

Role of the gut-lung axis in bronchopulmonary dysplasia: Physiological basis, pathogenesis and immunological modulation (Review)

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Abstract. Bronchopulmonary dysplasia (BPD) is a severe respiratory condition that affects preterm infants, which is frequently associated with a poor long-term prognosis. The gut-lung axis is a bidirectional communication pathway mediated by microbial communities and shared immune mechanisms that has emerged as an important area of research. It has been indicated that gut microbiota can influence the progression of various pulmonary diseases, where the gut-lung axis can affect the progression of BPD through various mechanisms, such as bacterial translocation, microbial metabolite exchange, inflammatory cytokine spillover and immune cell migration. Although the relationship between the gut-lung axis and BPD remains under exploration, understanding this interaction may identify early warning markers and novel therapeutic strategies for BPD. The present review summarizes the influence of the gut-lung axis on BPD, focusing on the bidirectional communication and gut microenvironmental changes during BPD and the possible immunoregulatory mechanisms involved. By elucidating these associations, the present review aims to provide novel insights into the prevention and treatment of BPD.

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1. Introduction

Bronchopulmonary dysplasia (BPD) is a critical respiratory disease with notable implications for the survival and long-term prognosis of preterm infants (1,2). It is particularly prevalent among severely preterm infants (gestational age <28 weeks) and infants of very low birth weight (VLBW; birth weight <1,000 g) (3). In recent years, with advancements in perinatal and neonatal medicine, there has been a marked increase in the survival rate of preterm infants but the incidence of BPD has increased accordingly. Notably, BPD is associated with elevated mortality in the neonatal period, where surviving infants will frequently develop persistent airway hyperresponsiveness and abnormal lung function (4). These sequelae contribute to a poor long-term prognosis, imposing burdens on the quality of life of affected children.

The prevailing perspective on the etiology of BPD attributes its development to a number of factors, such as premature lung structural immaturity, elevated oxygen exposure, mechanical ventilation-induced injury and infection (1,5). However, emerging evidence has highlighted the important role of intestinal dysbacteriosis in the pathogenesis and progression of BPD. Gut microecology, defined as the microbial community of the intestinal flora, comprises both symbiotic and pathogenic microorganisms residing in the tissues and intestines. Dysbiosis of the intestinal flora has been associated with immune dysregulation and is associated with multisystemic diseases, including obesity, diabetes, atherosclerosis and non-alcoholic fatty liver disease (6,7). The lung microenvironment is likely to be affected by changes in the gut microbiota, since microbiomes also exist in the upper and lower respiratory tract. This notion is supported by clinical observations where respiratory diseases also present with concomitant gastrointestinal symptoms, whereas gastrointestinal disorders are frequently accompanied by respiratory manifestations (8,9). Patients with influenza virus infection may exhibit gastrointestinal symptoms (8), whilst ~50% patients with inflammatory bowel disease, which is characterized by alterations in gut microbiota composition, have been

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reported to exhibit impaired lung function (9). This bidirectional crosstalk between the intestines and lungs is referred to as the gut-lung axis, which may provide novel insights into the pathophysiology of BPD.

The gut-lung axis has been shown to serve a notable role in respiratory disease. Gut microecology evolves with age, where infants with BPD are more prone to early-life gut dysbiosis (10). A previous study showed that in vaginally delivered preterm infants, the BPD group exhibits increased relative abundance of *Escherichia/Shigella* and decreased levels of *Klebsiella* and *Salmonella* in their gut flora compared with those in the non-BPD group (10). Chen *et al* (11) documented that the intestinal flora diversity in preterm infants with BPD was markedly lower compared with that in controls at postnatal day 28. The gut-lung axis may influence BPD development through immune cell migration, mucosal immune disruption and alterations in gut-lung microenvironmental cytokines.

Previous studies have explored alterations in the intestinal flora of patients with BPD (10,11). However, these studies remain fragmented, where a gap exists between the theoretical framework of the gut-lung axis and the clinical management of BPD. To address this, there is a pressing need to synthesize existing research on the gut-lung axis and its relationship with BPD, thereby enhancing strategies for disease prognosis management. The present review systematically consolidates advances in understanding the role of the gut-lung axis in BPD pathogenesis, aiming to provide a robust theoretical foundation for the development of targeted interventions.

2. Bidirectional communication in the gut-lung axis

Similarities between the respiratory and intestinal tracts

Embryonic developmental homology. During early embryonic development, the endoderm gives rise to the pro-intestinal tube, which subsequently differentiates into the foregut, midgut and hindgut. The foregut further develops into the respiratory tract and upper digestive tract, including the esophagus, stomach and duodenum, whilst the midgut and hindgut form the remaining intestinal tract. This shared embryonic origin from the endoderm-derived pro-intestinal tube establishes the homology between the respiratory and intestinal tracts (12-14).

Similar signaling pathways and transcription factor regulatory networks. During development, the formation of the respiratory and intestinal tracts is orchestrated by analogous signaling pathways and transcription factors. The Wnt, Bmp and Fgf signaling pathways are essential for modulating cell proliferation, differentiation and migration, thereby ensuring the normal development of the respiratory and intestinal tracts (15-17). In addition, various transcription factors, such as Nkx2.1 and Sox9, are pivotal in driving the development of both systems (18-20). These factors regulate the expression of key genes involved in organ morphogenesis, underscoring their critical role in the coordinated development of the respiratory and intestinal tracts. Collectively, these signaling pathways and transcription factors highlight the shared regulatory mechanisms between these two systems, providing insights into their interrelated functions and potential shared pathologies.

Structural and functional parallels. The respiratory and intestinal tracts exhibit notable structural and functional parallels. Structurally, the mucosa of both tracts belongs to the mucosal immune system and comprises epithelium and lamina propria. They both feature a luminal structure consisting of endoderm-derived epithelial cells, which undergo comparable morphogenetic processes during development, such as the establishment of epithelial cell polarity and the formation of intercellular junctions (13). Functionally, both tracts are essential for maintaining ventilation and material exchange to support the normal physiological functions of the body, whilst also being capable of producing secretory immunoglobulin A. These structural and functional similarities underscore their homology in embryonic histogenesis (21).

