Exposure to prescribed medication in early life and impacts on gut microbiota and disease development

Huan Huang,[a,b,c] Jiayin Jiang,[a,c] Xinyu Wang,[a,c] Kui Jiang,[a,**] and Hailong Cao[a,*]

[a]Department of Gastroenterology and Hepatology, General Hospital, Tianjin Medical University, Tianjin Institute of Digestive Diseases, Tianjin Key Laboratory of Digestive Diseases, Tianjin, China
[b]Department of Gastroenterology, the Affiliated Jinyang Hospital of Guizhou Medical University, the Second People's Hospital of Guiyang, Guiyang, China

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Summary

The gut microbiota during early life plays a crucial role in infant development. This microbial-host interaction is also essential for metabolism, immunity, and overall human health in later life. Early-life pharmaceutical exposure, mainly referring to exposure during pregnancy, childbirth, and infancy, may change the structure and function of gut microbiota and affect later human health. In this Review, we describe how healthy gut microbiota is established in early life. We summarise the commonly prescribed medications during early life, including antibiotics, acid suppressant medications and other medications such as antidepressants, analgesics and steroid hormones, and discuss how these medication-induced changes in gut microbiota are involved in the pathological process of diseases, including infections, inflammatory bowel disease, metabolic diseases, allergic diseases and neurodevelopmental disorders. Finally, we review some critical methods such as dietary therapy, probiotics, prebiotics, faecal microbiota transplantation, genetically engineered phages, and vagus nerve stimulation in early life, aiming to provide a new strategy for the prevention of adverse health outcomes caused by prescribed medications exposure in early life.

Keywords: Early life; Gut microbiota; Medications; Health outcomes

Introduction

Early life, which encompasses the period from conception to the age of 2 years, is recognised as a crucial time for the establishment and maturation of the human microbiome.[1,2] The early-life microbiome, including the gut microbiota, plays a fundamental role in long-term human development and health.[2] However, early environmental factors such as prenatal environment, mode of delivery, feeding patterns, and medications, can shape human gut microbiota. Among these factors, medications, including antibiotics and non-antibiotic drugs, are considered to be one of the strongest predictors of gut microbiota composition, acutely affecting microbial communities.[3,4] Currently, numerous studies have focused on the epidemiological connections between early medication exposure and diseases later in life. Gaining a better understanding of the relationships between early medication exposure, gut microbiota, and health outcomes will open up opportunities for early prevention and treatment. Therefore, this Review primarily centres on the impacts of commonly prescribed medications on the gut microbiota during early life, how these effects contribute to the development of diseases, and potential solutions such as dietary therapy, probiotics, prebiotics, faecal microbiota transplantation (FMT), genetically engineered phages and vagus nerve stimulation (VNS) to mitigate the effects of early pharmaceutical interventions. The medications discussed in our review are frequently essential for the well-being of both mothers and infants, and the related recommendations will not jeopardise the health and welfare of mothers.

Development of human gut microbiota during early life

Rackaityte et al.[5] recently confirmed that bacteria colonise the fetal intestine during the second trimester, of which *Micrococcaceae* and *Lactobacillus* are the most abundant. During birth, newborns experience their first significant exposure to microbes. The longitudinal and successional transmission of maternal microbes plays a crucial role in the development of the neonatal microbiome, with delivery mode being the most influential factor in this process.[6,7] Vaginally delivered newborns have dominant bacterial communities such as

*Corresponding author. Department of Gastroenterology and Hepatology, General Hospital, Tianjin Medical University, Tianjin Institute of Digestive Diseases, Tianjin Key Laboratory of Digestive Diseases, Anshan Road No.154, Heping District, Tianjin 300052, China.
**Corresponding author. Department of Gastroenterology and Hepatology, General Hospital, Tianjin Medical University, Tianjin Institute of Digestive Diseases, Tianjin Key Laboratory of Digestive Diseases, Anshan Road No.154, Heping District, Tianjin 300052, China.
E-mail addresses: caohailong@tmu.edu.cn (H. Cao), kjiang@tmu.edu.cn (K. Jiang).
[c]These authors contributed equally to this work.

Lactobacillus spp., *Bifidobacterium*, *Bacteroides*, *Parabacteroides*, and *Escherichia/Shigella*, while newborns delivered by caesarean section exhibit enrichment of *Staphylococcus*, *Propionibacterium* spp., *Enterobacter*, and *Haemophilus* in their gut.[6,7] However, these differences resulting from the mode of delivery are minimal and gradually diminish with age.[6,7] Feeding patterns also shape the gut microbiota in infants. Exclusive breastfeeding leads to higher levels of protective *Lactobacillus* spp. and *Bifidobacterium*, such as *L. paracasei* and *Bacteroides longum*, and lower levels of *Veillonella* and opportunistic pathogens like *Clostridium difficile* and *Enterobacter cloacae* compared with formula-fed infants.[7–9] These differences in bacterial communities are closely related to the lack of human milk oligosaccharides (HMOs) and Immunoglobulin (Ig) A in formula milk.[10,11] The introduction of solid foods gradually transforms the infant gut microbiota to resemble that of adults, characterised by a rich presence of *Bacteroides*, *Clostridium*, *Bilophila*, *Roseburia*, and anaerobic bacteria.[7] In summary, the current consensus is that the human gut microbiota begins with the initial colonisation of facultative anaerobes, gradually transitions to dominance by obligate anaerobes, and finally forms adult-like microbial communities within 2–3 years of life (Fig. 1).

