LITERATURE REVIEW Open Access

Bagaimana Mikrobiota Usus Mendukung Imunitas, Pertumbuhan, dan Perkembangan Bayi Prematur: Sebuah Kajian Pustaka

How Gut Microbiota Supports Immunity, Growth and Development of Preterm Infants: A Narrative Review

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ABSTRAK

Latar belakang: *Mikrobiota usus, yang merupakan suatu ekosistem kompleks yang terdiri dari sejumlah besar mikroorganisme, berperan dalam imunitas, pertumbuhan, dan perkembangan bayi prematur. Disbiosis atau gangguan mikrobiota usus dapat memperberat berbagai penyakit, seperti alergi atau penyakit autoimun pada bayi prematur.*

Tujuan: *Tujuan penelitian ini adalah untuk mengkaji mikrobiota usus pada bayi prematur dan perannya dalam mendukung imunitas, pertumbuhan dan perkembangan bayi.*

Ulasan: *Bifidobactericeae adalah mikrobiota paling dominan dalam saluran pencernaan bayi prematur. Namun, ada berbagai faktor yang dapat memengaruhi mikrobiota usus, seperti genetik, gaya hidup ibu (merokok, diet, penggunaan antibiotik, obesitas), jenis persalinan, cara pemberian ASI, dan faktor lingkungan. Disbiosis pada saluran cerna dapat menyebabkan gangguan sistem imun yang membuat bayi prematur lebih rentan mengalami infeksi atau bahkan kejadian menyimpang yang fatal. Selain itu, pertumbuhan dan perkembangan juga dapat terganggu serta terjadi berbagai kelainan neurologi dan psikiatri, Air susu ibu (ASI) adalah salah satu sumber prebiotik yang dapat menstimulasi pertumbuhan Bifidobactericeae dan Bacteroidetes. Apabila ASI tidak adekuat atau tidak dapat diberikan, intervensi yang direkomendasikan untuk memperbaiki mikrobiota usus pada bayi prematur adalah pemberian suplemen probiotik, prebiotik, atau keduanya (sinbiotik). Pemberian prebiotik dan probiotik berhubungan dengan rendahnya morbiditas dan mortalitas pada bayi prematur, serta dengan lebih singkatnya lama rawat di rumah sakit dan lebih singkatnya waktu hingga pemberian makanan enteral penuh dapat dilakukan.*

Kesimpulan: *Imunitas, pertumbuhan, dan perkembangan bayi prematur sangat dipengaruhi oleh mikrobiota usus. Kurangnya keragaman mikrobiota memajankan bayi prematur terhadap berbagai masalah kesehatan. Maka, masalah ini perlu ditangani dengan baik, salah satunya adalah dengan pemberian prebiotik dan probiotik..*

Kata kunci: *Mikrobioma Gastrointestinal, Prematur, Imunitas, Pertumbuhan, Perkembangan*

ABSTRACT

Background: Gut microbiota, a complex ecosystem consisting of abundant microorganisms, plays a role in preterm infants' immunity, growth, and development. Dysbiosis or disruption of the gut microbiota can precipitate various diseases, such as allergy or autoimmune disorders in premature infants.

Purpose: This study aimed to review gut microbiota in preterm infants and its role in supporting the infants' immunity, growth, and development**.**

Discussion: *Bifidobactericeae* is the predominant microbiota in GI tract of preterm infants. However, various factors can influence this gut microbiota e.g., genetics, lifestyle of the mothers (smoking, diet, use of antibiotic, obesity), birth mode, type of feeding, and environmental factors. Gut dysbiosis can result in impaired immune system which predisposes the preterm infants to infections, even fatal adverse event. Furthermore, the growth and development might be affected as well as lead to various neurodevelopmental and psychiatric disorders. Human milk is a prebiotic source which can stimulate the growth of *Baifidobactericeae* and *Bacteroidetes*. If the human milk is inadequate or unavailable, the recommended interventions for gut dysbiosis in premature infants are probiotics, prebiotics, or both supplementations (synbiotics). The administration of prebiotics and probiotics associates with lower morbidity and death rates in preterm infants, as well as shorter duration of hospital stay and duration to achieve full enteral feeding.

