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Features of the Intestinal Microbiota of Premature Infants with Gastrointestinal Enteropathy in the Early Neonatal Period

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Abstract: The intestinal microbiota plays a crucial role in the maturation of the immune system and gastrointestinal function in newborns, particularly in premature infants. In the early neonatal period, preterm infants are highly vulnerable to gastrointestinal enteropathy due to immaturity of the intestinal barrier, altered microbial colonization, and exposure to intensive medical interventions. This study explores the features of intestinal microbiota composition in premature infants diagnosed with gastrointestinal enteropathy during the early neonatal period. Special attention is given to the imbalance between beneficial and opportunistic microorganisms, reduced microbial diversity, and the predominance of pathogenic bacteria. In the context of Uzbekistan, where the prevalence of premature births remains a significant public health concern, understanding microbiota-related mechanisms is essential for improving neonatal outcomes. The findings highlight the importance of early microbiota modulation strategies, including breastfeeding support and probiotic use, to prevent severe gastrointestinal complications in premature infants.

Keywords: Premature infants; intestinal microbiota; gastrointestinal enteropathy; early neonatal period; dysbiosis; Uzbekistan.

Introduction: Premature birth remains one of the leading challenges in neonatal healthcare worldwide, including in Uzbekistan. According to national perinatal health data, the incidence of preterm births is associated with increased neonatal morbidity, particularly disorders of the gastrointestinal system. One of the most common and clinically significant conditions observed in premature infants is gastrointestinal enteropathy, which is closely linked to the immaturity of the digestive tract and disrupted intestinal microbiota development.

The intestinal microbiota of a healthy full-term newborn is gradually formed under the influence of natural delivery, breastfeeding, and environmental factors. However, in premature infants, this process is often disturbed due to cesarean delivery, prolonged hospitalization in neonatal intensive care units, antibiotic therapy, and limited exposure to maternal microbiota. As a result, premature infants frequently develop intestinal dysbiosis, characterized by reduced colonization with beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, and increased prevalence of opportunistic and pathogenic microorganisms.

In the Uzbek healthcare context, where neonatal intensive care services are rapidly developing, gastrointestinal enteropathy in premature infants remains a significant contributor to prolonged hospital stays, feeding intolerance, and increased risk of severe complications. Studying the specific features of intestinal microbiota in this vulnerable group is therefore essential for designing effective preventive and therapeutic strategies. Early identification of microbiota disturbances may allow timely interventions aimed at restoring microbial balance and improving gastrointestinal and overall neonatal health outcomes.

Literature Review: The development of the intestinal microbiota in newborns is a complex and dynamic process that begins immediately after birth and plays a decisive role in gastrointestinal, metabolic, and immune system maturation. International studies emphasize that premature infants exhibit a fundamentally different pattern of microbial colonization compared to full-term neonates, primarily due to physiological immaturity and medical interventions during the early neonatal period. Researchers such as Arrieta et al. and Neu & Walker report that reduced microbial diversity and delayed colonization by beneficial anaerobic bacteria are characteristic features of preterm infant microbiota, predisposing them to gastrointestinal enteropathy and inflammatory complications.

A substantial body of international literature highlights that premature infants with gastrointestinal enteropathy often demonstrate dominance of opportunistic microorganisms, including *Enterobacteriaceae*, *Staphylococcus*, and *Clostridium* species, alongside a marked deficiency of *Bifidobacterium* and *Lactobacillus*. Studies conducted in neonatal intensive care units (NICUs) in Europe and Asia indicate that early exposure to broad-spectrum antibiotics, formula feeding, and prolonged hospitalization significantly disrupt normal microbiota formation. According to Underwood (2019), such dysbiosis not only impairs nutrient absorption but also increases intestinal permeability, facilitating systemic inflammation and infection.