Perturbations of prescribed medications exposure on gut microbiota in early life

During infancy and even the toddler period (1–3 years of life), the richness and diversity of the gut microbiota undergo dynamic changes. This dynamic variation at the strain level provides crucial metabolic and immune functions for infants.[7,12] However, several factors, including the environment, preterm birth, diet, and medications, can influence the development trajectory of the gut microbiota during early life and impact the health outcomes of both infants and adults.[8,13] For instance, when compared to exclusive breastfeeding, non-exclusive breastfeeding of infants for the initial 6 months led to a higher presence of intestinal genera like *Bacteroides*, *Eubacterium*, and *Veillonella*, as well as a more active carbohydrate metabolism-associated flora. Conversely, there was a decrease in the presence of lipid metabolism-associated flora. These changes in the infant's gut microbiota could potentially increase the risk of diseases like obesity and diabetes.[8] Among them, prescribed medications are considered to be one of the strongest predictors of gut microbiota composition. According to reports, in Western countries, 30%–40% of pregnant women and 40%–70% of infants have been exposed to antibiotics, and over 80% of children have received at least one course of antibiotic treatment before the age of 2 years.[14–17] Due to symptoms such as nausea, vomiting, and acid reflux, pregnant women and infants are often prescribed acid suppressant medications (ASMs)—primarily proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2RAs).[18] In addition, pregnant women also commonly use hypotensive medications, levothyroxine sodium, methimazole, antidepressants, analgesics, hypoglycaemics, and corticosteroids. Both perinatal and infantile pharmaceuticals exposure may lead to long-term alterations in intestinal bacteria.[19] Other medications, such as ambroxol, curosurf (poractant alfa), vasoactive medications (most commonly dopamine), and steroid hormones, are commonly used within the first 2 years of life (Fig. 2). Our Review was centred on antibiotics and ASMs (Table 1).

Antibiotics

Antibiotics are among the most frequently administered medications during early life.[27] Whether it is a urinary tract infection in pregnant women or premature birth or sepsis in infants, early-life antibiotic use can have immediate benefits.[28,29] Studies have identified that early-life antibiotics may result in microbiome dysregulation connected with poor health outcomes. Maternal antibiotic exposure during pregnancy has been found to result in the detection of more than a dozen antibiotics in neonatal meconium, with penicillin showing the highest concentration.[20] The diversity and richness of gut microbiota were negatively associated with intrauterine penicillin.[20] Administration of antibiotics during childbirth, a common practice, may change the pattern of gut microbiota in newborns, characterised by lower relative abundance of *Actinobacteria* and *Bacteroidetes*, and higher relative abundance of *Proteobacteria* and *Firmicutes*.[30] Two prospective cohort studies which respectively included 266 vaginally delivered mother-infant pairs and 83 mother-infant pairs had showed the similar conclusions. 1-year-old infants with intrapartum antibiotic exposure to penicillins or cephalosporins had a slower increase in *Bifidobacterium*, *Bacteroides*, *Bacteroides fragilis*, *Enterococcus*, and *Escherichia coli* (*E. coli*), and a greater proportionate increase in *Coprococcus*.[21,22] Direct postnatal antibiotic use was a significant source of early-life antibiotic exposure, which disrupted the maturation pattern of the gut microbiota. In comparison to near-term infants (born at 36–37 weeks gestational age) who did not receive antibiotics during early life, preterm infants (born at 25–27 weeks gestational age) with very low birth weights (less than 1000 g) and antibiotic exposure to extensive antibiotics had a lower abundance of *Prevotellaceae* and a higher colonisation of *Enterobacteriaceae* and *Enterococcaceae*.[29] Pre-school children who were exposed to antibiotics early in life exhibited a lower abundance of *Actinobacteria* (including *Bifidobacterium*, *Collinsella*, and unassigned *Coriobacteriaceae*), and a higher abundance of *Bacteroidetes* (including *Bacteroides* and *Parabacteroides*), *Lactobacillales* and *Proteobacteria*.[23]

The magnitude of an antibiotic's effect on the gut microbiota depends on various factors. In contrast to the penicillin exposure, intrapartum cephalosporin exposure increased the growth of *Bacteroides fragilis* in