The extensive similarities between the respiratory and intestinal tracts not only enhance the comprehension of their interplay during physiological development, but also establish the biological foundation for bidirectional communication within the gut-lung axis. While acknowledging that structural homology alone does not guarantee communication, we contend that the anatomical and developmental parallels between respiratory and intestinal tracts create a permissive biological framework for bidirectional crosstalk. These parallels further offer insights into the mechanisms underlying related diseases, providing a framework for exploring pathophysiological connections between these systems (22).

Intestinal microbiota: A foundation of bidirectional communication in the gut-lung axis. The gut-lung axis displays dynamic bidirectional crosstalk between the intestinal and pulmonary systems (21). Lung diseases have been previously shown to impact intestinal function and vice versa (21,23-28). Amongst the key elements facilitating this interaction is the bacterial flora, which serves as a critical link between these two systems (29). Accumulating evidence has indicated that commensal bacteria residing in the gut and lungs are indispensable for the development and maintenance of immune homeostasis (30,31). These microbiota begin to colonize newborns not only at birth but also during fetal development. A previous study identified overlapping gut and lung microbiota in human fetuses as early as 10-18 weeks of gestation (32). It has also been reported that gut and lung microbiota can translocate between these organs through fluid circulation, where metabolites derived from gut microbiota can influence lung physiology through various immune-mediated pathways (such as immune cell migration, mucosal immune disruption and alterations in gut-lung microenvironmental cytokines) (33). The gut-lung axis therefore provides a framework for understanding the interplay between local microbiota and distal immune mechanisms, offering novel perspectives on disease pathogenesis and progression. This conceptual model not only improves the comprehension of the physiological connections between the gut and lungs, but also highlights potential therapeutic targets for disorders affecting these interconnected systems.

3. Characteristics of intestinal microbiota in preterm infants

The gut microbiota in early human life is dynamic, gradually stabilizing to resemble adult profiles after the age of

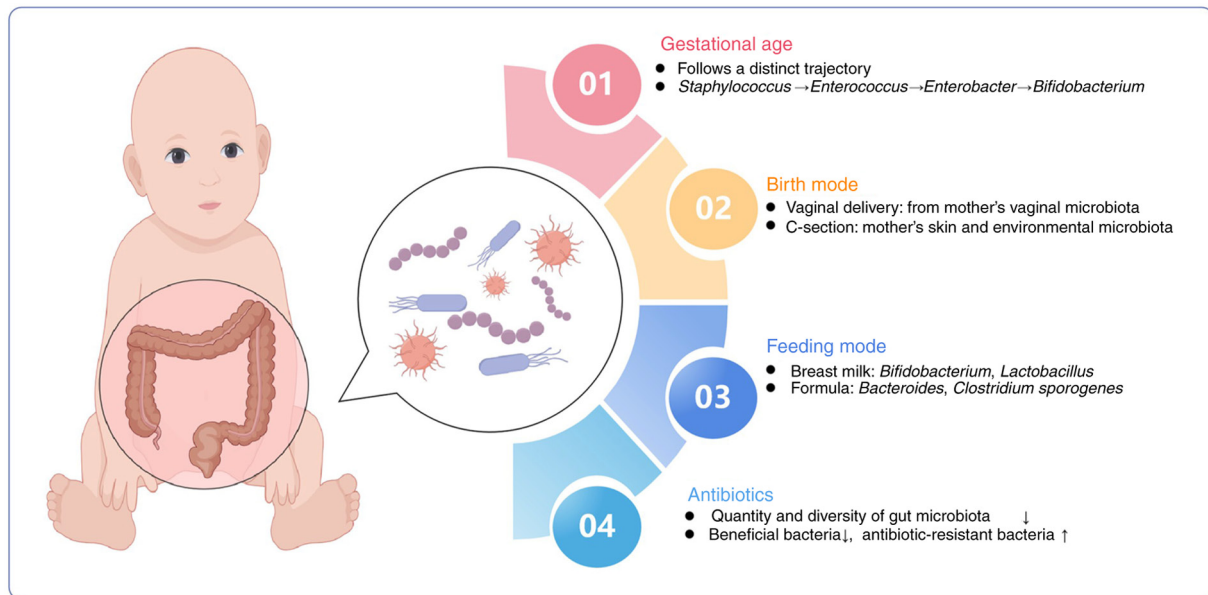


Figure 1. Characteristics of intestinal microbiota in preterm infants. The development of intestinal microbes in preterm infants is influenced by key perinatal factors, including gestational age, delivery mode, feeding mode and antibiotics. Figure drawn with Figdraw software 2.0 (ID: YSWWI01d07, www.figdraw.com; provided by Home for Researchers, China). C-section, cesarean section.

2-3 years. The precise timing of the colonization of the gut by bacteria remains controversial. It has previously been considered that the fetus and placenta are sterile, but advances in testing techniques (such as 16S ribosomal DNA-based and whole-genome shotgun metagenomic studies) have enabled the identification of a unique placental microbiome niche that is comprised of non-pathogenic commensal microbiota (such as *Firmicutes*, *Tenericutes*, *Proteobacteria*, *Bacteroidetes* and *Fusobacteria phyla*) (34). Collado *et al* (35) also previously identified a unique bacterial community in the amniotic fluid dominated by *Proteobacteria* and successfully cultured bacteria from the placentas of healthy pregnant women. The observation that the amniotic fluid and placenta have their own microbiota suggests the potential for fetal colonization by bacteria during the intrauterine environment, which may contribute to the maturation of early immune cells (36). However, contamination could not be ruled out as one of the causes of the aforementioned phenomena (37,38).

Bacteria can be detected in the fetal stool of preterm infants after birth (39). Compared with healthy term infants, preterm infants tended to have more *Staphylococcaceae* and delayed colonization by *Bifidobacteriaceae* in their feces (40). The intestinal microbiota of preterm infants does not have a specific 'phenotype' and develops in a manner similar to that of healthy term infants, from *Gram-positive cocci* to *Enterobacteriaceae* and then to *Bifidobacteriaceae* (39,40). The development of intestinal microbes in preterm infants is influenced by key perinatal factors, including gestational age, delivery mode, feeding mode and the profile of antibiotics use (Fig. 1).