Conclusions: Immunity as well as growth and development of preterm infants are affected greatly by gut microbiota The less diverse microbiota in preterm infants' gut predispose them to various health problems. Hence, this problem should be managed properly, one of which is prebiotic and probiotic supplementation

Keywords: Gastrointestinal Microbiome, Premature, Immunity, Growth, Development

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INTRODUCTION

Gut microbiota is an intricate microbial ecosystem comprising extensive variants of microorganisms within the gastrointestinal system. Allegedly, gut microbiota contributes to the development of numerous diseases e.g., infectious diseases, allergic diseases, autoimmune disorders, metabolic disorders, or colorectal cancer. Dysbiosis, or disturbed microbiota components, is inferred as the precipitating or aggravating factors for these diseases. There are six main phyla which constitute the gut microbiota, which are Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria, and Tenericutes. The dominant phyla are different between infants and adults. In infants, Actinobacteria is the predominant phylum with the most commonly identified genus of *Bifidobacterium.*[1] Human milk is a source of human milk oligosaccharides (HMO), a prebiotic, which can stimulate the growth of *Bifidobacterium* and *Bacteroidetes*. However, HMO in preterm mothers is different from term mothers due to genetic factors, lactation stage, maternal diet, and maternal weight that predispose preterm infants to gut dysbiosis.[2]

Preterm infants, defined as babies born prior to full-term gestation (37-40 weeks),[3] often suffers from gut dysbiosis or imbalance of gut microbiome. Dysbiosis is determined through microbiome study. However, the clinical signs are not clear. It could be impairment in immunity, growth, or development. Graspeuntner et al. reported gut dysbiosis in 29 out of 31 preterm infants with late-onset sepsis.[4] Another study by Ho et al. reporting increasing Gammaproteobacteria in preterm infants with peak of 75.5% abundance at week 4. These bacteria are associated with gut dysbiosis in preterm infants.[5] Various factors affect this gut dysbiosis and it can lead to disruption of immune system, growth, and development.[6] Immune system is a protection system which functions through collaborative action of innate and adaptive system.[7] To date, there has been no standard operating procedures for the management of gut dysbiosis since the microbiome study is relatively new in Indonesia.

Growth is an increase in the infants' body measurement, including weight and height, which is determined by Fenton growth chart for preterm infants.[8] Several pathogeneses of growth disruption are linked with gut dysbiosis. High level of *Enterobactericeae* was found in preterm infants with failure to throve. This growth failure is caused by disruption of short-chain fatty acid (SCFA) metabolism and increased incidence of feeding intolerance due to disrupted intestinal barrier function.[9,10]

Development is a process of an infant getting abilities, such as cognitive, language, social, emotion, and behavior.[11] Gut dysbiosis is linked to neurodevelopmental disorders because it alters immune responses which induces neuroinflammation of the brain. SCFA metabolism is also impaired due to gut dysbiosis which can impair the integrity, function, and development of blood-brain barrier.[12] Hence, this review aims to discuss how gut microbiota supports immunity, growth, and development in preterm infants.

DISCUSSION

Gut microbiota composition in preterm infants

Preterm infants might undergo early life conditions which can modify the process of acquiring normal microbiota. In this early life, dysbiosis can occur, which can influence the health and well-being of the preterm infants. Previously, the GI tract of a newborn was believed to be sterile; however, intrauterine conditions apparently can affect the gut microbiota.[6] Tauchi et al. reported that in neonatal intensive care unit (NICU), the preterm infants' guts were dominated by *Bifidobactericeae* (30.5%), *Enterobacteriaceae* (21.2%), and *Staphylococcaceae* (15.1%).[13] Several factors can be taken into account for the gut dysbiosis in preterm infants, which include low oxygen level, delivered with C-section, quantity and type of HMO. Antibiotic use, and inpatient care in neonatal intensive care unit.[10,14]

Factors influencing gut microbiota composition in preterm infants

Various aspects affect the expansion of gut microbiota in preterm infants, from pregnancy to after birth. Since the fetus in utero, the development of gut microbiota is affected by internal and external factors. Internal factors include genetic influence while external factors include maternal factors, birth mode, feeding type, antibiotic use, and environmental factors. Intrauterine infections or dysbiosis might results in preterm birth. This is supported by the findings of vaginal commensal microbes in amniotic fluid of preterm infants whose mothers have intraamniotic infections. Ascending infection from lower genital tract is the main cause of this event.[10,14]