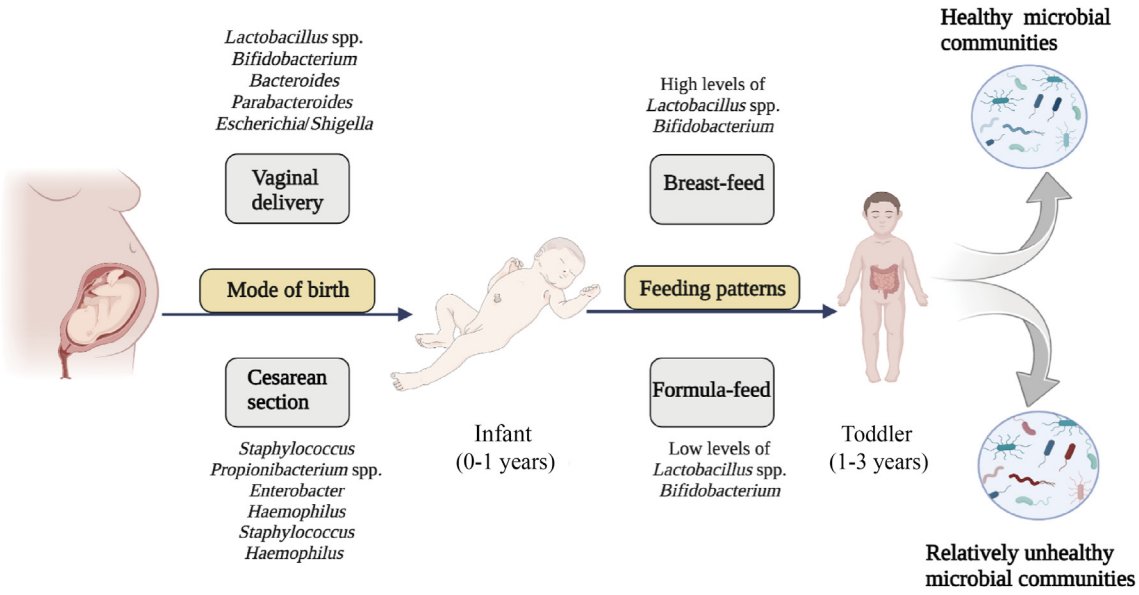

Fig. 1: Development of human gut microbiota during early life. Age is the most important factor affecting the development of gut microbiota. With age, the gut microbiota gradually shifts to an adult-like structure. In addition, birth modes and feeding patterns also play an important role. Newborns experience their first major microbial exposure at birth, during which mode of delivery is the most important factor affecting intestinal microbial colonisation. Feeding pattern also plays a critical role in regulating gut microbiota, which is mainly manifested by the levels of Lactobacillus and Bifidobacterium. By age 3, children who born vaginally and breastfed develop a healthy adult-like gut microbiome, while those who are delivered by C-section or fed by formula may develop a relatively unhealthy microbiome.

infants.[21] Penicillin appeared to have a lesser effect on the gut microbiota than macrolides.[23] These studies suggest that different antibiotic classes have distinct effects on gut microbiota. The dominant gut microbiota was different between infants exposed to maternal cefuroxime after umbilical cord clamping and those whose mothers were exposed to cefuroxime 30 min before skin incision,[31] indicating that different timing of antibiotic exposure had distinct effects on gut microbiota. The persistent reduction in *Bifidobacterium* was linked to the length of antibiotic usage, as longer antibiotic use was connected to slower recovery.[24] This implied that the duration of antibiotic exposure was a significant variable. Furthermore, different antibiotic combination regimens yielded varying effects on the gut microbiota.[32] These studies highlight the importance of considering antibiotic types, duration, timing, combination regimens, and underlying conditions as confounding factors when using antibiotics during early life.

Acid suppressant medications

Acid-suppressing drugs, particularly PPIs, are mostly used to treat acid-related diseases, but in recent years, their use for conditions beyond the core indications has been increasing.[33] Early administration of ASMs has been reported to disrupt the development of infant gut microbiota.[25,26] Gupta et al.[25] have suggested that H_2RAs treatment decreased the gut microbial diversity in preterm infants, with an increasing relative abundance of *Proteobacteria* (mainly *Enterobacteriaceae*) and less *Firmicutes*.[25] PPI administration for infant GERD had no significant effect on the phylum level of gut microbiota in infants, but showed prominent effects at the genus level.[26] The number of *Haemophilus* increased, and the number of *Lactobacillus* and *Stenotrophomonas* decreased. While there have been limited reports on the impact of early ASMs treatment on the gut microbiota, the potential negative effects later in life should not be ignored.

Other medications

Other commonly used medications during early life, such as steroid hormones, antidepressants, and analgesics, have been implicated in increasing the risk of various disorders associated with gut dysbiosis, including infections, neurodevelopmental disorders, and obesity.[34–36] Both population-based studies and animal models have demonstrated that these medications can alter the diversity and composition of the gut microbiota.[37–39] We therefore hypothesise that exposure to these medications may impact the developmental patterns of microbial communities, thereby increasing susceptibility to multiple diseases later in life. However, both population-based studies and animal experimental models are lacking in this area, further research is needed to fully understand the mechanisms by which these medications during early life contribute to the development of specific diseases. The interplay between these medication-induced changes in

