terms of the number of species blocked, the gut microbiota of children and adolescents may differ in the relative proportions of bacterial genera. Children have a higher abundance of Bifidobacterium spp., Faecalibacterium spp., and members of the Lachnospiraceae family compared to adults, whose microbiota is dominated by Bacteroides spp (SAEED et al., 2022).

The microbiome also differentiates in children, with more genes involved in amino acid manipulation, vitamin synthesis, mucosal inflammation activation, and oxidative phosphorylation, in contrast to adults, who have more genes associated with inflammation and obesity. Thus, as expected, both the microbiota and the gut microbiome undergo continuous development throughout life (SAEED et al., 2022).

The gut microbiota strongly influences the normal physiological development of the gut, aiding in the maturation and differentiation of the intestinal mucosa as well as the immune system. It limits the growth of pathogenic and environmental pathogenic microorganisms, competing with them and inhibiting their ability to invade and establish themselves in the ecosystem. Some strains of the microbiota are capable of secreting bacteriocins, antimicrobial substances that prevent hydration from other bacteria (SAEED et al., 2022).

The gut microbiome plays an essential role in child development. This development encompasses the biological, psychological, and emotional transformations that occur from birth to the end of adolescence. There are specific milestones that ensure that development progress is on schedule, and each area is carefully monitored. In addition, anthropometric indicators generally follow pre-established growth curves. At each visit to the pediatrician, physical growth, broad motor development, fine motor development, social and emotional development, language development, and cognitive development are evaluated. Child development can be divided into four distinct phases: infancy, preschool years, middle childhood, and adolescence. Deviations from predefined milestones can be early signs of disease, whether due to malnutrition or obesity, delayed social development in cases of Autism Spectrum Disorder (ASD), or conditions such as food allergies and asthma. In each of these issues, the gut microbiome plays a relevant role. The suggested connection between the gut microbiome and child development offers a unique opportunity for new approaches to health prevention, one of the pillars of pediatric medicine. (RONAN et al., 2021)

The objective of this article is to analyze the complex synergistic interaction between the role of the gut microbiome in the development of several pediatric pathologies, exploring the clinical and epidemiological implications of the condition. In-depth analysis of the evidence is intended to be a useful resource for healthcare professionals, researchers, and academics, contributing to the improvement of diagnostic and therapeutic approaches.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of the role of the gut microbiome in the various pediatric pathologies, as well as to demonstrate the main methods used in the treatment of these conditions, aiming to ensure a greater clinical elucidation of this topic. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What is the

biological and immunological mechanism related to the interaction between the microbiome in susceptibility and in the development of different pathologies in pediatric patients?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Three descriptors were used in combination with the Boolean term "AND": Intestinal Microbiome, Dysbiosis and Children. The search strategy used in the PMC database was: Intestinal Microbiome AND Dysbiosis AND Children. From this search, 210 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 210 articles were found. After applying the inclusion and exclusion criteria, 31 articles were selected from the PubMed database, and a total of 14 studies were used to compose the collection.

DISCUSSION

In the human body, more than 40 trillion bacteria from about 1000 species inhabit the intestines, oral cavity, respiratory system, skin, and genitourinary tract. There is bacterial microbiota in each region, but most bacteria are located in the intestines. The gut microbiota encodes more than three million genes that are capable of generating various metabolites. Research focused on the gut microbiota has shown that it plays a crucial role in human health by adjusting the host's immune defenses, as well as regular metabolism and brain function. The imbalance in the gut microbiota, known as dysbiosis, during early life is related to the emergence of various diseases, such as allergic diseases, inflammatory bowel diseases (IBD), irritable bowel syndrome, necrotizing enterocolitis, diabetes, obesity, cardiovascular diseases, autism spectrum disorder, among others (AKAGAWA; KANEKO, 2022)

The gut microbiota ferments dietary fibers and produces short-chain fatty acids (SCFAs) in the gut. SCFAs are fatty acids with less than six carbons, such as butyric acid, acetic acid, and propionic acid. SCFAs are absorbed by the colon. Butyric acid serves as an energy source for the epithelial cells of the colon, while acetic acid and propionic acid are absorbed through the portal vein, occurring as substrates for energy and lipid production. SCFAs are considered important nutrients for energy generation in the human body, but

recent chemical analysis has revealed that they also have positive effects on the host's metabolism and immune system. There are several receptors that regulate SCFAs and regulate human metabolism: G-protein-adapted accessories (GPRs) (GPR41, GPR43, and GPR109A); olfactory receptor 78 (Olfr78), which is also identified as GPR; and the hydrocarbon receptor aryl. In addition, the gut microbiota influences the metabolism of vitamins, amino acids (such as methionine and tryptophan), melatonin, gamma-aminobutyric acid, bile acids, urea, cholesterol, and drugs (AKAGAWA; KANEKO, 2022).

