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THE ROLE OF GUT MICROBIOTA IN THE DEVELOPMENT OF THE IMMUNE SYSTEM IN CHILDREN

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ABSTRACT: The gut microbiota plays a fundamental role in the development, maturation, and regulation of the immune system during childhood. The early years of life represent a critical period in which intestinal microbial communities and immune responses develop simultaneously and interact continuously. Microbial colonization contributes to the maturation of the intestinal barrier, development of innate and adaptive immune responses, production of regulatory T cells, and establishment of immune tolerance to harmless environmental and dietary antigens. The composition of the pediatric gut microbiota is influenced by multiple factors, including mode of delivery, breastfeeding, diet, antibiotic exposure, maternal microbiota, gestational age, and environmental conditions. Disruption of normal microbial development, known as dysbiosis, has been associated with an increased risk of allergic, autoimmune, inflammatory, and metabolic disorders in children. This article examines the major mechanisms through which gut microbiota influences immune system development and discusses the importance of maintaining a balanced intestinal microbial ecosystem during early childhood.

Keywords:gut microbiota, children, immune system, immune development, intestinal microbiome, dysbiosis, regulatory T cells, short-chain fatty acids, mucosal immunity, early life.

INTRODUCTION: The human gastrointestinal tract contains a complex and dynamic community of microorganisms collectively referred to as the gut microbiota. This microbial ecosystem includes bacteria, viruses, fungi, archaea, and other microorganisms that coexist with the host and contribute to numerous physiological processes. In children, particularly during infancy and the first years of life, the gut microbiota plays an especially important role because its development occurs simultaneously with the maturation of the immune system. This period is increasingly recognized as a critical “window of opportunity” during which interactions between microorganisms and immune cells can influence both immediate and long-term health outcomes [1].The immune system of a newborn is functionally immature and undergoes extensive development after birth. During this period, the infant must develop the ability to distinguish between potentially harmful pathogens and harmless antigens derived from food, commensal microorganisms, and the environment. The gut microbiota provides continuous microbial signals that contribute to this process. Appropriate microbial exposure promotes immune maturation and tolerance, whereas disturbed microbial colonization may lead to abnormal immune responses and increase susceptibility to inflammatory and immune-mediated diseases [1, 2].

Initial microbial colonization begins rapidly around birth and changes significantly throughout infancy and early childhood. The composition of the intestinal microbiota during this period is influenced by gestational age, mode of delivery, maternal microbial communities, feeding practices, antibiotic exposure, introduction of complementary foods, infections, geographical environment, and other lifestyle factors. The microbiota continues to develop dynamically during the first years of life and gradually progresses toward a more mature and relatively stable microbial ecosystem [3].Mode of delivery is one of the major early factors influencing intestinal microbial colonization. Infants born vaginally are exposed to maternal vaginal and intestinal microorganisms, whereas infants delivered by cesarean section may initially acquire a different microbial community influenced more strongly by maternal skin, hospital, and environmental microorganisms. These early differences may persist for varying periods and can influence microbial functions relevant to immune maturation. However, microbiota development is complex and cannot be attributed to delivery mode alone because feeding, antibiotic exposure, environment, and maternal factors also have important effects [3].

Breastfeeding is another major determinant of early gut microbiota composition. Human breast milk contains nutrients, immune components, microorganisms, and human milk oligosaccharides that selectively promote the growth of beneficial bacterial groups, particularly several Bifidobacterium species. These microorganisms participate in the metabolism of human milk components and contribute to the production of metabolites that support intestinal barrier integrity and immune regulation. The transition to complementary foods later increases microbial diversity and changes the metabolic capacity of the gut microbiome.The relationship between gut microorganisms and the developing immune system is bidirectional. Microorganisms influence immune maturation, while host immune responses regulate the composition and localization of intestinal microbial communities. This continuous interaction contributes to the establishment of intestinal homeostasis. Innate immune cells recognize microbial structures through pattern-recognition receptors, including Toll-like receptors and other microbial-sensing pathways. Controlled stimulation of these pathways contributes to the maturation of intestinal epithelial cells, macrophages, dendritic cells, innate lymphoid cells, and other components of mucosal immunity [2].