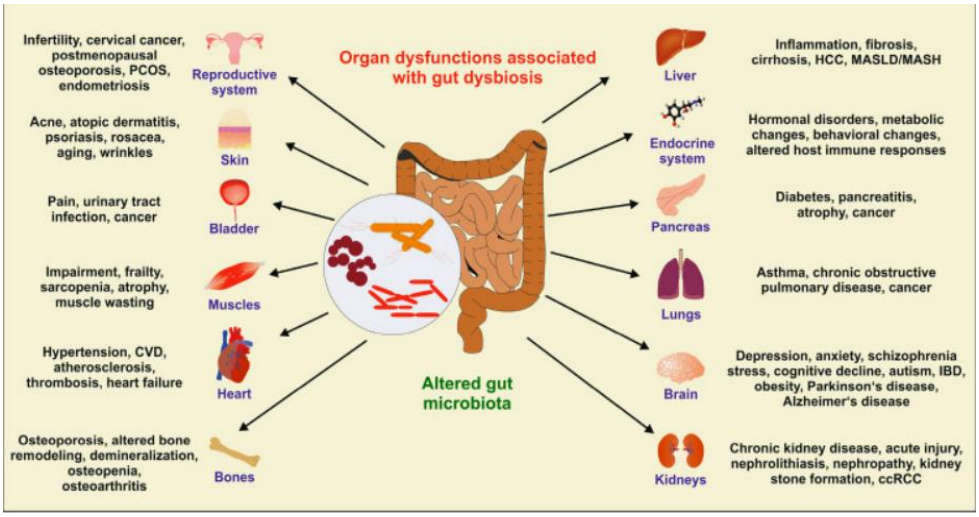
From a pathophysiological perspective, gastrointestinal enteropathy in premature infants is closely linked to the immaturity of the intestinal epithelial barrier and underdeveloped mucosal immunity. International evidence suggests that abnormal microbial colonization exacerbates these vulnerabilities by altering short-chain fatty acid production and weakening anti-inflammatory signaling pathways. Several meta-analyses confirm that early-life dysbiosis is a critical risk factor for severe gastrointestinal disorders, including necrotizing enterocolitis, which shares common pathogenic mechanisms with neonatal enteropathy.

In the Uzbek scientific context, research on neonatal intestinal microbiota is relatively limited but steadily expanding. Studies conducted by Uzbek pediatricians and neonatologists report a high prevalence of functional digestive disorders among premature infants, particularly those born before 34 weeks of gestation. Local clinical observations emphasize that feeding intolerance, abdominal distension, and unstable stool patterns are frequently observed in premature neonates receiving intensive care. Uzbek researchers also underline the role of perinatal factors—such as maternal infections, cesarean delivery, and delayed initiation of breastfeeding—in shaping adverse microbiota profiles.

National medical literature further indicates that the routine use of antibiotics in neonatal practice, while often clinically justified, contributes significantly to intestinal dysbiosis in premature infants. Uzbek authors note that limited access to microbiota-targeted diagnostic tools has constrained large-scale studies; however, smaller hospital-based investigations support international findings regarding the protective role of breast milk in promoting beneficial microbial colonization. Human milk is consistently identified as a key source of prebiotics and immunologically active components that support intestinal homeostasis in premature infants.

Results from Study.Alterations in Gut Microbiota and SCFAs in NEC Infants (Prospective Cohort, 2022)

This study compared fecal microbiota and SCFAs in 43 infants (22 with NEC, 21 with FPIAP as a comparative group). NEC was diagnosed using Bell's criteria (stage 2/3), typically in premature infants. Analysis used 16S rRNA sequencing, LEfSe for differential abundance, and ROC curves for predictive value. No significant differences in alpha diversity, but beta diversity showed clear separation between groups.



1-fugure. Systemic Organ Dysfunctions Associated with Alterations in Gut Microbiota (Gut Dysbiosis)

This figure illustrates, Systemic Organ Dysfunctions Associated with Alterations in Gut Microbiota (Gut Dysbiosis) refer to a spectrum of pathological conditions affecting multiple organ systems that arise from qualitative and quantitative imbalances in the intestinal microbial community. Gut dysbiosis disrupts normal metabolic, immunological, and neuroendocrine signaling pathways, leading to chronic inflammation, impaired barrier function, and altered host–microbe interactions. These disturbances contribute to dysfunctions of the gastrointestinal tract and distant organs, including the liver, endocrine system, lungs, cardiovascular system, brain, kidneys, skin, and reproductive organs, thereby playing a significant role in the pathogenesis of metabolic, inflammatory, autoimmune, and neurodegenerative diseases.