Gestational age. In preterm neonates, gut microbiota development is predominantly determined by gestational age. A previous study has indicated that the gut microbiota of premature infants residing in a tightly controlled microbial

environment progresses through a choreographed succession of bacterial classes from *Bacilli* to *Gammaproteobacteria* to *Clostridia* (41). Antibiotics, vaginal vs. caesarian birth, diet and age of the infants when sampled influence the pace, but not the sequence of progression (41). Korpela *et al* (42) delineated four phases of gut microbiota maturation in preterm infants, where the first three phases are dominated by *Staphylococcus*, *Enterococcus* and *Enterobacter*, then the fourth phase is characterized by the prevalence of *Bifidobacterium*. This progression is closely associated with postmenstrual age. Compared with term infants, preterm neonates exhibit reduced gut microbiota diversity, increase in conditionally pathogenic bacteria and delayed colonization by beneficial species, such as *Bifidobacteriaceae* and *Bacteroidetes* (43).

Birth mode. The intestinal microbiota of preterm infants delivered vaginally is primarily sourced from the vaginal microbiota of the mother, including *Lactobacillus*, *Prevotella* and *Sneathiella* spp (44). By contrast, the gut microbiota of preterm infants born through cesarean section (C-section) more closely resembles the skin of the mother and the environmental microbiota, which is predominantly comprised of *Staphylococcus*, *Corynebacterium* and *Propionibacterium* spp. Notably, the colonization of beneficial bacteria, such as *Lactobacillus*, *Bifidobacterium* and *Bacteroides* spp., is delayed in infants delivered by C-section (44,45). This disparity in gut microbiota composition between infants delivered vaginally and by C-section diminishes at 4 and 12 months after birth (45).

Feeding mode. Feeding practices notably influence the gut microbiota composition of preterm infants, with breastfed infants exhibiting greater microbial diversity. Breast milk is rich in diverse microbiota and human milk oligosaccharides (HMOs), which promote the growth of *Bifidobacterium* (46).

Consequently, the gut of breastfed preterm infants is predominantly colonized by *Bifidobacterium* and *Lactobacillus*, whereas *Bacteroides* spp. and *Clostridium sporogenes* are more prevalent in formula-fed infants (46). In particular, pasteurized donor breastmilk has been shown to assist preterm infants in developing a gut microbiota profile resembling that of breastfed healthy neonates, accelerating the acquisition of microbial diversity (47).

Antibiotics. Antibiotics can exert a profound impact on the gut microbiota. Preterm infants frequently receive antibiotics for extended durations during the perinatal period, longer than their term counterparts. This prolonged exposure can markedly reduce the quantity and diversity of gut microbiota, leading to a depletion of beneficial bacteria (48). In addition, extended antibiotic use is associated with increased colonization by potentially pathogenic bacteria, such as *Escherichia coli*, *Shigella*, Enterobacteriaceae and *Enterococcus*, which may contribute to the emergence of antibiotic-resistant bacteria (49).

Gut microbiota is integral to the health of preterm infants, where it serves a key role in maintaining intestinal immune homeostasis. A balanced symbiotic relationship between commensal microbiota and the host is essential for establishing effective immune defense and immune tolerance. Conversely, dysbiosis of the gut microbiota can disrupt this delicate balance, leading to immune system dysfunction and increasing the risk of various morbidities in preterm infants (50).

4. The cause-and-effect of intestinal microecology on BPD

BPD induces alterations in intestinal microenvironment. BPD is a multifactorial and heterogeneous disease, the pathogenesis of which is rooted in repeated injury to immature lungs and aberrant repair processes triggered by a number of factors, such as infection, mechanical ventilation and hyperoxia (1,4). Maintaining a healthy gut microbiota is crucial for immune homeostasis in preterm infants. Furthermore, emerging evidence has indicated that both pulmonary and gut microbiota are altered in infants with BPD (10,51). Clinical studies have demonstrated that in preterm infants, the progression of BPD is associated with dynamic changes in the Proteobacteria and Firmicutes phyla and the *Lactobacillus* genus within the lung microbiota, where that pulmonary dysbiosis may exacerbate BPD severity (52,53). Specifically, preterm infants with severe BPD exhibit more pronounced changes in the respiratory microbiota, characterized by reduced *Staphylococcus* and increased *Ureaplasma* during early postnatal colonization (54,55).

The interaction between lung and gut microbiota is bidirectional, with alterations in one able to influence the other. This interplay is mediated through shared immune signaling pathways, including cytokine signaling and Toll-like receptor (TLR) activation, in addition to neuroendocrine pathways, such as the hypothalamic-pituitary-adrenal axis and vagus nerve-mediated communication, which collectively impact respiratory and gastrointestinal health. Previous studies have shown associations between gut dysbiosis and changes in lung microbiota composition, with reciprocal effects of lung microbiota perturbations on gut health (56,57). Chen *et al* (11) divided preterm infants with a gestational age of 26-32 weeks into a BPD and non-BPD group and demonstrated that gut microbiota

diversity was significantly reduced in the BPD group compared with non-BPD group at postnatal day 28. Furthermore, other clinical studies reported lower Shannon diversity of the gut microbiota indices in infants with BPD, which documented that the relative abundance of Proteobacteria was elevated in the gut microbiota of the BPD group whereas the abundance of the Firmicutes phylum was decreased, between postnatal days 14 and 28 (54,58). To address confounding factors, such as preterm birth and delivery mode, Lal *et al* (59) investigated the gut microbiota of vaginally delivered preterm infants and revealed that BPD was associated with increased relative abundance of *Escherichia coli* and *Shigella*, with decreased levels of *Klebsiella* and *Salmonella* in the gut microbiota (10). These findings collectively support the existence of intestinal dysbiosis in BPD, highlighting the gut-lung axis as a potential therapeutic target for mitigating disease progression.

Gut microecological disorders contribute to BPD progression through the gut-lung axis. Infants with BPD exhibit disruptions in both the respiratory and gut microbiota. This can influence BPD progression by both regulating immune-related gene expression and inducing systemic and intrapulmonary inflammatory responses (60). In a BPD mouse model, antibiotic-induced intestinal commensal disruption during the perinatal period promotes a more severe BPD phenotype, characterized by increased lung fibrosis, vascular remodeling, alveolar inflammation and higher rates of morbidity and mortality. This was attributed to the disruption of intestinal commensal bacterial colonization, highlighting the gut-pulmonary axis as a key factor in BPD development (61).