Dorsal region of yolk sac develops into gut since the 22nd days following conception. Five weeks following conception, stomach is developed. In 20 weeks following conception, the gut is well-developed. Amniotic fluid which surrounds the fetus is swallowed by the fetus starting from 10 weeks following conception. This event leads to introduction of various microorganism products into the fetus' gut. Amniotic fluid comprises fetal urine, secreted lung liquid, transmembrane fluid, buccal secretions, growth regulators, hormones, immune modulating proteins, and microbial constituents. Aside from those, maternal

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microbes are also suggested to influence the gut microbiota by being transferred to the amniotic fluid.[10]

The mother's aspects e.g., smoking, obesity, use of antibiotics, and diet, will influence the gut microbiota of her infants. High-fat diet is linked to less diverse gut microbiota while high fruit diet increases colonization of *Streptococcus* and *Clostridium*. Maternal obesity is linked with gut microbiota dysbiosis that high levels of *Staphylococcus* and *Bacteroides* are identified. Similarly, mothers with diabetes mellitus show high level of *Proteobacteria* and low levels of *Firmicutes, Bacteroides*, and *Acinetobacter* in their newborns' gut microbiota. This is believed to predispose the newborns, including preterm infants, to metabolic syndromes, atopic dermatitis, and allergy in their childhood.[14,15]

After birth, there are various factors influencing the neonates' gut microbiota i.e., age, genetics, diet, antibiotic use, mode of birth, feeding, and the environment. Environmental factors include household exposures from furry animals and siblings as well as geographic location.[10,14,16]

Different modes of birth differ the newborn's gut microbiota. Vaginal birth will expose the newborns to microorganisms in the birth canal, such as *Lactobacillus. Bacteroides fragilis* is also most commonly identified in infants delivered with vaginal birth. This microorganism is associated with more diverse gut microbiota and more rapid maturation. Caesarean section (C-section) is not a determining factor, but the air, surgical equipment, other infants, and healthcare workers affect the newborn's gut microbiota. *Clostridium difficile*, a common microorganism in the hospital, is identified in high levels in newborn born with C-section. *Bacteroides* is identified lower in C-section newborn than vaginal birth newborn because *Bacteroides* is associated with maternal stool. In addition, C-section is also associated with delayed colonization and less diverse microbiota. However, there is different gut microbiota in newborns born with elective C-section compared to emergency C-section, in which Bifidobacterium is dominant in elective C-section. Progesterone promotes colonization of Bifidobacterium in the late pregnancy so the longer the baby in utero, the higher Bifidobacterium growth.[10,14,17]

Type of feeding is also associated with gut microbiota as milk is the first nutrition presented into the newborn's GI tract. *Bifidobacterium longum, Staphylococcus epidermidis,* and *Streptococcus thermophilus* are identified in the human milk as well as newborn's feces. Newborn who is given formula milk is reported to have higher levels of strict anaerobes and facultative anaerobes, relatively stable, and diverse microbiota. On the other hand, breastfed newborn has higher level of aerobes, less diverse microbiota, and experiences more dramatic changes in microbiota composition in their first year of life. In human milk, over 200 types of oligosaccharides, known as prebiotic, are identified in human milk and becomes the third major constituent of human milk. This promotes the growth of *Bifidobactericeae* and *Bacteroidetes*.[8,9,14]

Antibiotic use is more frequent in preterm infants.[18] A total of 73% of preterm infants got antibiotics when hospitalized in NICU. This overuse of antibiotics is due to various reason e.g., prophylactic for invasive procedures, suspected infection, and established infection.[19] Conversely, a study in Norway reported only 39% of term infants hospitalized in neonatal units.[20] Both infant and maternal uses of antibiotics after birth are associated with higher risks of asthma, allergy, obesity, inflammatory bowel disease, and inflammatory diseases in the future. Antibiotic use will interrupt the microbial maturation. Antibiotic prophylaxis during labor is associated with lower level of *Bifidobactericeae, Bacteroidetes* and *Actinobacteria* but higher level of *Firmicutes* and *Proteobacteria*.[4] The dysbiosis induced by antibiotic use can increase the risk of colitis in newborns.[18,21,22]