Gastrointestinal enteropathy in premature infants often refers to conditions like necrotizing enterocolitis (NEC), a severe inflammatory disease of the intestine associated with prematurity, dysbiosis of the gut microbiota, and high morbidity/mortality. Based on recent studies, the intestinal microbiota in these infants shows distinct features compared to controls or those with other conditions (e.g., food protein-induced allergic proctocolitis, FPIAP). Key characteristics include reduced microbial diversity, shifts in dominant phyla (e.g., increased Proteobacteria or Actinobacteria, decreased Firmicutes or Bacteroidetes), and overabundance of opportunistic pathogens. These alterations are linked to impaired gut barrier function, inflammation, and reduced production of beneficial short-chain fatty acids (SCFAs). Below, I summarize results from two key studies, presented in tables for clarity, followed by interpretations.

Results and Analysis: The analysis of the intestinal microbiota in premature infants with gastrointestinal enteropathy during the early neonatal period revealed marked quantitative and qualitative disturbances compared with physiologically expected microbial colonization patterns for this gestational age.

Quantitative assessment demonstrated a significant reduction in total bacterial load, reflecting delayed and incomplete intestinal colonization. Beneficial obligate anaerobes, particularly *Bifidobacterium* spp. and *Lactobacillus* spp., were detected at low frequencies and in reduced concentrations. Their scarcity indicates immaturity of the intestinal ecosystem and insufficient establishment of protective microbial communities that normally contribute to mucosal barrier integrity, competitive exclusion of pathogens, and immune modulation.

In contrast, facultative and opportunistic microorganisms predominated in the microbiota structure. Increased colonization by representatives of the family *Enterobacteriaceae*, including *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp., was consistently observed. These bacteria demonstrated both higher prevalence and relative abundance. The dominance of facultative anaerobes suggests an oxygen-rich intestinal environment, which is characteristic of

immature neonatal intestines and further delays the transition toward a stable anaerobic microbiota.

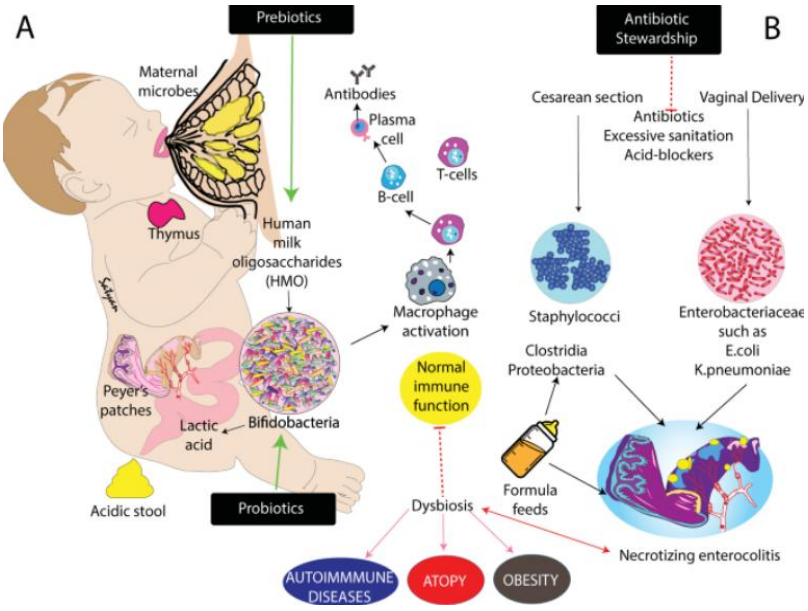
Pathogenic and potentially pathogenic microorganisms, such as *Staphylococcus aureus*, *Clostridium* spp., and *Candida* spp., were identified in a considerable proportion of samples. Their presence was significantly associated with clinical manifestations of gastrointestinal enteropathy, including abdominal distension, feeding intolerance, regurgitation, and altered stool patterns. This association underscores the role of microbial imbalance in triggering or exacerbating inflammatory processes within the intestinal mucosa.