Intestinal microecology disorders can promote BPD progression through the gut-lung axis and the mechanisms may include the following: i) Intestinal barrier disruption, where gut dysbiosis can compromise the intestinal barrier, increasing intestinal permeability to allow bacterial translocation to the lungs. Additionally, dysbiosis-generated metabolites may trigger immune cell activation, leading to local or systemic inflammation and metabolic disturbances (62). ii) Amplification of pulmonary inflammation, where gut dysbiosis can exacerbate lung injury by promoting pulmonary inflammation. A previous study indicated that TLRs can recognize lipopolysaccharides (LPS) from gut bacteria, upregulating IL-1 β expression to activate NF- κ B in a rodent model. This initiates an inflammatory cascade to exacerbates lung injury (63). iii) Metabolic dysregulation, where gut dysbiosis influences BPD development through various metabolic pathways. Li *et al* (64) determined that 129 differentiated metabolites were changed in patients with BPD via metabolomics analysis, and a correlation analysis revealed a remarkable relationship between gut microbiota and metabolites. Other studies have shown that oral administration of *Lactobacillus plantarum* L168 may play a protective role in BPD by regulating the systemic metabolome, such as glutathione metabolism and arachidonic acid metabolism (65). iv) Association with growth restriction. Gut dysbiosis is strongly associated with growth restriction and BPD in preterm infants. Given the critical role of the gut microbiota in the extrauterine growth of VLBW infants and the protective effects of nutritional support against BPD (66), modulating gut microbiota to improve nutritional status may reduce BPD risk in preterm infants.

Compared with term infants, preterm infants have a reduced diversity of gut microbial communities, where factors such as exposure to hyperoxia, antibiotic exposure and nosocomial infections, further disrupt microbial homeostasis. These disruptions compromise the gut barrier, trigger inflammatory responses, metabolic disorders and malnutrition, all of which further impair lung tissue repair through the gut-lung axis, ultimately accelerating the progression of BPD (53).

Unique mechanism of the gut-lung axis in BPD. The core pathological feature of BPD in preterm infants is the developmental arrest of immature lungs due to injuries, such as hyperoxia and mechanical ventilation (1). The gut-lung axis may contribute to BPD through the following mechanisms: i) Early disruption of gut microbiota diversity, where both the gut and lungs of preterm infants are immature. Prolonged hyperoxia inhibits the growth of beneficial bacteria, such as *Lactobacillus*, increasing pathogen abundance and causing dysbiosis. This dysbiosis can intensify pulmonary inflammation and alveolar developmental disorders by altering metabolites, including short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), volatile organic compounds (VOCs) and butyrate, as soon as impairing immune regulation (67,68). BPD-related dysbiosis is characterized by reduced biodiversity and the absence of specific bacteria (such as *Lactobacillus*) (11,58). By contrast, necrotizing enterocolitis (NEC)-associated lung injury involves a complete gut microbiota collapse, with endotoxins (including LPS) entering the circulation and triggering systemic inflammation (69). ii) Hyperoxia-induced microbiota-inflammation interactions. Hyperoxia exposure induces alveolar epithelial cells damage in BPD, simultaneously alters gut microbiota composition and promotes bacterial translocation to the lungs. This process activates immune and inflammatory pathways, releasing cytokines (such as IL22, IL6 and IL17) that inhibit alveolar development (60,61). NEC-related lung injury, however, results from systemic inflammation and sepsis caused by acute intestinal necrosis, rather than the direct effects of hyperoxia (69,70).

5. Immunological modulation of the gut-lung axis in BPD progression

Gut microbiota and its metabolites mediate the pulmonary immune response through the gut-lung axis. The neonatal immune response consists of both innate and adaptive components. In preterm infants with an immature immune system, airway and gut microbiota serve a crucial role in immune development. The 'intestinal microbiota translocation' theory posits that gut microbiota or bacterial products can directly transfer to the lungs through the gut-lung axis, disrupting pulmonary microecological balance. Additionally, gut microbial metabolites entering the pulmonary circulation through systemic circulation can stimulate lung immune cells, activating inflammatory responses and inducing lung injury (71). Furthermore, these metabolites, including SCFAs, can enter the bone marrow through the bloodstream, promoting hematopoiesis and stimulating hematopoietic stem cell differentiation (31). These cells then migrate to the respiratory tract, modulating lung inflammation in conjunction with the aforementioned mechanisms.

Gut microbiota. The gut barrier is a critical defensive system within the gastrointestinal tract, preventing pathogen and endotoxin invasion to avert inflammation and bacterial translocation. Numerous factors, such as gestational age, feeding practices and antibiotic use, can all disrupt the intestinal microecological balance, affecting gut barrier maturation in preterm infants (10). In neonates with NEC, intestinal mucosal macrophages and immune cells clear the majority of bacteria. However, surviving bacteria or their inflammatory fragments can reach the lungs, activating alveolar macrophages and causing lung injury (72). Gut-derived bacterial products, including bacterial fragments and metabolites, can enter the pulmonary circulation through the systemic circulation to stimulate lung immune cells (such as macrophages, T cells and neutrophils) to trigger inflammation (29). Dickson *et al* (73) previously detected live gut bacteria in the lungs of septic mouse models and in the bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome, suggesting that local or systemic inflammation can mediate gut microbiota translocation, disrupting lung microecological homeostasis. Intestinal microecological imbalances can also increase gut permeability, potentially allowing bacterial products to directly transfer to the lungs and exacerbate pulmonary inflammation. Notably, recent studies have drawn attention to the impact of strain-specific microbiota (65,74). Shen *et al* (65) observed reduced lung injury and improved lung development in BPD rats exposed to *Lactiplantibacillus plantarum* L168. These results suggested that L168 may improve BPD through downregulation of the TLR4/NF- κ B/Chemokine (C-C motif) ligand 4 pathway (65). By contrast, although supplementing *Lactobacillus reuteri* DSM17938 has been shown to improve intestinal health, it has no notable therapeutic effects on BPD (75). The differences between the two suggest strain-specific microbiota effects.