Gut microbiota also has an important influence on the development of adaptive immunity. Commensal microorganisms and their metabolites can promote the differentiation and function of regulatory T cells, which are essential for maintaining immune tolerance and limiting excessive inflammatory responses. At the same time, microbiota-derived signals influence B-cell maturation, immunoglobulin production, and the balance between different T-helper cell populations. These mechanisms help the immune system develop appropriate responses to pathogens while maintaining tolerance toward commensal microorganisms and harmless dietary antigens [1, 2].Microbial metabolites are important mediators of microbiota–immune communication. Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are produced through microbial fermentation of dietary carbohydrates and other substrates. These metabolites can influence intestinal epithelial integrity, immune-cell metabolism, inflammatory signaling, and

regulatory T-cell function. SCFAs therefore represent one of the important pathways through which intestinal microorganisms influence both local mucosal immunity and systemic immune regulation.

The intestinal epithelial barrier represents another important component of this relationship. A healthy gut microbiota supports mucus production, epithelial-cell function, tight-junction integrity, and colonization resistance against potentially pathogenic microorganisms. The microbiota also competes with pathogens for nutrients and ecological niches and contributes to the production of substances that inhibit pathogen growth. Thus, normal microbial development participates not only in immune education but also in direct protection against gastrointestinal and systemic infections.Disturbances in the normal development of the gut microbiota are generally described as dysbiosis. Dysbiosis may involve reduced microbial diversity, loss of beneficial microorganisms, excessive expansion of potentially harmful organisms, or altered microbial metabolic functions. Antibiotic exposure, particularly during critical periods of infancy, is one factor that can substantially modify gut microbial communities. Other factors such as cesarean delivery, dietary changes, infections, and environmental exposures may also influence microbiota development [2, 3].

Increasing evidence suggests that abnormal early-life microbiota development may be associated with later immune-mediated diseases. A large CHILD birth cohort study involving 1,115 children demonstrated that delayed maturation of the gut microbiota during the first year of life was associated with several allergic conditions diagnosed at five years of age, including atopic dermatitis, asthma, food allergy, and allergic rhinitis [4]. These findings support the concept that early microbial development may influence immune programming and subsequent susceptibility to allergic disease.Alterations in early-life gut microbiota have also been investigated in relation to autoimmune and chronic inflammatory disorders. The mechanisms may involve altered intestinal permeability, abnormal microbial metabolite production, impaired immune tolerance, and dysregulated interactions between innate and adaptive immunity. Nevertheless, many associations identified in microbiome research remain observational, and the exact causal relationships between specific microbial patterns and individual diseases are still being investigated.

The first three years of life appear to be particularly important for microbiome maturation. During this period, the intestinal microbial ecosystem undergoes substantial changes in diversity and functional capacity. Recent evidence suggests that disturbances occurring during this developmental period may have long-lasting effects on physiological, metabolic, and immune processes [3]. Consequently, early childhood provides an important period for studying potential approaches to support healthy microbial and immune development.Interest has therefore increased in interventions capable of modifying the intestinal microbiota, including breastfeeding promotion, appropriate nutrition, rational antibiotic use, probiotics, prebiotics, synbiotics, and other microbiome-directed approaches. However, the effects of such interventions are dependent on microbial strain, dose, age, underlying health status, and clinical outcome. Consequently, routine microbiome manipulation for prevention or treatment of immune diseases should be based on high-quality clinical evidence rather than on microbiota composition alone.

Understanding the relationship between gut microbiota and pediatric immune development has important implications for preventive medicine. Identification of microbial factors that promote appropriate immune maturation may contribute to future strategies for reducing the risk of allergic, autoimmune, inflammatory, and infectious diseases.Therefore, the aim of this article is to analyze the role of the gut microbiota in the development and maturation of the immune system in children, with particular emphasis on early microbial colonization, mucosal and systemic immune regulation, microbiota-derived metabolites, environmental influences on microbial composition, and the potential consequences of intestinal dysbiosis for pediatric health.