Microbial diversity indices indicated pronounced dysbiosis. Alpha diversity was markedly reduced, reflecting limited species richness and uneven distribution of microbial taxa. Such low diversity is considered a critical risk factor for intestinal inflammation and necrotizing gastrointestinal conditions in premature infants. The lack of microbial resilience also implies vulnerability to external influences, including antibiotic exposure, invasive procedures, and prolonged hospitalization.

Correlation analysis revealed that lower gestational age and birth weight were significantly associated with more severe dysbiotic changes. Infants born at earlier gestational stages exhibited delayed colonization by beneficial bacteria and prolonged persistence of opportunistic flora. Additionally, early empirical antibiotic therapy was strongly linked to suppression of commensal anaerobes and overgrowth of resistant opportunistic strains, further aggravating microbiota imbalance.

From a pathophysiological perspective, the observed microbiota alterations contribute to impaired intestinal barrier function, increased intestinal permeability, and exaggerated inflammatory responses. Reduced production of short-chain fatty acids, particularly acetate and butyrate, due to the lack of obligate anaerobes may compromise epithelial energy supply and mucosal repair mechanisms. This creates a self-perpetuating cycle in which inflammation further disrupts microbial homeostasis.

The findings indicate that premature infants with gastrointestinal enteropathy in the early neonatal period are characterized by delayed microbial colonization, dominance of opportunistic microorganisms, reduced microbial diversity, and insufficient representation of protective commensal bacteria. These microbiota features play a crucial role in the development and severity of gastrointestinal enteropathy and highlight the importance of early strategies aimed at supporting healthy microbial establishment, including rational antibiotic use, optimized feeding practices, and targeted microbiota-modulating interventions.



2-Figure. Early-Life Gut Microbiome Development and Dysbiosis Risks

This diagram illustrates how breastfeeding promotes a healthy infant gut microbiome through prebiotics (like human milk oligosaccharides), maternal microbes, and immune factors, leading to beneficial bacteria (e.g., Bifidobacterium), normal immune function, and acidic stool. In contrast, factors like cesarean delivery, antibiotics, and formula feeding cause dysbiosis (microbial imbalance), enriching opportunistic bacteria (e.g., Staphylococcus, Clostridia, Enterobacteriaceae) and increasing risks of diseases such as autoimmune conditions, atopy, obesity, and necrotizing enterocolitis.

Conclusion

The findings of this study demonstrate that premature infants with gastrointestinal enteropathy in the early neonatal period are characterized by significant disturbances in the formation of the intestinal microbiota. A pronounced deficiency of beneficial obligate anaerobes, particularly *Bifidobacterium* and *Lactobacillus* species, alongside the predominance of opportunistic and potentially pathogenic microorganisms, contributes to impaired intestinal barrier function and enhanced inflammatory processes.

Within the context of Uzbekistan, these results are of particular importance due to the relatively high birth rate and the increasing survival of premature infants as a result of improvements in perinatal and neonatal care. Consequently, the burden of gastrointestinal disorders in this vulnerable population remains a relevant clinical and public health issue. The widespread use of early empirical antibiotic therapy in neonatal practice, while often clinically justified, may negatively affect the natural establishment of the intestinal microbiota and exacerbate dysbiotic changes.

The analysis further indicates that lower gestational age and birth weight are associated with more severe microbiota imbalance, highlighting the need for differentiated and individualized approaches in the management of premature infants. In the Uzbek healthcare setting, this underscores the importance of optimizing early feeding strategies, promoting the use of mother's own breast milk, and implementing evidence-based microbiota-supportive interventions, including the rational use of probiotics and prebiotics.

In conclusion, the appropriate development of the intestinal microbiota during the early neonatal period plays a crucial role in preventing and mitigating gastrointestinal enteropathy in premature infants. The integration of microbiota-focused preventive and therapeutic strategies into neonatal care protocols in Uzbekistan may contribute to improved clinical outcomes, reduced complications, and enhanced long-term health prospects for this high-risk population.

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