Microbiota metabolites. Alterations in gut flora composition can impact pulmonary immune function, with bacterial metabolites serving a key role in gut-lung immune communication and potentially contributing to BPD progression. SCFAs are essential gut microbiota metabolites that exhibit anti-inflammatory properties by reducing immune cell migration and adhesion and increasing anti-inflammatory cytokine release. SCFAs can traverse the gut-lung axis to modulate pulmonary immunity, with two primary immunomodulatory mechanisms suggested: i) Driving anti-inflammatory responses through downstream effector molecules; and ii) inhibiting histone deacetylase (HDAC) activity to regulate immune responses. SCFAs can also promote anti-inflammatory responses in extraintestinal organs, mitigating airway inflammation. Low fecal acetic acid levels in preterm infants have been associated with higher BPD incidence, whereas acetic acid supplementation could reduce inflammation in mice with hyperoxia-exposed BPD, decrease the proportion of *Escherichia-Shigella*, increase the abundance of *Ruminococcus* and attenuate lung injury, potentially preventing neonatal BPD (76).

Other gut microbiota metabolites, such as TMAO and VOCs, can also influence BPD pathology by reducing airway inflammation and restoring epithelial function. Altered urinary metabolites, including lactate, taurine, TMAO, inositol and gluconate, have all been observed in infants with BPD (77).

Specifically, alanine and betaine levels are elevated whereas TMAO, lactate and glycine levels are reduced in patients with BPD compared with those in non-BPD controls (78). Notably, gut microbiota can alter TMAO levels, and TMAO can activate inflammation and induce oxidative stress, thereby modulating BPD susceptibility (79). Fecal VOCs, produced by intestinal flora during polysaccharide fermentation, can influence lung function by altering the air-liquid interface properties of pulmonary surfactants, stimulating pro-inflammatory factor production and exacerbating oxidative stress. These effects suggest a potential link between VOCs and BPD development (80). Previous studies have shown associations between fecal VOC changes and BPD severity, where VOCs have demonstrated potential for early BPD diagnosis and prediction within the first 2 weeks of birth (81,82). Furthermore, it has been shown that butyrate can enhance gene expression (such as p16INK4a, p14ARF, and p15INK4b) by inhibiting HDACs, thereby promoting histone acetylation and a more relaxed chromatin structure (83,84). SCFAs can also influence DNA methylation patterns by modulating DNA methyltransferases, chromatin remodeling complexes, microRNAs and transcription factors (85,86). However, the exact role of these epigenetic mechanisms in BPD pathogenesis remains to be fully clarified.

Gut microenvironment alters the levels of pulmonary inflammation through the lung-gut axis. It has been previously demonstrated that the gut microenvironment serves a crucial role in modulating pulmonary immunity through the gut-lung axis. Gut microenvironment disruption can lead to increased cytokines and inflammatory mediators, which then spill over into the systemic circulation, driving lung inflammation, disrupting the lung microenvironment and worsening BPD. This process involves alterations in key inflammatory pathways, including changes in IL-17, IL-22, IL-6 and TNF- α signaling (87). Metabolites from gut microbiota, such as polysaccharide A, α -galactosylceramide and tryptophan metabolites, can activate proinflammatory factors, including IL-17 and IL-22, triggering local or systemic inflammation and immune dysfunction. Aberrant signaling from these metabolites can alter the developing lungs, contributing to lung disease (88). In neonatal mice with BPD, T helper (Th)17 inflammatory responses are heightened in the lung tissue, where neutralizing IL-17 with specific antibodies can alleviate BPD-associated lung injury (89). Additionally, *Lactobacillus* species degrade tryptophan to produce IL-22, which suppresses immune responses and promotes regulatory T-cell development, in turn protecting both gut and lung tissues (81). FMT has also shown promise in mitigating acute lung injury in rats by reducing inflammatory cell infiltration and lung interstitial exudation through downregulating TNF- α , IL-1 β , IL-6 and TGF- β expression (90). These findings underscore the influence of the gut microbiota on inflammatory mediator levels and its subsequent impact on pulmonary pathology.

Immune cell migration-mediated mucosal immunoregulatory mechanisms in the gut-lung axis. A primary communication pathway within the gut-lung axis involves the migration of immune cells between the gut and lungs, activating mucosal immunoregulatory mechanisms and influencing BPD progression (91). Certain intestinal mucosal immune cells, such as

CD4⁺ and CD8⁺ cells, can reside in both the gut and lungs, suggesting that mucosal immunity may constitute the immune network between the lungs and the intestines (29). In BPD, lung inflammation involves immune cell infiltration, some of which originate from the gut and are activated by intestinal immune responses before migrating to the lungs (91). Innate lymphoid cells (ILCs) and dendritic cells (DCs) migrating along the gut-lung axis may serve a notable role in BPD pathogenesis (92,93).

ILCs are widely distributed in the mucosa of the intestine and respiratory tract, where they regulate immunity and mucosal barrier homeostasis through cytokine secretion (92,94). Gut ILCs can enter the bloodstream through the mesenteric lymphatic system and migrate to the lungs, contributing to epithelial repair (71). In neonatal mice with BPD, type 2 ILCs (ILC2) numbers are elevated in the lung tissue and are associated with alveolar differentiation arrest (92,94). ILC2 depletion by anti-CD90.2 antibodies has been reported to alleviate BPD-related lung injury (94). ILC2 can migrate from the intestine to the lungs under the induction of IL-25 and participate in the immune inflammatory response of the lungs (90). This was demonstrated in a previous study where connecting the circulatory systems of two mice and injecting IL-25 into one led to ILC2 migration from the gut of the treated mouse to the lungs of both, exacerbating lung inflammation (63). This suggests that inflammatory stimulus may drive ILC2 recruitment to the lungs through the gut-lung axis, impacting BPD pathogenesis, but the exact molecular mechanisms require further investigation.