In preterm infants, pathogenic microbes, such as *C. difficile* and *Klebsiella pneumoniae*, can be identified, along with low level of short chain fatty acids. Facultative anaerobic bacteria e.g., *Enterobactericeae* then *Enterococcaceae*, are predominant, accompanied by lower level of anaerobic bacteria e.g., *Bifidobacterium, Bacteroides,* or *Atopobium*. Continuous positive airway pressure (CPAP) is believed to enhance air uptake in GI tract, leading to delayed colonization of commensal bacteria. Despite insufficient evidences, different oxygen levels between preterm and term infants are thought to play a role in this matter.[10]

Gut microbiota and immunity

Weaning period is a period in which gut microbiota expand and induce T-cells to produce more interferon (IFN)-γ and tumor necrosis factor (TNF)-α. This event is also mitigated by T-regulatory cells. Gut microbiota also associates with the growth of intraepithelial lymphocytes and isolated lymphoid follicles. The gut microbiota will also induce monocytes recruitment. Innate immune cells are also believed to be stimulated by gut microbiome. Various cells indicate immaturity in neonates due to lack of microbial stimulation, such as neutrophils and antigen presenting cells (APCs). Dysbiosis of gut microbiome, which is often seen in preterm infants, will lead to reduced circulating neutrophils and resistant towards colonization of gut pathobionts.[23] The dysbiosis regulates granulocytosis through interleukin (IL)-17A, which induce granulocytes-colony stimulating factor (G-CSF) and neutrophil recruitment. Lower SCFA in gut dysbiosis also play a role in decreased granulocytosis.[24] These will predispose the infants to late-onset sepsis. In infants which experience late-onset sepsis, *Escherichia coli,* which is identified as the causative agent, is known to be a part of the gut microbiota. Premature infants are also more vulnerable to develop sepsis from enteric infections. The premature organ, in this case the gut, along with dysbiosis increases the possibility of the fatal adverse event i.e., necrotizing enterocolitis (NEC). Before the event of NEC, gut microbiota is dominated by Proteobacteria and there are low levels of *Bacteroidetes* and *Firmicutes*.[23] Proteobacteria contains lipopolysaccharides which is associated with the activation of Toll-like Receptor 4

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(TLR). This event leads to disrupted epithelial proliferation, impaired barrier, and apoptosis of intestinal tissue, resulting in NEC.[25]

Gut microbiota and growth

Younge et al reported that preterm infants often experience growth disturbances after birth. They have shorter length, lower lean body mass and weight than term infants. The growth rate is significantly lower than intrauterine growth rates. This poor growth predisposes the newborn to neurodevelopmental problems and metabolic diseases in the future. Furthermore, preterm infants with failure to thrive had higher *Staphylococcaceae* level in the early life and constant high level of *Enterobactericeae* (comprising *Citrobacter, Enterobacter, Klebsiella, Serratia,* and so on) in the later weeks. On the other hand, the ones with normal growth had greater *Bacillaceae, Lachnospiraceae, Micrococcaceae, Peptostreptococcaceae, Streptococcaceae,* and *Veillonellaceae* level. This different microbiota will also cause difference in microbiota functions and metabolites.[8] *Staphylococcaceae* plays a role in degradation of aromatic amino acids and β-glucuronide as well as decreased nitrite level which exerts harmful effects.[26] *Enterobactericeae* are Gram-negative bacteria which are can induce mucosal inflammation. Enterobacteriaceae are also linked with celiac disease because they are thought to impair gluten metabolism.[27] On the other hand, *Bacillaceae, Lachnospiraceae, Micrococcaceae, Peptostreptococcaceae, Streptococcaceae,* and *Veillonellaceae* constitute the normal gut microbiome. *Bacillaceae*, *Peptostreptococcaceae,* and *Streplococcaceae* are members of *Firmicutes* phylum, which helps carbohydrate metabolism in healthy gut.[26,28] *Lachospira* resides in cecum with role of producing SCFA and degrading pectin which is beneficial for the preterm infants' health.[29] *Micrococcaceae* induces immune tolerance through inhibition of interferon (IFN)-γ production.[23] *Veillonellaceae*, also members of *Firmicutes*, induce metabolism of amino acid, carbohydrates, vitamins, cofactors, enzymes, and glycan.[28]