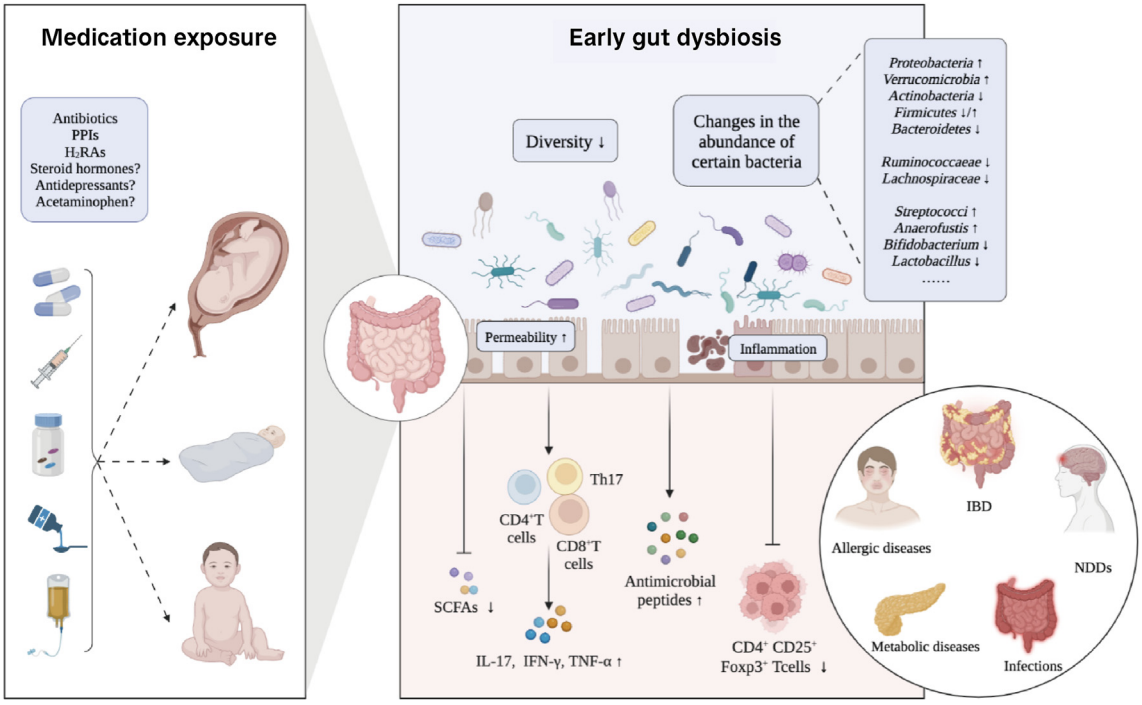

Fig. 2: Effects of early medication exposure on gut microbiota and long-term health outcomes. Early exposure to antibiotics and ASMs (mainly PPIs and H2RAs) affects the development of infant gut microbiota, which is characterised by the decreased diversity of gut microbiota and changes in the abundance of certain bacteria, such as Proteobacteria, Bacteroidetes and Bifidobacterium. This intestinal imbalance increases intestinal permeability, inflammation and the expression of antimicrobial peptides, as well as reduces the levels of SCFAs. The development of immune cells has been also changed, with increased numbers of CD4+ T cells, CD8+ T cells and Th17 cells, and decreased numbers of CD4+CD25+Foxp3+ T cells. These disturbances in host increase the susceptibility to a variety of diseases later in life, including infections, IBD, allergic diseases, metabolic diseases and NDDs. Other medications, such as steroid hormones, antidepressants and analgesics, have been reported to alter the diversity and composition of gut microbiome. Early exposure to these medications increases the risk of various diseases associated with intestinal ecological disorders, such as infections, obesity and NDDs. However, whether these adverse effects are realised by affecting the development of early gut microbiota is still unknown. ASMs, acid suppressant medications; PPIs, proton pump inhibitors; H2RAs, histamine-2 receptor antagonists; SCFAs, short-chain fatty acids; Th17, T helper cell 17; IBD, inflammatory bowel disease. NDDs, neurodevelopmental disorders.

intestinal metabolites and the development of subsequent diseases is also a theme in our review. Numerous studies have shed light on the significant impact of specific antibiotics on gut microbiota and the progression of diseases. The antibiotics mentioned above have been linked to substantial reductions in crucial metabolites, particularly short-chain fatty acids (SCFAs) such as butyrate and propionate.[40] The decreased levels of these metabolites are closely associated with the advancement of gastrointestinal disorders, including inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), as well as metabolic disturbances such as obesity. Furthermore, a range of non-antibiotic medications, such as non-steroidal anti-inflammatory medications (NSAIDs) like diclofenac and ibuprofen, are known to influence the production of protective mucin-degrading metabolites within the gut.[41] This disruption has been correlated with the development of gastrointestinal conditions, including ulcerative colitis.

Early-life medications exposure and later adverse health outcomes

Infections and necrotising enterocolitis

The association between early medications exposure and infections has been well established. In the neonatal intensive care unit (NICU), nosocomial infections were associated with either H_2RAs or steroids treatment alone, and the risks rose dramatically when the two medications were combined.[42] Offspring of mothers exposed to corticosteroids during the second and/or third trimester of pregnancy also faced an increased risk of serious infections in infancy.[34] A meta-analysis conducted by Santos et al.[43] further supported this association, revealing that H_2RAs were associated with infections and necrotising enterocolitis (NEC) in neonates. In addition, H_2RAs used in NICU increased the risk of late-onset sepsis in infants.[44]

Exposure to H_2RAs in preterm infants has been found to reduce the diversity of the gut microbiota and alter