MATERIALS AND METHODS:This study was conducted as a literature-based review to evaluate the role of the gut microbiota in the development and maturation of the immune system in children. Scientific articles, systematic reviews, clinical studies, and recent microbiome research focusing on pediatric populations were analyzed. The literature search was performed using PubMed, Google Scholar, and other scientific databases. Priority was given to peer-reviewed publications published between 2019 and 2026, as well as highly relevant earlier studies that provided fundamental information on microbiota–immune interactions. The main search terms included “gut microbiota in children,” “pediatric microbiome,” “immune system development,” “early-life microbiota,” “intestinal immunity,” “regulatory T cells,” “short-chain fatty acids,” “dysbiosis,” “breastfeeding and microbiota,” “cesarean section and microbiome,” and “microbiota and allergic diseases.” Studies were included if they evaluated the composition or development of the gut microbiota in infants, children, or adolescents and investigated its relationship with innate or adaptive immune responses, mucosal immunity, immune tolerance, allergic disease, infection, or other immune-related outcomes. Studies focusing exclusively on adult populations, isolated case reports, duplicate publications, and studies without sufficient methodological information were excluded. The selected literature was analyzed according to several major thematic areas, including early microbial colonization, factors influencing microbiota composition, mechanisms of interaction between intestinal microorganisms and immune cells, the role of microbial metabolites, development of mucosal immune tolerance, and the consequences of dysbiosis. Particular attention was paid to the effects of delivery mode, breastfeeding, complementary feeding, antibiotic exposure, maternal microbiota, environmental factors, and diet on the establishment of the intestinal microbiome. The role of microbial metabolites such as short-chain fatty acids, especially acetate, propionate, and butyrate, was also evaluated because of their importance in epithelial barrier function, regulatory T-cell development, and modulation of inflammatory responses. In addition, the literature was examined for associations between early-life gut dysbiosis and the subsequent development of atopic dermatitis, food allergy, allergic rhinitis, asthma, autoimmune disorders, and recurrent infections. The findings from the selected studies were comparatively analyzed to identify the most consistently reported mechanisms through which the gut microbiota contributes to immune maturation in childhood. Since this study was based entirely on previously published scientific literature and did not involve direct participation of patients or collection of personal clinical information, ethical approval and informed consent were not required.

RESULTS: The analysis of the selected literature demonstrated that the development of the gut microbiota during infancy and early childhood is closely associated with maturation of the immune system. The most consistently identified factors influencing this process were breastfeeding, mode of delivery, antibiotic exposure, diet, and the production of microbiota-derived metabolites. These factors affected both the composition of intestinal microbial communities and their functional interaction with the developing innate and adaptive immune systems.Breastfeeding was identified as one of the most important factors supporting the establishment of the early-life gut microbiota. Human milk contains not only macronutrients and micronutrients but also human milk oligosaccharides, antibodies, lactoferrin, lysozyme, complement components, microorganisms, and other biologically active molecules. These components contribute to selective enrichment of beneficial intestinal bacteria, particularly members of the genus Bifidobacterium, while simultaneously supporting epithelial barrier development and immune maturation [5]. Human milk oligosaccharides are especially important because they are not primarily digested by the infant but are utilized by selected intestinal microorganisms. This process contributes to the establishment of a microbial environment favorable for immune tolerance and protection against pathogenic microorganisms.

The reviewed evidence also demonstrated an important role for microbiota-derived short-chain fatty acids. Acetate, propionate, and butyrate are among the major metabolites generated during microbial fermentation of dietary substrates. These compounds contribute to maintenance of the intestinal epithelial barrier and influence both local and systemic immune responses [6]. Short-chain fatty acids can regulate the activity and differentiation of several immune-cell populations, including dendritic cells, macrophages, B cells, and regulatory and effector T cells. Butyrate, in particular, has important anti-inflammatory properties and contributes to intestinal homeostasis. Therefore, the metabolic activity of the microbiota may be as important as the presence of individual bacterial species in the development of normal pediatric immunity.Antibiotic exposure during infancy was identified as an important factor capable of disturbing normal microbiota development. A 2024 study from the CHILD Cohort demonstrated that systemic antibiotic exposure during the first year of life was associated with alterations in the infant gut microbiome and an increased subsequent risk of atopic dermatitis. Children exposed to systemic antibiotics during the first year had a higher risk of developing atopic dermatitis, and repeated antibiotic courses were associated with progressively greater risk [7]. The study also identified reductions in beneficial organisms, including Bifidobacterium and Eubacterium species, and alterations in microbial fermentative pathways. These observations suggest that disruption of the microbiota during a critical period of immune maturation may influence subsequent immune regulation, although antibiotics remain essential when they are clinically indicated.