Type 3 ILCs (ILC3), a critical component of mucosal immunity, serve an essential role in defending against lung infections in preterm infants. A previous study showed that the level of ILC3 expression is notably elevated in the lung tissue of mice with BPD, promoting Th17 inflammatory responses and exacerbating lung injury (89). In preterm infants with NEC, gut mucosal DCs can recognize intestinal dysbiosis, triggering ILC3 migration to the lungs of neonatal mice. This disrupts pulmonary innate immunity and impairs type II alveolar epithelial cell secretion of surfactants, leading to lung injury (88). Gray *et al* (93) previously demonstrated that intestinal DCs can drive ILC3 migration to the lungs. Disrupting postnatal bacterial colonization or selectively deleting DCs blocks IL-22 and ILC3 migration, increasing susceptibility to *Streptococcus pneumoniae* in neonatal mice (93). This highlights the role of commensal gut bacteria in orchestrating pulmonary mucosal immunity, crucial for lung defense system maturation. Disrupting ILC3 homeostasis in neonatal lungs may impair the pulmonary mucosal defense system, raising the risk of respiratory infections and inflammatory diseases, worsening BPD incidence and severity. Novel insights into mucosal immunoregulation may offer promising avenues for understanding BPD development, emphasizing the complex gut-lung axis interactions. In conclusion, the present review discussed the immunological modulation of the lung-gut axis in BPD (Fig. 2).

6. Emerging therapeutic approaches for BPD via the gut-lung axis

The treatment implications of the gut microbiome in BPD remain under investigation. However, several potential

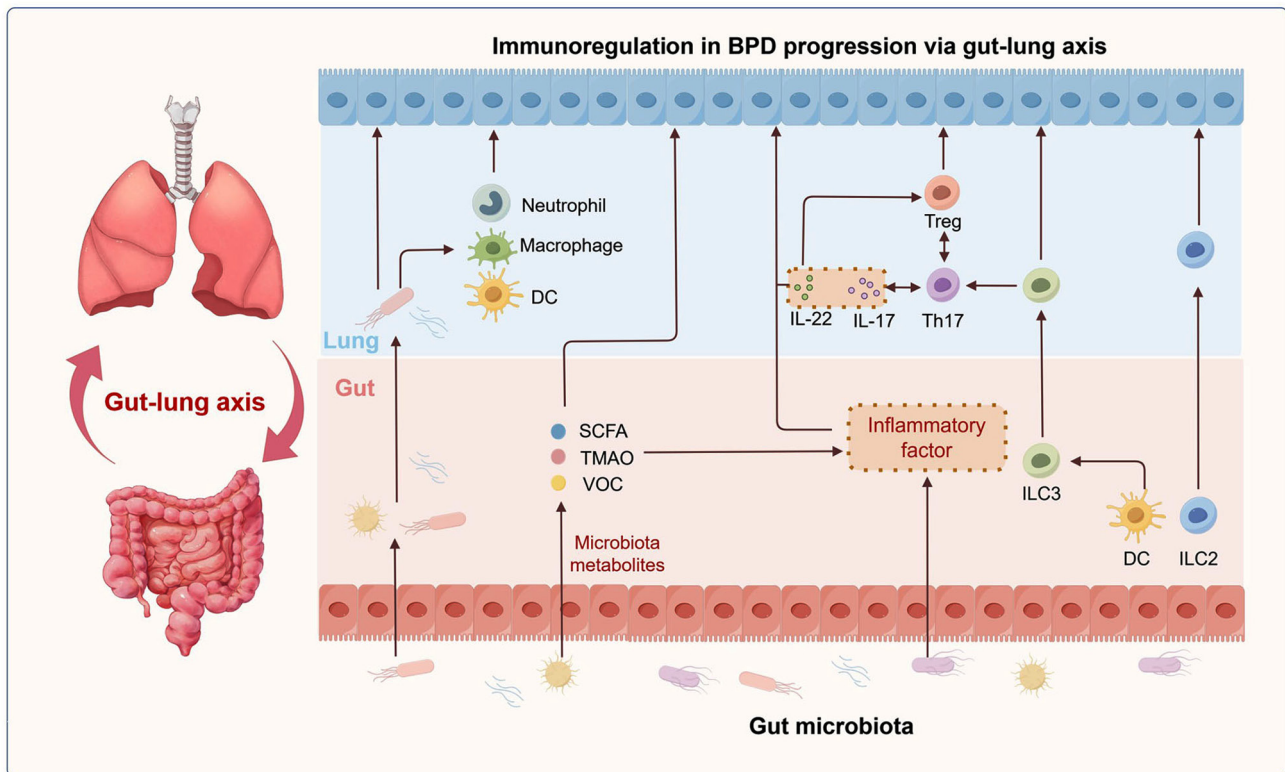


Figure 2. Mechanism of the gut-lung axis in the progression of BPD. The mechanism underlying immunological modulation of the gut-lung axis in BPD includes: i) Gut microbiota and its metabolites mediate the pulmonary immune response; ii) gut microenvironment alters the level of pulmonary inflammation; and iii) immune cell migration-mediated mucosal immunoregulatory mechanisms. Figure drawn with Figdraw software 2.0 (ID: IRWIA45788, www.figdraw.com; provided by Home for Researchers, China). BPD, bronchopulmonary dysplasia; DC, dendritic cell; ICL2, type 2 ILCs; ILC3, type 3 ILCs; ICLs, innate lymphoid cells; SCFA, short-chain fatty acid; Th, T helper; TMAO, trimethylamine N-oxide; Treg, regulatory T cells; VOC, volatile organic compound.

treatment implications have emerged (Fig. 3). Probiotics offer a potential approach to restoring the balance of gut microbiota, which in turn can have a positive impact on lung health. Accumulating evidence has suggested that specific probiotics may confer protection against BPD and other respiratory conditions (e.g., asthma, COPD, cystic fibrosis, lung cancer and respiratory infection). These probiotics, such as *Filamentous bacteria*, *Limosilactobacillus reuteri* and *Bifidobacterium bifidum*, achieve their beneficial effects through immune modulation, reduction of inflammation and the preservation of barrier integrity in both the gut and lungs (94-96). Qu *et al* (97) previously investigated the effects of *Clostridium butyricum* supplementation on extremely preterm infants and found that probiotic-treated infants had lower rates of BPD and invasive mechanical ventilation use, suggesting that probiotics may be a notable factor influencing BPD risk (odds ratio=0.034; 95% CI, 0.012-0.096). However, a meta-analysis by Villamor-Martínez *et al* (98) found no significant effect of probiotic supplementation on BPD risk. These contradictory results should be interpreted cautiously and may stem from methodological differences in randomized controlled trials, such as variations in enrollment criteria, timing and dosing regimens. Additionally, different probiotic strains, doses and formulations may yield varying results. Future research should focus on optimizing probiotic usage, including strain selection, dosing, timing and administration methods, to understand their potential in BPD management.