The role of the host genotype in determining the composition of gut bacteria has recently been recognized. To study the genetic factors involved, the classic approach used is the comparison of data between monozygotic (MZ) and dizygotic (DZ) twins. A large study conducted with women (n = 416) showed that monozygotic women have a gut microbiota composition more similar to that of dizygotic women, highlighting the influence of genetic factors on the gut microbiome. In addition, the study includes several hereditary bacterial species, most of which belong to the twin family. Another relevant factor that impacts the development of the microbiome is the type of delivery. Babies born vaginally acquire bacterial species from the vaginal and perianal region, such as Lactobacillus, Prevotella, or Sneathia spp., while those born by cesarean section have lower exposure to these bacteria, resulting in a different microbiome composition (PANTAZI et al., 2023).

Gestational age is another important factor; the intestine of premature infants is colonized mostly by Enterobacter, Staphylococcus, and Enterococcus, while in full-term infants, colonization is dominated by Bacteroides, Bifidobacterium, Parabacteroides, and Escherichia. Breastfeeding also plays a vital role in shaping babies' microbiome. Breast milk contains several prebiotics, such as human milk oligosaccharides, which selectively promote the growth of beneficial bacteria, such as Bifidobacterium and Lactobacillus. However, infants fed with milk formulas have microbiomes composed of Roseburia, Clostridium and Anaerostipes. Dietary factors also influence the microbiome, such as high-fiber diets, which stimulate the development of bacteria capable of degrading fiber, resulting in a more diverse and stable microbiome (PANTAZI et al., 2023).

The concentration of bacteria (such as ampicillin, cephalothin, and clindamycin) in umbilical cord blood reaches its peak within 1 hour of maternal serum peak during pregnancy. Due to the limited activity of fetal liver enzymes responsible for drug metabolism, compared to adults, the unmetabolized drug accumulates in fetal tissues. Exposure to antibiotics during childbirth, both to prevent sepsis due to group B streptococci and due to cesarean section, is quite common and impacts the neonatal gut microbiota. In addition to antibiotics, other medications often given to mothers and/or infants that affect

the gut microbiota include acid blockers, selective serotonin reuptake inhibitors, metformin, and laxatives. Recent studies have also shown that the infant microbiota can be altered by exposure to environmental toxins and maternal smoking (UNDERWOOD et al., 2020) (WANG et al., 2020).

Dysbiosis, characterized as an imbalance or inadequacy in the microbiota, is increasingly recognized as a relevant factor in the emergence of allergies in children. The healthy gut microbiota supports fundamental physiological processes such as digestion, metabolism, and modulation of the immune system. The complex interaction between gut dysbiosis and the development of allergic diseases has recently emerged as a topic of great scientific interest (PANTAZI et al., 2023).

The constitution of the gut microbiota is considered intrinsically related to the maturation and regulation of the host's immune system; therefore, any changes in this delicate balance, such as those brought about by dysbiosis, can potentially result in abnormal immune responses and, consequently, allergic diseases. The "hygiene hypothesis" suggests that less exposure to commensal and pathogenic microorganisms in the first years of life may result in inadequate stimulation and maturation of the immune system. In this scenario, dysbiosis can be a determining factor in the increase in allergies. In addition, certain bacterial species, such as Bifidobacteria and Lactobacilli, play a crucial role in maintaining immune homeostasis. They contribute to the activation of regulatory T cells, capable of reducing allergic responses, in addition to promoting anti-inflammatory cytokines, such as IL-10 (PANTAZI et al., 2023).

In addition, an innovative hypothesis suggested that dysbiosis, caused by factors such as cesarean section and antibiotic use, decreases butyric acid producing bacteria (BAPB), which reduces intestinal levels of butyric acid. This reduction can inhibit the differentiation of T cells into regulatory T cells (Tregs). The lower amount of Tregs compromises the immune system's ability to control exacerbated immune responses, thus contributing to the onset of allergic diseases (PANTAZI et al., 2023).

Asthma is a chronic and heterogeneous respiratory disease with many risk factors, which usually manifest in childhood. The interaction between environmental factors and genetic predisposition is seen as a determinant in the formation of the lung and intestinal microbiome in the first years of life. Studies show that changes in the abundance of microorganisms (microbial dysbiosis) and lower microbial diversity are associated with the development of asthma, by deregulating the gut-airway axis. Several mechanisms explain the relationship between microbial dysbiosis and the development of childhood asthma. For example, bacterial infections in the airways of infants can dysregulate inflammatory

pathways, contributing to bronchoconstriction and bronchial hyperresponsiveness. Childhood gut dysbiosis can also influence immune differentiation, resulting in an imbalance between innate and adaptive immunity, and predisposing to chronic airway inflammation and, subsequently, asthma (LIU et al., 2022).