Gut dysbiosis in preterm infants causes lower level of good bacteria and higher level of bad bacteria which leads to impaired SCFA. It is not caused by merely one bacterium but disproportion of good and bad bacteria levels. In growth failure, SCFA reduction causes disturbances in lipid and glucose hemostasis. In addition, the innate immune responses are disrupted in preterm infants due to increase of *Enterobactericeae* level compared to term infants, which induce mucosal inflammation and leads to increased lipolysis and reduced insulin sensitivity. The low microbial diversity in preterm infants also correlates with inflammatory diseases, such as NEC, also disrupted intestinal barrier function. As NEC manifests as feeding intolerance and severe manifestation presents as bowel ischemia, infant growth can be further impaired since the intake will be reduced.[30]

Gut microbiota and development

Microbiota-gut-brain axis concept has been established with brain affecting GI functions and vice versa.[16,21] Developmental disorder, particularly neurodevelopmental disorders, are linked with dysbiosis of gut microbiota. There are three most common neurodevelopmental disorders linked with dysbiosis e.g., schizophrenia spectrum disorder, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD). There are higher levels of *Actinobacteria* and *Bifidobacterium* in ADHD patients compared to healthy controls. In preterm infants with ASD, *Bifidobacterium, Clostridium, Bacteroidetes, Firmicutes, and Proteobacteria* are identified to be predominant gut microbiota with significant higher level of SCFA albeit inconsistent findings in several studies. These inconsistent results might be caused by variations of diet and antibiotic use in ASD patients. For schizophrenia, preterm birth and dysbiosis highly correlate with this disorder. High level of *Brucellaceae, Halothiobacillaceae, Lactobacillaceae,* and *Micrococcineae* followed by low level of *Veillonellaceae* were observed in patients with first episode psychosis.[12]

Dysbiosis in preterm infants will affect the early brain development. As gut microbiota is known to modulate the immune system, dysbiosis might result in modifications of histone and DNA methylation of innate lymphoid cells. This altered immune responses induces neuroinflammation in the brain. In addition, SCFA produced by the microbes is thought to influence the development of various neurological conditions e.g., Parkinson's disease, Huntington's disease, and. Alzheimer's disease. Gut microbiota also induces production of neuromodulator and neurotransmitter, such as serotonin by *Escherichia, Enterococcus,* and *Streptococcus.* In addition, gut microbiota sends signals to vagal nerve, in which dysbiosis can induce depression and anxiety. In preterm infants, dysbiosis of gut microbiota along with the premature blood-brain barrier (BBB) affect the BBB integrity, function, and development.[12]

Attempts to Modify Preterm Infants' Gut Microbiota

Since gut dysbiosis results in impairment of immunity, growth, and development, various attempts have been made to modify gut microbiome in preterm infants. Since in utero, probiotic supplementation can be given to pregnant women with risk of preterm labor, albeit unproven.[9] Maternal intake can modify the constituents of HMO, one of the important factors affecting gut microbiome in preterm infants. Maternal diet consisting of fruit, fish, and seafood is associated with increased *Streptococcus* level while dairy food is associated with high *Clostridium* level in their infants. Maternal weight also influences the infants' microbial diversity as more weight gain is associated with less *Bacteroides* level and poor microbial diversity.[31] Supplementation of bovine lactoferrin has also been studied since it has anti-inflammatory, antibacterial, antiviral, and antifungal properties. This supplementation is associated with

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shortened hospital's length of stay (LOS) in infants with extremely low birthweight.[9] Lactoferrin aids the growth of beneficial microbes, such as *Lactobacilli* and *Bifidobacteria* in preterm infants. Furthermore, lactoferrin is presumed to induce better immune responses in preterm infants.[32] Other commonly used interventions are prebiotics and probiotics supplementation which have been proven for their beneficial effects on gut microbiome in preterm infants.[33,34] Further studies are still necessary for immunoglobulin, protein, arginine, and glutamine supplementation as well as antacids administration in order to establish their effects on gut microbiome in preterm infants.[9]