Mode of delivery was another consistently reported determinant of early intestinal colonization. Infants delivered vaginally are exposed to maternal microorganisms during birth, whereas cesarean delivery is associated with a different pattern of early microbial acquisition. A systematic review reported that cesarean-born infants demonstrate distinct intestinal microbial communities, including differences in the establishment and abundance of several bacterial groups

involved in early microbiome development [8]. These microbial differences have been investigated in relation to allergy and other immune-related outcomes; however, delivery mode interacts with many additional factors, including maternal health, perinatal antibiotic exposure, breastfeeding, gestational age, and the postnatal environment. Consequently, cesarean delivery alone should not be considered a direct cause of later immune disease.The findings further indicated that the intestinal microbiota contributes to maturation of mucosal immunity through continuous interaction with intestinal epithelial cells and immune cells. Microbial signals participate in the development of innate immune recognition, production of antimicrobial substances, maturation of dendritic cells, and regulation of lymphocyte responses. Beneficial commensal microorganisms also contribute to colonization resistance by competing with potentially pathogenic organisms for nutrients and ecological niches.

The adaptive immune system is similarly influenced by microbial colonization. Appropriate microbial stimulation during early life contributes to the development of regulatory T-cell responses and immune tolerance. These mechanisms are important because the infant immune system must simultaneously develop effective defenses against pathogens while avoiding excessive responses to harmless dietary antigens and commensal microorganisms. Disturbance of this balance may contribute to inappropriate inflammatory or allergic responses.

Table 1. Major Factors Linking Gut Microbiota with Immune Development in Children

Factor	Main effect on gut microbiota	Immunological significance
Breastfeeding	Promotes Bifidobacterium and provides human milk oligosaccharides and bioactive factors	Supports immune maturation, epithelial barrier function, and immune tolerance [5]
Human milk bioactive components	Selectively influence microbial colonization and activity	Support mucosal defense and protection against excessive inflammation [5]
Short-chain fatty acids	Produced by microbial fermentation; mainly acetate, propionate, and butyrate	Regulate epithelial integrity, T-cell responses, dendritic cells, and inflammatory pathways [6]
Vaginal delivery	Facilitates early transfer of maternal microorganisms	Contributes to normal early microbial colonization and immune–microbiota interaction [8]
Cesarean delivery	Associated with altered early microbial composition	May modify early immune stimulation; long-term effects depend on multiple additional factors [8]
Antibiotic exposure	Can reduce beneficial microbial populations and alter	May disturb immune maturation and has been associated with increased

	microbial metabolic pathways	risk of some allergic outcomes [7]
Dietary diversification	Increases microbial diversity and metabolic capacity	Supports development of more mature microbial and immune functions
Dysbiosis	Loss or reduction of beneficial microbes and altered microbial functions	May impair immune tolerance and promote abnormal inflammatory responses
Balanced microbial ecosystem	Maintains microbial diversity and functional stability	Supports mucosal immunity, pathogen resistance, and immune homeostasis

The analysis also demonstrated that microbiota composition changes substantially after the introduction of complementary foods. Increasing dietary diversity provides new substrates for intestinal microorganisms and promotes expansion of bacterial groups capable of fermenting complex carbohydrates. This transition contributes to increased microbial diversity and production of metabolites involved in intestinal and systemic immune regulation.

Importantly, the findings suggest that a healthy microbiome cannot be defined by the presence of a single bacterial species. Instead, immune development appears to depend on the combined composition, diversity, functional capacity, metabolic activity, and stability of the intestinal microbial ecosystem. Different microorganisms may perform overlapping biological functions, and microbial metabolites can influence immune responses even at sites outside the gastrointestinal tract.The reviewed studies also support the concept of a critical early-life developmental period. During infancy and the first years of childhood, both the microbiota and immune system undergo rapid changes. Disturbances occurring during this period may therefore have more significant consequences than similar disturbances occurring later in life. Nevertheless, the relationship between gut microbiota and disease remains complex, and many studies demonstrate associations rather than direct causality.