Cystic fibrosis (CF) is a genetic disease of autosomal recessive inheritance, resulting from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulatory protein (CFTR). CFTR protein regulates fluid secretion and mucus hydration in the epithelial cells of the airways, intestine, pancreas, and hepatobiliary system. Chronic suppurative respiratory disease, resulting from the difficulty in eliminating dehydrated secretions from the airways, is the main cause of mortality. However, the majority (>90%) of individuals with CF also have gastrointestinal symptoms. CFTR dysfunction in the digestive system leads to low intestinal pH levels, thick mucus, absence of pancreatic enzymes, reduced motility, and possible poor innate immunity. These factors are pointed out as causes of gastrointestinal inflammation and increase the risk of cancer in the digestive tract in young adults. From the beginning of life, children with CF have intestinal dysbiosis, lower species diversity, and altered functionality when compared to healthy children, aggravating the inflammatory effects of the disease (TAM et al., 2022) (VAN DORST et al., 2022).

The configuration of the gut microbiota during childhood can considerably influence body growth and development. Children with low body weight tend to have a less diverse gut microbiota compared to healthy ones. Researchers suggest that lower microbiota diversity may impair nutrient absorption, resulting in poor growth. Individuals with obesity have a microbiota with a greater capacity to ferment dietary polysaccharides, increasing the absorption of monosaccharides and short-chain fatty acids, which promotes hepatic conversion of complex lipids and the subsequent formation of adipocytes (PANTAZI et al., 2023).

Metabolic syndrome (MS) has become a relevant topic globally, as it is associated with the development of diseases such as type 2 diabetes (T2DM) and cardiovascular problems. The prevalence of MS in children and adolescents has grown alarmingly. Although the condition is reversible and preventable, early diagnosis and treatment are essential to prevent future complications. Recently, microbiome-based interventions have been gaining popularity to treat and prevent metabolic disorders, as studies suggest a possible relationship between the gut microbiota and T2DM (CARRIZALES-SÁNCHEZ et al., 2021).

The relationship between the gut microbiota and obesity is well documented in adults, but still poorly investigated in childhood. Obesity correlates with an altered gut

microbiota, characterized by increased Firmicutes and reduced Bacteroidetes. This correlation occurs due to the metabolic and immunological effects of the microbiota. Obese children have higher levels of SCFAs, which tighten the link between the microbiota and obesity. Microbiota maturation patterns in childhood may influence the risk of overweight and obesity. Pregnant women with a high BMI have a higher bacteroid load, which can influence the newborn's microbiota and increase the risk of childhood obesity (SAEED et al., 2022).

The gut microbiota can influence obesity through metabolic and digestive regulation. The microbiota has effects outside the gut, affecting the brain, liver, and adipose tissue, linking to obesity, insulin resistance, type 2 diabetes, and cardiovascular disease. It can also influence dietary intake and satiety through gut peptide signaling, impacting energy regulation and systemic inflammation, both critical factors for obesity. Early modulation of the gut microbiota may be a promising strategy to combat metabolic disorders, including childhood obesity (SAEED et al., 2022).

The immune system and the nervous system are the main regulators of homeostasis, interacting to ensure the proper functioning of the body. Microglia, a component of the immune system, plays an essential role in the development of the nervous system, monitoring synapses and influencing their development. Thus, a healthy immune system in childhood is crucial for cognitive development and neurogenesis. The disruption of the gut microbiota can impact the immune system and, consequently, the nervous system and cognitive functions. Maintaining a healthy microbiota can contribute to the proper development of the immune and cognitive system (KARTJITO et al., 2023).

There is evidence that the gut microbiome influences psychiatric disorders. It is correlated with conditions such as autism spectrum disorder (ASD) and depression. Neurodevelopmental disorders are characterized by deficits that affect motor, social, and cognitive skills. Early research suggested that children with ASD have gut dysbiosis, with a higher number of Bacteroidetes and a lower number of Firmicutes, compared to neurotypical children. This dysbiosis correlates with cytokines and tryptophan homeostasis, affecting both the gastrointestinal system and the intensity of ASD symptoms. These findings support the concept of the "gut-brain axis," which suggests a bidirectional interaction between the microbiota and the brain. Although this communication occurs through neurotransmitters released by the intestinal endocrine system, the exact mechanisms are not yet completely clear (LIGEZKA et al., 2021) (DI GESÙ et al., 2021).

The existence of the brain-gut axis is widely discussed in the literature. The communication model is bidirectional: the brain influences the motor and secretory

functions of the gastrointestinal tract, while the gut microbiota affects areas of the brain, such as the amygdala and hypothalamus. Metabolites produced by the microbiota function as neurotransmitters, including serotonin, dopamine, and GABA. Microglia, which are essential for neurodevelopment, also coordinates neuroinflammation and interacts with systemic inflammation (RONAN et al., 2021).