Reference	Drug classification	Cohort characteristics	Effect on gut microbiota	Health outcomes
Zhou et al.[20] (2021)	Antibiotics (mainly penicillin)	295 mother-child pairs (all with antibiotic exposure)	↓Pielou and Simpson indexes ↓*Firmicutes, Lactobacillales, Bacillales,* and *Staphylococcaceae* ↑*Proteobacteria, Bacteroidetes* and *Gammaproteobacteria*	Accelerate the growth of 2-6-month infants and may increase the risk of obesity.
Coker et al.[21] (2020)	Antibiotics (mainly penicillin)	87 infants with antibiotic exposure vs 179 infants without antibiotic exposure	6 weeks: ↓*Bacteroides, Bifidobacterium* ↑*Veillonella* 1 year: ↑*Coprococcus, Ruminococcus gnavus* ↓*Bacteroides, Bacteroides fragilis, Clostridium, Meganomas* and *Streptococcus*	Affect the development of immune system, potentially linked to diseases like asthma, allergies, and atopic diseases.
Stearns et al.[22] (2017)	Antibiotics (mainly penicillin)	21 infants with antibiotic exposure (14 born via delivery and 7 born via C-section) vs 53 infants born vaginally without antibiotic exposure	↑*Escherichia* ↓*Bifidobacterium, Streptococcus, Lachnospiraceae* other	Delay the maturation of microbial community.
Korpela et al.[23] (2016)	Antibiotics (macrolide)	218 children with antibiotic exposure vs 43 children without antibiotic exposure (aged 2–7 years)	↓*Actinobacteria* ↑*Bacteroidetes* and *Proteobacteria*	Increase the risks of asthma and predisposes to antibiotic-associated weight gain.
Zwittink et al.[24] (2018)	Antibiotics (amoxicillin and ceftazidime)	10 preterm infants with antibiotic exposure vs 5 preterm infants without antibiotic exposure	↓*Enterobacteriaceae* ↓*Bifidobacterium* But allowed *Enterococcus* to thrive.	Disrupt gut microbiota, impair immune and gut development, and hinder infant's healthy growth.
Gupta et al.[25] (2013)	H_2RAs (ranitidine)	25 preterm infants with H_2RAs treatment vs 51 preterm infants without H_2RAs treatment	↓*Proteobacteria* phylum (mainly *Enterobacteriaceae*) ↓*Firmicutes*	Increased the risk of necrotizing enterocolitis.
Castellani et al.[26] (2017)	PPIs (esomeprazole)	12 infants with GERD (all with PPIs treatment)	↓*Haemophilus* ↓*Lactobacillus* and *Stenotrophomonas*	Did not significantly increased the risk of *Clostridium difficile* infections.

Table 1: **Summary of studies relating medications during early life and effects on health outcomes.**

microbial patterns, which potentially contribute to the development of NEC. This was evidenced by an increase in the relative abundance of *Proteobacteria* and a decrease of *Firmicutes*.[25] Although this study did not directly examine the role of H_2RAs on NEC, it provided us an idea that H_2RA-induced changes in gut microbiota might increase the risk of NEC, suggesting that the indications should be strictly followed when using H_2RAs in preterm infants. Long-term use of steroid hormones has been reported to reduce the diversity of gut microbiota and alter its composition.[45] However, it is not known whether early steroid use increases the risk of infection by affecting the development of gut microbiota. Relevant studies have not been reported, which will be one of the directions worth studying in the future.

Inflammatory bowel disease

IBD refers to a group of non-specific chronic intestinal inflammatory diseases without clear etiology, including ulcerative colitis (UC) and Crohn's disease (CD), which have been experiencing a gradual rise in both occurrence and prevalence over time.[46] Epidemiological studies have shown that early antibiotic exposure can increase the risk of later IBD. Kronman et al.[47] demonstrated that antibiotic exposure during early childhood increased the risk of later IBD, with the adjusted hazard ratio decreasing as the age of exposure increases.[47] However, Örtqvist et al.[48] suggested that the increased risk of IBD was significantly associated with antibiotic exposure during pregnancy but not in infancy.

It is consistent that IBD is closely related to gut ecologic imbalance. Studies have demonstrated that an imbalance in gut microbiota caused by early antibiotics, including decreased diversity and distinct composition of gut microbiota, played a critical role in this condition.[49,50] At the phylum level, *Bacteroidetes* was decreased while *Proteobacteria*, *Firmicutes* and *Verrucomicrobia* were increased after antibiotic treatment during early life, and these changes persisted even after dextran sodium sulphate administration.[49] Multiple studies have demonstrated that *Bacteroides* species, including *Bacteroides ovatus* and *Bacteroides thetaiotaomicron*, played a role in alleviating intestinal inflammation.[51,52] Moreover, these alterations in microbial patterns resulted in a decrease in short-chain fatty acids (SCFAs) and an increase in intestinal inflammation, which were present in patients with IBD.[53] At the family level, the early-life antibiotic intervention group exhibited a higher abundance of proinflammatory-related *Enterobacteriaceae* and a lower abundance of commensal bacteria like S24-7 family and *Prevotellaceae*.[50]

Metabolic diseases

Metabolic diseases, such as obesity and diabetes, refer to diseases caused by biological accumulation or deficiency of certain substances (such as fats and proteins) caused by abnormal metabolism in the human body. Early-life

medications, including antibiotics, ASMs, and metformin, have been reported to increase the risk of metabolic diseases.[36,54–56] Antibiotic use during early life increased the risk of childhood obesity by 26%.[54] Similarly, other medications during early life like ASMs and metformin, have also been reported to be correlated to overweight, obesity, and elevated body mass index (BMI) Z scores in childhood.[36,54,55]

Stanislawski et al.[57] found that infant gut microbiota composition at 2 years old could account for 53% of the differentiation of BMI z-score at age 12, suggesting that early changes in gut microbiota may serve as a predictive marker of later metabolic disorders.[58] Korpela et al.[59] confirmed that antibiotic use during the first 3 months of life was strongly associated with increased BMI in childhood, specifically linked to elevated levels of *Streptococci* and reduced levels of *Bifidobacteria*. Some bacterial genera, including *Anaerofustis*, were significantly increased and were positively correlated with obesity.[60] Conversely, there was a decline in genera belonging to the families *Ruminococcaceae* and *Lachnospiraceae*, which were important for SCFA production and were negatively associated with obesity.[60] The transplantation of cecal microbiota from 18-week-old mice exposed to low-dose penicillin during early life into germ-free mice accelerated total and fat mass accumulation, which was negatively correlated with *Lactobacillus*, *Allobaculum* and *Rikenellaceae*.[61] These organisms increased the expression of Th17 cells and antimicrobial peptides that are involved in metabolic changes.