Overall, the results indicate that breastfeeding, balanced nutrition, appropriate microbial colonization, microbiota-derived metabolites, and rational use of antibiotics are among the most important factors influencing the gut–immune axis during childhood. Preservation of a functionally balanced intestinal microbiota may contribute to the development of effective immune defense, appropriate immune tolerance, and maintenance of intestinal homeostasis.

DISCUSSION: The findings of this review indicate that the gut microbiota is an important regulator of immune system development during childhood, particularly during infancy and the first years of life. The close interaction between intestinal microorganisms, microbial metabolites, epithelial cells, and immune cells supports the concept that the gut microbiome functions as an active component of immune maturation rather than as a passive collection of microorganisms. Early microbial exposure appears to contribute to the development of both innate and adaptive immune responses, while disturbances in microbial colonization may alter immune tolerance and inflammatory regulation.One of the most important observations is the strong influence of breastfeeding on early microbiota development. Human milk provides not only nutrients but also

immunoglobulins, human milk oligosaccharides, antimicrobial proteins, and other bioactive substances that shape microbial composition and support mucosal immunity [5]. The enrichment of Bifidobacterium species in breastfed infants may be particularly important because these microorganisms participate in the metabolism of human milk oligosaccharides and contribute to the production of beneficial metabolites. This supports the view that breastfeeding may promote a microbial environment favorable for immune tolerance and protection against excessive inflammatory responses.

The role of microbiota-derived short-chain fatty acids is also highly significant. Acetate, propionate, and butyrate are not simply products of bacterial metabolism; they are important signaling molecules that influence epithelial integrity, immune-cell differentiation, and inflammatory pathways [6]. Butyrate, in particular, has been associated with regulatory T-cell development and anti-inflammatory effects. This suggests that the functional activity of the microbiome may be as important as microbial composition itself. Therefore, future microbiome research should focus not only on which microorganisms are present, but also on what metabolic functions they perform.The findings regarding antibiotic exposure are particularly relevant for pediatric practice. Antibiotics are essential for treating bacterial infections, but unnecessary or repeated exposure during early life may disrupt normal microbiota development. The association between first-year antibiotic use, microbiome disruption, and increased risk of atopic dermatitis described in recent cohort research supports the importance of rational antibiotic prescribing [7]. However, it is also important to avoid overinterpretation. Observational studies may be influenced by confounding factors, including the underlying infections for which antibiotics were prescribed. Therefore, antibiotics should not be avoided when clinically necessary, but their use should be evidence-based and appropriately targeted.

Mode of delivery is another factor that affects early microbial colonization. Cesarean delivery is associated with a different early microbiota profile compared with vaginal delivery [8]. Nevertheless, the long-term immunological significance of these differences remains complex. Delivery mode interacts with breastfeeding, maternal antibiotic use, gestational age, hospital exposure, maternal microbiota, and environmental factors. Consequently, it would be inappropriate to consider cesarean delivery alone as a direct cause of immune dysfunction. Instead, it should be viewed as one of several early-life factors that influence the trajectory of microbiome development.The association between delayed microbiota maturation and allergic disease is also an important finding. Previous cohort studies have shown that delayed development of the gut microbiota during infancy is associated with a higher risk of atopic dermatitis, food allergy, asthma, and allergic rhinitis later in childhood [4]. These findings are biologically plausible because early microbial exposure contributes to immune tolerance and regulation of inflammatory responses. However, the exact microbial patterns that protect against or predispose to allergic disease have not yet been fully defined.

Another important issue is the concept of dysbiosis. Although dysbiosis is frequently used to describe an unhealthy microbial state, there is no single universally accepted definition. Different children may have different microbial profiles while remaining healthy, and microbial composition

varies according to geography, diet, age, genetics, and lifestyle. Therefore, dysbiosis should be interpreted in a functional and clinical context rather than simply as a deviation from a fixed "normal" microbiome.