Prebiotics and gut microbiome in preterm infants

Prebiotics are non-digestible, selectively fermented ingredients, which are metabolized by the gut microbiota, resulting in changes in microbiota composition and activity.[23] Prebiotics promote colonization of gut with probiotics. These nutrients are often in form of short-chain carbohydrates, predominantly oligosaccharides.[25] The direct effects of prebiotics include serving as source of energy for gut epithelia and improving access to transcription factors, intestinal barrier, absorption of metabolite, gastrointestinal motility, lipid and glucose homeostasis, as well as immune system. These direct effects are mediated by SCFA, the end-products of fermentation which also reduce the gut pH to hinder pathogen's development. Prebiotics also offer energy source for normal flora of the gut to enhance protection, immune system, intestinal barrier, and brain function. One of the prebiotics, galactooligosaccharides (GOS), bind to the microbes on enterocytes and inhibit the adherence of pathogen to gut epithelia.[35] In preterm infants, administration of prebiotics increases Bifidobacterium. Increase of *Lactobacillus spp.* level is also observed in preterm infants receiving 1% lactulose as prebiotics.[9] These changes in gut microbiota by prebiotics are believed to improve gut immunity as well as decrease the occurrence of allergy, infection, inflammatory disorders, and gastrointestinal disorders in later life.[35] Srinivasjois et al. also found that oligosaccharides supplementation in preterm infants leads to development of beneficial microbiota and they are safe to be administered.[34] The latest meta-analysis concluded that preterm infants with prebiotics supplementation had reduced mortality, sepsis, duration to achieve full enteral feeding, and duration of hospital stay.[12] However, prebiotics supplementation is not associated with incidence of NEC.[34,36] As prebiotics are the third most abundant constituent of human milk, this can benefit the infants. However, preterm infants which often needs special care in NICU, fresh human milk might not be administered. Hence, these preterm infants can benefit from prebiotic supplementation.[35]

Probiotics and gut microbiome

The beneficial bacteria in human milk are destroyed by pasteurization while antibiotic use in the infant's mother can reduce the *Bifidobacteria* in their human milk.[37] Hence, probiotics supplementation in preterm infants is a growing research these days as it shows potential for reducing morbidity and death rates in preterm infants.[38] Despite low evidence, European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends supplementation of *L. rhamnosus* GG ATCC53193 or mixture of *S. thermophilus* TH-4, *B. infantis* Bb-02, and *B. lactis* Bb-12 for preterm infants to decrease incidence of NEC. Insufficient evidences lead to no recommendation for use of *L. reuteri* DSM 17938, *L. acidophilus* NCDO 1748, and *B. bifidum* NCDO 1453 in preterm infants. The committee is also against *B. breve* BBG-001 and *S. boulardii* supplementation due to safety consideration and lack of evidence, also probiotics producing D-lactate because it can induce acidosis, especially in preterm infants who already have predisposition to be acidotic.[37]

Probiotics may affect both bacterial and fungal microbiota in GI tract of preterm infants. As for viral colonization, there is lack of evidence for probiotic's effect in preterm infants. The mechanisms of probiotic's effect on gut microbiota are by competing for nutrients with pathogen, production of metabolic products (SCFA), preventing growth of pathogen through bacteriocins, anti-inflammatory effects, and reducing intestinal permeability. Probiotics supplementation is not linked with any serious adverse events in preterm infants. Few reports stated the occurrence of sepsis which is caused by product contamination. Another potential problem is cross-contamination in preterm infants being cared in NICU since the probiotic microbials were found to be transferred from infant to infant in NICU.[38]

There is no official recommendation for daily dose of probiotic supplementation. However, most studies use $1x10^8$ - 10^9 Colony Forming Unit (CFU). Esaiassen et al. used $1x10^9$ CFU of *L. acidophilus* mixed with *B. longum* during their study in preterm and reported good outcomes.[33] A meta-analysis by Chi et al. reported that the dose for probiotic supplementation ranged from $1.2x10^7$ CFU to $1x10^{11}$ CFU with duration of 1-9 weeks in preterm infants. This study concluded that combination of *Lactobacillus* and *Bifidobacterium* along with prebiotic supplementation reduce mortality rate, sepsis rate, NEC, duration of hospital stay, and improve duration to achieve full enteral feeding.[39,40]

CONCLUSION

Gut microbiota is crucial for the immunity as well as growth and development of preterm infants. Preterm infants are linked with less diverse microbiota which can predispose them to various health problems. Therefore, special measures should be taken to improve gut microbiota, one of which is prebiotic and probiotic supplementation. Future researches are necessary to investigate how gut microbiota affects various diseases as well as the interventions to improve its development in preterm infants.

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