In addition, studies have also shown that antibiotic use hastens the development of type 1 diabetes (T1D) in children.[56] In a mouse model, prenatal antibiotic exposure increased intestinal permeability and induced a sustained overabundance of *Proteobacteria* and a remained low abundance of *Actinobacteria*, which increased the number of $CD4^+$ and $CD8^+$ T cells.[62] The upregulation of Interleukin-17 (IL-17), interferon-γ (IFN-γ), and tumour necrosis factor-α (TNF-α) in T cells accelerated the development of T1D.

It has been shown that early exposure to ASMs affects the development of gut microbiota, but whether these changes are the cause of increased metabolic disease resulting from ASMs remains to be investigated. In adults, metformin was thought to improve metabolic disease by regulating intestinal microbial populations.[39,63] But metformin exposure early in life may lead to the opposite outcome. The unknown factor lies in whether this difference is due to the changes in the normal development pattern of gut microbiota in infants. Thus, further evidence-based medication and experimental research are required to support these findings.

Allergic diseases

Allergic diseases are allergen-induced inappropriate or exaggerated immune responses in different organs that cause various symptoms, such as asthma, allergic rhinitis, eczema and wheeze. Studies have indicated that antibiotic exposure early in life is associated with an increased risk of allergic disease during childhood. Furthermore, there was a dose-response relationship between antibiotics and asthma risk, with a 10% increase in early-life antibiotic exposure associated with a 24% increase in childhood asthma risk.[58] Recently, the influence of ASMs on allergic diseases has also gained attention. In 2009, Dehlink et al.[64] provided the first evidence of the correlation between early-life ASM exposure (during pregnancy) and childhood asthma. In addition, Cea Soriano et al.[65] found that prenatal exposure to H_2RAs carried a greater risk for childhood asthma than exposure to PPIs.

Studies have reported the changes in gut microbiota composition in asthmatic children, with reductions in *Rothia*, *Faecalibacterium*, *Dialister,* and some members of *Lachnospiraceae* family (*Lachnobacterium*, *Lachnospira*), as well as more abundance in *Blautia* and *Coprobacillus*.[23,66] Numerous population-based studies have confirmed that allergic diseases may be reflected by the gut microbiome in early life.[66–68] Gut microbial diversity at 5 weeks was negatively correlated with allergic diseases, while microbial maturity was positively correlated with allergic diseases.[66] Moreover, a decreased abundance of *Faecalibacterium*, *Lactobacillus*, *Akkermansia* and *Bifidobacteria* in newborns, as well as reduced faecal microbiota of *Bacteroides* and *Bifidobacterium* at 3 months of age, were found to increase the risk of childhood atopy and asthma.[67,68] These findings suggest that alterations in gut microbiota composition early in life may increase the risk of allergic diseases. Patrick et al.[58] found that infants exposed to antibiotics in their first year of life and who later developed asthma had significantly reduced levels of short-chain fatty acid bacteria (such as *Ruminococcus bromii* and *Faecalibacterium prausnitzii*), and increased abundance of *Clostridium perfringens* inhibited by SCFAs, indicating the mediating role of bacterial metabolites. Early antibiotics or ASMs can alter the infant intestinal flora that indicated allergic diseases, such as reduced abundance of *Lactobacillus* and *Bifidobacterium*. Animal models have provided valuable insights into how gut microbiota dysbiosis induced by early-life antibiotic administration led to early asthma. Notably, *Bacteroidetes* has been confirmed as a candidate for a possible association with asthma exacerbation and was shown to be reduced after perinatal vancomycin treatment.[69] Reduction in $CD4^+$ $CD25^+$ $Foxp3^+$ T cells played a mediating role in this process.[69]

Neurodevelopmental disorders

Neurodevelopmental disorders (NDDs), including autism, attention deficit hyperactivity disorder (ADHD), and language disorder, are chronic conditions caused by atypical development of the central nervous system.

Similar to the gut microbiome, early life is a critical "window" for the development of nervous system. Any factor that affects brain development during this time can lead to NDDs, and medications are among the various detrimental factors. Despite the common presence of conditions like pain, fever, and depression during pregnancy or infections in infants, there has been widespread exposure to antibiotics, antidepressants, and acetaminophen in early life. Studies have suggested that these medications may be linked to the risk of NDDs in the offspring, although other research has presented contrasting perspectives.[17,35,70,71] Slykerman et al.[17] found that antibiotic use within the first year of life was associated with neurocognitive dysfunction in childhood after adjusting for confounding factors, reinforcing the link between the development of the cerebral-intestinal axis early in life. However, since the cause of early antibiotic use was not investigated, a causal relationship could not be demonstrated.[17] Eliminating the impact of maternal depression, the utilisation of antidepressants (especially selective serotonin reuptake inhibitors) in the middle and late trimesters of pregnancy has been associated with a heightened likelihood of ASD in the offspring.[35] However, it has been demonstrated that using antidepressants in the early trimesters of pregnancy did not increase the risk of ASD in the offspring after removing confounding variables.[70] Ji et al. reported that cord blood burden of acetaminophen was positively associated with the risk of ADHD and ASD in children, while further exploration of the relationship between the two is still needed.[71]