The reviewed evidence also supports the existence of a critical developmental window during early childhood. During this period, both the microbiota and immune system change rapidly, and environmental influences may have long-term consequences. The first three years of life appear to be especially important for the establishment of microbial stability, immune tolerance, and metabolic function [3]. This developmental window may therefore represent an important period for preventive strategies aimed at supporting healthy microbiota development.Dietary diversification is another important contributor to microbiome maturation. The transition from milk-based nutrition to complementary foods increases the availability of complex carbohydrates and other substrates for microbial fermentation. This promotes microbial diversity and metabolic capacity, including production of short-chain fatty acids. Therefore, age-appropriate and nutritionally balanced complementary feeding may support both gastrointestinal and immune development.

The potential use of probiotics, prebiotics, and synbiotics is of considerable interest, but current evidence remains heterogeneous. The effect of a probiotic intervention depends on the strain, dose, duration, host age, underlying health condition, and clinical endpoint. It is therefore inappropriate to assume that all probiotics have the same immunological effect. Future studies should identify specific microbial strains or metabolic pathways that provide reproducible clinical benefits in well-defined pediatric populations.The gut microbiota may also influence immune responses beyond the intestine. Microbial metabolites can enter the circulation and affect distant organs, suggesting the existence of systemic gut–immune communication. This may partly explain why intestinal microbial patterns have been investigated in relation to respiratory allergy, autoimmune disease, metabolic disorders, and even neuroimmune development. However, many of these associations remain under investigation and should not yet be interpreted as proof of direct causation.

From a clinical perspective, the findings support several practical principles. Breastfeeding should be encouraged when possible, antibiotics should be used rationally, complementary feeding should be nutritionally diverse and age-appropriate, and unnecessary microbiome-directed interventions should be avoided in the absence of evidence. At present, routine microbiome testing is not sufficiently standardized to guide immune-related treatment decisions in healthy children.This review also has limitations. The available studies differ in design, population, geographical location, sequencing methods, definitions of microbiota composition, and clinical outcomes. Many studies are observational and therefore cannot establish direct causal relationships. In addition, microbiome analysis is technically complex, and differences in laboratory methodology may limit comparability between studies.

Despite these limitations, the overall evidence strongly supports an important role of the gut microbiota in pediatric immune development. The most convincing mechanisms involve epithelial barrier support, regulation of innate immune signaling, development of regulatory T-cell responses,

production of short-chain fatty acids, and promotion of immune tolerance.Future research should focus on longitudinal studies beginning during pregnancy and infancy, standardized microbiome analysis, integration of microbial composition with metabolomic and immunological data, and randomized controlled trials of targeted microbiome interventions. Such studies may eventually allow the development of personalized strategies for supporting immune health in children.

CONCLUSION: The gut microbiota plays a fundamental role in the development and regulation of the immune system during childhood. Early microbial colonization contributes to maturation of the intestinal barrier, development of innate and adaptive immune responses, formation of immune tolerance, and protection against pathogenic microorganisms. The first years of life represent a particularly important developmental period because both the microbiota and immune system undergo rapid and interconnected changes.Breastfeeding, mode of delivery, dietary diversification, environmental exposure, and antibiotic use are among the major factors influencing the composition and function of the pediatric gut microbiota. Microbiota-derived metabolites, especially short-chain fatty acids, contribute to epithelial integrity, regulatory T-cell development, and control of inflammatory responses. In contrast, disturbances in normal microbial development may impair immune regulation and have been associated with allergic and other immune-mediated diseases.The reviewed evidence also indicates that microbiome development should be evaluated as a complex and dynamic process rather than by the presence or absence of individual microbial species. Functional activity, microbial diversity, metabolite production, and stability of the intestinal ecosystem are all important for maintaining immune homeostasis.In conclusion, supporting healthy gut microbiota development may contribute to appropriate immune maturation and long-term health in children. Breastfeeding when possible, balanced age-appropriate nutrition, rational antibiotic use, and avoidance of unnecessary microbiome-directed interventions represent important practical principles. Further longitudinal and interventional studies are required to clarify causal mechanisms and to develop safe, evidence-based strategies for microbiome-targeted prevention and treatment in pediatric populations.

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