The gut microbiota has a significant impact on a child's physical and mental development. The human brain exhibits an accelerated growth rate throughout the perinatal period, corresponding to the marked changes in the microbiota of the mother and child. The microbiota plays a key role in brain development through its effects on the production of gamma-aminobutyric acid and serotonin from tryptophan, as well as modified neurotransmitters such as norepinephrine and dopamine. Serotonin is vital for brain development. The reduction of serotonin in the brain compromises synaptogenesis and brain connectivity, resulting in long-term neurodevelopmental deficits. About 95% of the body's serotonin is produced by the gut microbiota, influencing mood and gastrointestinal function. However, scientists have discovered that serotonin is not able to cross the blood-brain barrier. Therefore, it acts predominantly on the peripheral enteric nervous system, functioning as a hormone that affects several tissues, including those responsible for regulating metabolic homeostasis (SAEED et al., 2022).

The gut microbiota plays an essential role in the health and well-being of a growing child. A combination of behaviors, such as lifestyle and eating patterns, can affect their richness and diversity early in life. In general, a varied and balanced diet seems to promote a positive modulation of the intestinal microbiota. During childhood, the food environment is crucial for forming proper eating habits, which can positively influence the gut microbiota and the health of the body. It is widely accepted that certain dietary patterns protect against chronic noncommunicable diseases (NCDs). Healthy children, who do not need special restrictions, adopt the eating habits of the environment in which they are raised (DI PROFIO et al., 2022).

CONCLUSION

The interaction between the gut microbiota and the development of various health conditions, including allergic, respiratory, metabolic, neurodevelopmental, and psychiatric diseases, highlights the central role of this ecosystem in immune, metabolic, and cognitive regulation, from early childhood. Dysbiosis, characterized by an imbalance in microbial composition, is strongly associated with the predisposition and evolution of diseases such as asthma, cystic fibrosis, obesity, metabolic syndrome, autism spectrum disorders, and

depression. The reviewed literature highlights the importance of early interventions, such as modulation of the microbiota through balanced and healthy diets, especially during the first years of life, as a promising strategy for the prevention and management of these conditions. Thus, future studies should focus on the development of targeted microbiological therapies, with the potential to act preventively and therapeutically in various pathologies associated with dysbiosis.

REFERENCES

1. Akagawa, S., & Kaneko, K. (2022). Gut microbiota and allergic diseases in children. Allergology International, 71(3), 301-309.

2. Carrizales-Sánchez, A. K., et al. (2021). Gut microbiota associations with metabolic syndrome and relevance of its study in pediatric subjects. Gut Microbes, 13(1), 1960135.

3. Di Gesù, C. M., Matz, L. M., & Buffington, S. A. (2021). Diet-induced dysbiosis of the maternal gut microbiome in early life programming of neurodevelopmental disorders. Neuroscience Research, 168, 3-19.

4. Di Profio, E., et al. (2022). Special diets in infants and children and impact on gut microbiome. Nutrients, 14(15), 3198.

5. Kartjito, M. S., et al. (2023). Defining the relationship of gut microbiota, immunity, and cognition in early life—a narrative review. Nutrients, 15(12), 2642.

6. Ligezka, A. N., et al. (2021). A systematic review of microbiome changes and impact of probiotic supplementation in children and adolescents with neuropsychiatric disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 108, 110187.

7. Liu, C., et al. (2022). Microbial dysbiosis and childhood asthma development: Integrated role of the airway and gut microbiome, environmental exposures, and host metabolic and immune response. Frontiers in Immunology, 13, 1028209.

8. Pantazi, A. C., et al. (2023). Relationship between gut microbiota and allergies in children: A literature review. Nutrients, 15(11), 2529.

9. Ronan, V., Yeasin, R., & Claud, E. C. (2021). Childhood development and the microbiome: The intestinal microbiota in maintenance of health and development of disease during childhood development. Gastroenterology, 160(2), 495-506.

10. Saeed, N. K., et al. (2022). Gut microbiota in various childhood disorders: Implication and indications. World Journal of Gastroenterology, 28(18), 1875.

11. Tam, R. Y., et al. (2022). Intestinal inflammation and alterations in the gut microbiota in cystic fibrosis: A review of the current evidence, pathophysiology, and future directions. Journal of Clinical Medicine, 11(3), 649.

12. Underwood, M. A., et al. (2020). Neonatal intestinal dysbiosis. Journal of Perinatology, 40(11), 1597-1608.

13. Van Dorst, J. M., Tam, R. Y., & Ooi, C. Y. (2022). What do we know about the microbiome in cystic fibrosis? Is there a role for probiotics and prebiotics? Nutrients, 14(3), 480.

14. Wang, S., et al. (2020). A good start in life is important—Perinatal factors dictate early microbiota development and longer term maturation. FEMS Microbiology Reviews, 44(6), 763-781.