The composition of gut microbiota during early life might reflect the risk of NDDs in adolescence,[72] suggesting that interference targeting early-life gut microbiota may affect nervous system development and increase the risk of NDDs. While not necessarily comparable in humans, mice exposed to perinatal low-dose penicillin exhibited alterations in gut microbiota and reduced social behaviour at 6 weeks of age.[73] Compared to the control group, the diversity decreased and composition changed in gut microbiota in antibiotic treatment group at week 1, among which *Bacteroidetes* and *Firmicutes* were significantly decreased, while *Proteobacteria* was increased largely, and the changes continued to weaning (at 4 weeks).[73] These changes in gut microbiota, resulted in increased expression of occludin and claudin-5 in hippocampus, which may represent a protective mechanism of the body.[73] Both antidepressants and acetaminophen have been reported to influence gut microbiota.[37,38] Nevertheless, whether their exposure early in life altered the development of intestinal microbiome has not been reported, and the influence of maternal genetic factors on disease risk needs to be seriously considered. Since NDD occurrence was closely associated with dysregulation of gut microbiota in early life, we hypothesised that antidepressants and acetaminophen may increase susceptibility to NDDs later in life by disrupting the normal developmental pattern of gut microbiota. However, relevant research has not yet covered this area, we believe that further investigations will provide a good perspective.

Therapeutic options

The developing gut microbiota is highly malleable, meaning that we can improve long-term health by specifically targeting gut microbiota. Dietary therapy, probiotics, prebiotics, FMT, genetically engineered phages and VNS have emerged as potential therapeutic options for addressing gut dysbiosis-related diseases by directly or indirectly modulating the composition of gut microbiota. Therefore, they can be used as a viable therapeutic option to combat medication-induced dysbiosis in young children and to ameliorate the long-term diseases that may occur.

Dietary therapy

Breastfeeding was found to be linked with elevated levels of *Bifidobacterium* spp, *Lactobacillus* spp, and *Clostridium* spp, as well as lower levels of *Clostridia difficile* when compared to formula feeding. On the other hand, the introduction of solid food was associated with increased levels of *Clostridium* spp.[74] Breast milk contains human milk oligosaccharides (HMOs), which are growth factors that inhibited the expression of pro-inflammatory factors in infants and promoted the growth of *Bifidobacteria*.[75] Furthermore, breastfed infants had elevated intestinal inflammatory markers calreticulin and β-defensin, which were negatively correlated with the levels of inflammatory factors in vivo, and thus may promote immune development in the infant gut.[76] Among various formulas, hydrolysed formulas were found to enhance the development of *Ruminococcus gnavus* in the intestinal tract of infants, regular formulas were found to promote the growth of *E. faecalis*, *Actinomyces radingae*, and *S. thermophilus*.[76] Additionally, infant formulas might be linked to increased levels of inflammatory factors. Solid food introduction has been demonstrated to promote the diversity of intestinal flora, including *Prevotellaceae* and *Escherichia/Shigella*.[77] Meat was found to be effective in raising the levels of *Lachnospiraceae*, a bacterium that effectively utilised dietary fibre in the gut to produce short-chain fatty acids.[78] Whole grains enhanced the presence of *Bacteroides* and *Lachnoclostridium*, while reducing the abundance of *Escherichia* compared to refined grains.[78] Thus breastfeeding or the addition of complementary foods to infants could potentially play an immunomodulatory role and influence long-term health outcomes by affecting gut microbes.

Probiotics or prebiotics

The International Scientific Association for Probiotics and Prebiotics (ISAPP) has defined probiotics as "live

microorganisms that, when administered in adequate amounts, confer a health benefit on the host".[79] Early probiotic supplementation promotes the colonisation of protective intestinal microflora and the maturation of gut microbiota. For infants, probiotics exert a direct effect on gut microbiota, including a positive effect on potential protective bacteria, particularly *Bifidobacterium*, and a negative effect on potential pathological microorganisms, such as *Bacteroides*, *Clostridium*, and *Veillonella*.[80,81] Similarly, prebiotic administration early in life modulates the gut microbiota composition. Supplementation with prebiotics in early life increases the number of beneficial bacteria, primarily *Bifidobacterium* and occasionally *Lactobacillus*, and decreases the populations of opportunistic pathogens, such as *Clostridium*, *E. coli* and *Enterococci*.[82,83] Population-based studies have demonstrated that early-life supplementation with probiotics or prebiotics confers protection against a range of diseases, including infections, IBD, metabolic diseases, allergic diseases, and NDDs.[84]