In addition to probiotics, prebiotics present another avenue for influencing the gut microbiota. These indigestible fibers can promote the growth of beneficial bacteria in the gut (99). By incorporating prebiotics (e.g. fructans, galactooligosaccharides, xylooligosaccharides, chitooligosaccharides, lactulose, resistant starch, polyphenols) as supplements, it is possible to affect changes in the microbiota and their metabolites within both the intestinal and pulmonary environments, potentially offering a novel intervention strategy (98). Furthermore, the direct administration of SCFAs has demonstrated efficacy in regulating immune responses, preserving barrier function and mitigating inflammatory processes in the gut and lungs (99,100). SCFAs can be delivered through various routes, including intranasal administration, in conjunction with milk or through drinking water (98,99). However, it is important to note that these findings have primarily been observed in animal models and therefore require further validation in clinical settings.

FMT represents another emerging therapeutic approach that may influence lung health, by enhancing gut microbiota diversity, reducing inflammation and modulating immune responses (101). To the best of our knowledge, FMT has not yet been investigated in the context of BPD, which presents a promising area for future research. The implementation of antibiotic stewardship programs in neonatal intensive care units is therefore crucial at present. By optimizing antibiotic use and minimizing unnecessary exposure, such programs can help preserve the integrity of the gut microbiome and potentially reduce the risk of BPD (102).

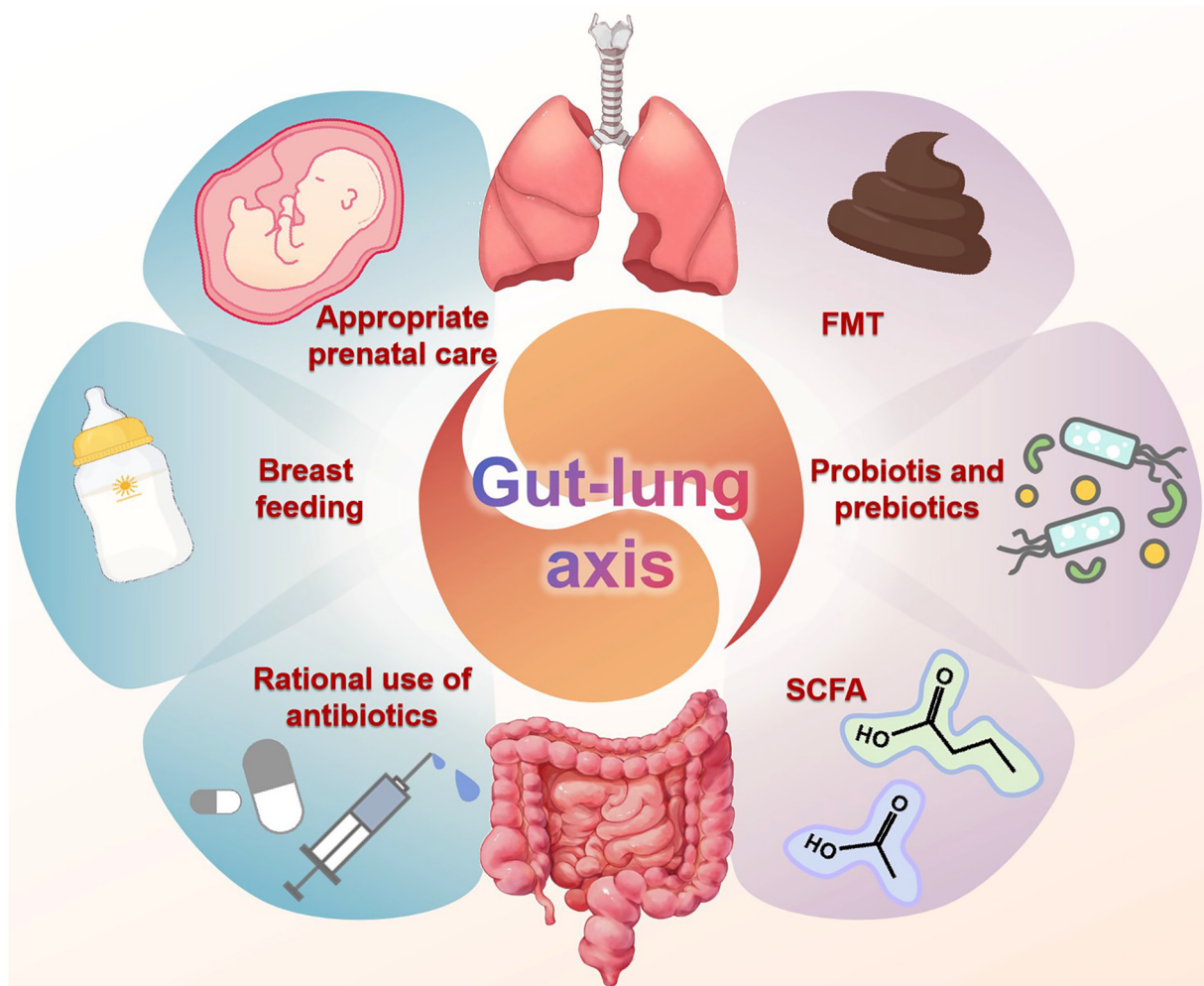


Figure 3. Emerging therapeutic approaches for BPD via the gut-lung axis. Several potential treatment implications of the gut microbiome in BPD have emerged, including probiotics and prebiotics, FMT, SCFA supplementation, avoiding premature birth, breast feeding and the rational use of antibiotics. Figure drawn with Figdraw software 2.0 (ID: TWPSObfadf, Obfadfwww.figdraw.com; provided by Home for Researchers, China). BPD, bronchopulmonary dysplasia; FMT, fecal microbiota transplantation; SCFA, short-chain fatty acid.

Gestational age is considered a pivotal factor in influencing both microbiota composition and lung development. Consequently, strengthening perinatal clinical care may be one of the important means to prevent premature birth. For cases of inevitable preterm birth, perinatal management strategies focused on lung protection for preterm infants are particularly vital. Breast milk has been shown to decrease the incidence of BPD, due to its rich nutritional content and bioactive components, including its microbial composition, exosomes and HMOs (46). Current optimal feeding strategies emphasize the importance of promoting breastfeeding and fortifying formula milk with HMOs (46).