Faecal microbiota transplantation

FMT is to transplant the faecal functional microbial communities from healthy donors into the gastrointestinal tract of patients. In recent years, FMT has emerged as a breakthrough in medication and has been used to treat various gut dysbiosis-related diseases, such as *Clostridium difficile* infection.[85] Beneficial strains or even bacterial consortia of pregnant women after FMT treatment could be longitudinally transmitted to their infants.[86] Postnatal maternal FMT could restore the gut microbiota of infants born via C-section, making their gut microbiota significantly similar to that of vaginally born infants.[87] Anders et al.[88,89] found that FMT could enhance resistance to mucosal bacterial adhesion and prevent NEC. Following FMT treatment, all 19 infants with allergic colitis showed clinical improvement, and most had a greater diversity of gut microbiota, suggesting that FMT is a safe and effective method for allergic colitis.[90] Furthermore, FMT has shown promise in improving symptoms of ASD by increasing the diversity and abundance of certain bacteria, including *Bifidobacterium*, *Prevotella*, and *Desulfovibrio*, among others.[91] Faecal microbiota encompassed not only bacteria, but also fungi, viruses, and related metabolites, all of which could impact the effectiveness and safety of FMT. Faecal filtrate transplantation (FFT) involved removing bacteria from donor feces through micropore filtration, reducing the risk of opportunistic bacterial infections.[89] At the same time, residual phages maintained the prophylactic effect against NEC, and oral FFT had the potential to completely halt NEC, making it a promising treatment approach.[89] Although minor, FMT has its challenges and potential adverse effects.[88,92] Gastrointestinal adverse events, including diarrhoea, abdominal distension, and vomiting, have been reported in some cases following FMT. These symptoms can be uncomfortable for patients and underscore the need for close monitoring and follow-up care. Moreover, as FMT involves the administration of faecal material through both the upper and lower digestive tracts, it carries the risk of adverse events such as aspiration, reflux pneumonia, and even intestinal perforation, which can have serious implications for patient safety. The clinical implementation of FMT, while promising, requires meticulous attention to safety protocols and guidelines to address these challenges and ensure its efficacy as a therapeutic approach in various medical conditions.

Genetically engineered phages

Since their discovery in the early 20th century, phages have been recognised as having great potential as antibacterial agents. However, due to the development of antibiotics, phage therapy has been largely abandoned by Western countries. Recently, with a better understanding of the beneficial effects of microbiome bacteria on human health and growing concerns regarding the adverse effects of antibiotics, there has been a renewed interest in the use of phages as antibacterial agents.[93] Phages can precisely edit the gut microbiota to avoid harm to the healthy microbiome and were ideal narrow range antibacterial agents.[94] An increasing amount of clinical research, along with humanised mouse models, indicated that phage therapy could exert an anti-disease effect by selectively targeting certain intestinal bacteria.[94,95] The use of phages in early life may be possible in the near future. This will be beneficial to avoid the adverse impacts of antibiotic disruption in the gut microbiota.

Vagus nerve stimulation

The brain-gut axis is known to communicate through immunomodulatory factors, the endocrine-metabolic axis, and the vagus nerve. In particular, the gut flora interacts with intestinal epithelial cells to activate vagal afferent fibres that send signals to modulate mood (including depression, etc.) and behavioural performance, while efferent fibres transmit anti-inflammatory signals to reduce pro-inflammatory factors.[96] In early life, both prenatal and postnatal fetal microbiota development overlap with the time of rapid neurological development.[97] Thus, research evidence supported that the gut microbiome influenced developmental indicators such as cognitive, emotional, and behavioural performance in infants and children.[98] Low vagal activity was found to be present in preterm infants and children with autism, and estimates of vagal nerve activity (VNA) were utilised to evaluate infant development.[99] VNS has been employed in the clinical treatment of depression and epilepsy-related disorders.[100] Animal models have demonstrated that vagotomy can also be utilised to alleviate neuropsychiatric disorders.[101] However, due to its invasive nature and the need to ensure safety and tolerability in infants and children, further

Search strategy and selection criteria

We searched for references on PubMed up to 2023, using a combination of keywords such as 'early life', 'gut microbiota', 'medications', 'health outcomes', 'antibiotics', 'acid suppressant medications', 'PPIs', 'ASMs', 'infections and necrotizing enterocolitis', 'inflammatory bowel disease', 'metabolic diseases', 'allergic diseases', 'neurodevelopmental Disorders', and 'preventive therapy'. The final list of references is highly relevant to our review topic.

exploration of clinical studies related to these treatments is necessary.

A call for focusing on medication exposure in early life

As mentioned above, the early life stage, a critical period, is crucial for the development of the gut microbiota, and any environmental factor that interacts with the gut microbiota can disrupt the normal development of the gut microbial community, leading to disease. Medications are one of the strongest predictors of gut microbiota, which are inevitably administrated to the majority of pregnant women or their children because of immediate benefits. However, corresponding health concerns will manifest later in life. Therefore, caution should be exercised when considering the use of medication during this critical period. As early life is the most malleable period of growth and development, preventive interventions to improve health or prevent disease at this stage such as probiotic/prebiotic supplements and FMT are becoming increasingly common. Although clinical evidence is currently limited, studies have suggested that early-life supplementation with probiotics, prebiotics, or FMT may serve as potential preventive measures against future diseases. However, further studies are required to ensure the safety and efficacy of the early-life medications exposure.

Outstanding questions

The connection between medications and early-life gut microbiota changes is a significant yet under-researched area. It is crucial to comprehend how medications impact the gut microbiota in early life and affect long-term health outcomes, and further exploration of the underlying mechanisms is necessary. Since early-life medication is often unavoidable, there is an urgent need to identify medications with minimal side effects and satisfactory efficacy. This presents a major challenge that demands immediate attention and offers potential for the development of more effective therapeutic regimens.

Contributors

HH collected literature, drafted the manuscript, and prepared figures. JYJ modified the figures and edited the manuscript. XYW collected data and designed tables. XYW and JYJ provided critical feedback and helped shape the manuscript. KJ and HLC reviewed the manuscript and provided funding acquisition. All authors contributed to the article and approved the submitted version.

Declaration of interests

The authors declare no conflicts of interest.

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