7. Conclusions and prospects

The gut-lung axis, a bidirectional communication pathway between the intestines and lungs, serves a pivotal role in shaping the progression of BPD through alterations in the gut microbiota and the immune microenvironment. Disruptions in intestinal microecology are closely associated with pulmonary pathogenesis. The gut-lung axis can influence the progression of BPD through a range of mechanisms, such as bacterial

translocation, microbial metabolite exchange, inflammatory cytokine spillover and immune cell migration. The present review delved into the role of the gut-lung axis in BPD pathogenesis, including the bidirectional communication of the gut-lung axis, the interplay between BPD and gut microenvironmental changes and the immune regulatory mechanisms of the gut-lung axis.

Emerging evidence from animal models and human studies has suggested that FMT and probiotics may offer promising therapeutic or preventive strategies for BPD. Additionally, analyzing the microbial composition and metabolite profiles of infants may enhance diagnostic accuracy and prognostic predictions of BPD. However, research into the relationship between gut microbiota and BPD remains in its infancy, with both progress and limitations. Key limitations include: i) Small and heterogeneous clinical samples, such that the majority of studies have small sample sizes, where preterm infants vary greatly in gestational age, birth weight and treatments (such as the duration of mechanical ventilation), making results difficult to generalize (11,52). ii) Limited microbiota analysis methods, since the majority of existing studies use 16S rRNA sequencing, which cannot detect strain-level differences or

direct metabolic effects (53,103). iii) Lack of longitudinal studies, since the majority of previous studies focused on short-term postnatal microbiota changes (52,104). However, the pathological process of BPD can last months, where long-term microbiota dynamics data remain scarce. A number of previous animal studies have explored the relationship between gut microbiota and BPD. However, animal experiments have difficulties in extrapolation of findings from animal studies to humans, specifically regarding model construction, physiological differences, microbiota complexity and clinical transformation, as follows: i) Physiological differences, where animal models differ physiologically from human preterm infants, particularly in developmental staging and immune system maturity (105,106). ii) Species-specific gut microbiota, where gut microbiota composition and metabolites vary by species. Differences exist in colonization patterns, strain functions, metabolic pathways and pathogen virulence (107,108). iii) Clinical translation barriers, where challenges remain in clinical translation, such as determining administration methods and assessing safety. Although FMT has shown promise in animal studies, its safety in immunocompromised preterm infants requires further evaluation.

Research on the relationship between gut microbiota in preterm infants and BPD remains in its early stages. The present study reviewed the role of the lung-gut axis in BPD in recent years through a qualitative synthesis. However, the cited evidence has limitations, as follows: i) Uncontrolled confounders, such that the majority of animal models failed to simulate concurrent nutritional deprivation in preterm infants; ii) measurement bias, where 16S rRNA sequencing in the vast majority of clinical studies could not resolve strain-specific functions (such as commensal vs. pathogenic *E. coli*); and iii) Generalizability, since the majority of included cohorts were single-center with limited ethnic diversity. By contrast, a meta-analysis would provide quantitative estimates of the gut-lung axis mechanisms in BPD and strengthen the evidence synthesis. However, a meta-analysis of the studies may have the following methodological and scope-related limitations: i) The available clinical studies exhibited substantial heterogeneity in patient populations [including varying gestational ages (24-32 weeks), birth weights (500-1,500 g)], intervention protocols (probiotic strains, dosing regimens) and outcome measures (BPD diagnostic criteria ranging from National Institutes of Health 2001 to 2018 consensus). Such heterogeneity would compromise the validity of pooled effect estimates. ii) A meta-analysis is typically suited for interventional trials with dichotomous outcomes (such as BPD incidence), whereas the present review focused on mechanistic pathways (such as immune cell migration, SCFA-induced epigenetic regulation) primarily derived from animal and *in vitro* studies, which cannot be meaningfully quantified by statistical pooling. iii) Critical data required for meta-analysis (including standard deviations of microbial abundance and exact cytokine levels) are rarely reported in mechanistic studies. Future large-scale, standardized cohorts are needed to enable meta-analyses of gut microbiota signatures in BPD.

The present review systematically consolidated advances in understanding the role of the gut-lung axis in BPD pathogenesis and demonstrates advantages over similar reviews in the following key areas (93,109): i) Focused mechanistic

depth on the gut-lung axis. The present study systematically focused on the bidirectional causal relationship between intestinal dysbiosis and the progression of BPD. In addition, by comparing the gut-lung axis mechanisms in BPD with those in NEC-related lung injury, the BPD-specific mechanisms were highlighted, which is rarely presented in similar reviews (93,109). ii) Integration of developmental immunology. The present review established the fundamental biological basis of the gut-lung axis by detailing the shared embryonic origin (endoderm), signaling pathways (Wnt/Bmp/Fgf) and transcription factors (Nkx2.1/Sox9). The review also clarified the immunomodulatory role of the gut-lung axis in BPD, a mechanism that is rarely covered in similar reviews (59,109). iii) Critical appraisal of therapeutics. The current review discussed the contradictory clinical evidence of probiotics, avoiding overgeneralization. Furthermore, the possibility of emerging therapeutic applications (FMT, SCFA supplementation and prebiotics) was explored, whilst acknowledging the translation gap from animals to humans. iv) Methodological rigor and transparency. The present review clearly outlined the shortcomings of the existing clinical studies (such as small heterogeneous cohorts, limitations of 16S rRNA sequencing and lack of longitudinal data). Furthermore, it was clearly explained as to why the performance of a meta-analysis was inappropriate (heterogeneity, mechanism focus and missing data), enhancing academic credibility. In the future, further elucidation of the role of the gut-lung axis in BPD is essential to uncover novel patho-mechanistic insights and therapeutic targets. The present study may facilitate a more integrated approach to BPD prevention, management and prognosis, ultimately improving the quality of life for affected patients.

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Authors' contributions

YZ was involved in the conception of the study, the formulation of overarching study aims, manuscript preparation and article revision. RDD contributed by preparing the manuscript, specifically its critical review, commentary and revision. Data authentication is not applicable. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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