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Review

The Tight Connection Between the Gut Microbiota and Childhood Acute Lymphoblastic Leukaemia: An Updated Review

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Abstract

The human microbiota, comprising bacteria, fungi, and viruses, primarily resides in the gut, skin, and oral and nasal cavities. The gut microbiota represents the largest and most functionally relevant microbial community, playing a crucial role in digestion, metabolism and immunity. Microbiota composition and diversity have been associated with several diseases such as cancer, affecting drug efficacy, toxicity and clinical outcome. Interactions between the gut microbiota and the host immune system may contribute to the aetiology and progression of childhood acute lymphoblastic leukaemia (ALL). In this review, we summarized the general features of the gut microbiota in cancer patients and its specific role in aetiology, treatment and prognosis of paediatric ALL. Profiling the gut microbiota may help to shed the light on the mechanism of onset and to support the development of personalized treatment strategies and follow-up in children with ALL, contributing to precision medicine.

Keywords: children; acute lymphoblastic leukaemia; microbiota; gut; microenvironment

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1. Introduction

The microorganisms living in the human gastrointestinal tract are part of the microbiota, an entity involved in different functions, including digestion, metabolism and immunity. The paediatric human gut microbiota is a dynamic ecosystem that switches from low-diversity, facultative anaerobe presence at birth to an adult-like, high-diversity, strict anaerobe-dominated system by age 3–5. In particular, in the gut microbiome of children, the prevalences are: at the phylum level, *Firmicutes* (51.1%) and *Bacteroidetes* (36.0%); at the genus level, *Bacteroides* (16.0%), *Prevotella* (8.69%), *Faecalibacterium* (7.51%), and *Bifidobacterium* (5.47%) [1]. In infants, *Proteobacteria* and *Actinobacteria* are more prevalent, while *Firmicutes* and *Bacteroidetes* appear as dominant by the end of the first year. Recently, our ability to detect the breadth of the gut microbiota has improved significantly due to emerging culture-independent approaches such as high-throughput and low-cost sequencing methods [2]. Targeting the bacterial 16S ribosomal RNA (rRNA) gene is a common

approach since this gene is present in all bacteria and archaea and presents nine highly variable regions (V1–V9), which permits species to be well distinguished. More predictable estimates of microbiota composition and diversity may be obtained by whole-genome shotgun metagenomics due to the higher resolution and sensitivity of these techniques. Despite growing interest in the role of the gut microbiota in childhood acute lymphoblastic leukaemia (ALL), several methodological challenges must be considered when interpreting current evidence. These include variability in sample types and collection procedures, lack of standardized protocols, and differences in sequencing technology (e.g., 16S rRNA versus shotgun metagenomics), all of which may affect taxonomic resolution and data comparability. Furthermore, multiple confounding factors—such as antibiotic exposure, diet, age, and treatment phase—can greatly influence microbiota composition, thereby limiting reproducibility across studies.

The gut microbiota composition is influenced by different factors, such as heredity, environment and lifestyle [3]. The various microorganisms contribute to many host functions such as digestion of food, synthesis of vitamins, short-chain fatty acids (SCFAs), essential amino acids and secondary metabolites, but also to the development and maturation of the immune system and the regulation of immune response [4]. Fibre fermentation by microbiota in the lower intestine generates SCFAs, mainly butyrate, propionate and acetate, which are transported into systemic circulation maintaining local barrier function and regulating immune homeostasis [5]. Microbiota features and diversity have been associated with several diseases such as cancer, influencing drug efficacy and chemotherapy/immunotherapy side effects [6]. Indeed, growing evidence suggests that the intestinal microbiome modulates the efficacy and toxicity of cancer therapy, having a role in incidence, progression, and treatment of different types of malignancy [7]. Cancer and chemotherapy damage the intestinal mucosal barrier, while dietary change and the use of broad-spectrum antibiotics profoundly disrupt the gut microbiota [8] and may affect its composition [9]. In particular, gut microbiota interacting with host immune response might have a contributing role in the development and outcome of childhood ALL, which is the most common malignancy in children deriving from the interplay between inherited or acquired genetic risk factors, exposure to infective agents, and immunological alterations [10]. This review aims to explore the alterations of the gut microbiota in children with ALL and its effects on disease progression and treatment.

2. Study Design

An electronic search was conducted in the medical database PubMed. Clinical and experimental articles about the association between ALL and microbiota were searched. Keywords used alone or in combination to collect relevant articles included: “acute lymphoblastic leukaemia”, “children”, “gut microbiota”, “microbiome”, “trained immunity”, and “microenvironment”. The following inclusion criteria were used: studies had to describe the connection between the gut microbiota and ALL in children under 18 years; articles should have been published between 1994 and 2025 and be written in the English language; and studies should be case series, original articles or reviews. Exclusion criteria were unreliably extracted data, leukaemia cases reported in adults, overlapped data sets, and abstract-only articles. All reported studies were thoroughly analysed.

3. Gut Microbiota and Cancer Microenvironment

The microbial composition of the gut microbiota can influence the development of diseases; conversely, the onset and development of some diseases can alter the composition of the gut microbiota. The Human Microbiome Project has shown many different

bacteria detectable in gut mucosa, with more than 2000 species isolated from the human intestinal microbiome [11].

The gut microbiota composition is established in early life under the influence of familial and geographical microbial environments [12], with *Bacteroides* and *Actinobacteria* accounting for about 90% of the total [13]. Microbiota may influence cancer microenvironment through cytokine release control, dendritic cell activation, and T-lymphocyte stimulation [14], and its dysbiosis, with the alteration of the intestinal epithelial barrier, can be involved in this inflammatory immune response with a consequent activation of immune cells contributing to cancer onset [15]. Different microbial taxa have been implicated in carcinogenesis through distinct mechanisms: for instance, *Bacteroides* species can modulate immune responses and metabolic pathways, while members of *Firmicutes* and *Actinobacteria* are often associated with immunoregulatory and protective functions. Conversely, genera such as *Fusobacterium* (phylum *Fusobacteria*) have been linked to pro-inflammatory and tumour-promoting activities, mainly described in adult cancers but increasingly investigated also in paediatric settings [16]. Chemotherapy and antibiotics alter the host gut microbiota [17], and microbial dysbiosis has been associated with cancer onset in several studies, showing a structural imbalance in the gut microbiota of ALL patients before chemotherapeutic treatment, compared with healthy controls [18–21]. Antibiotic therapies can induce a rapid depletion of microbial diversity and beneficial taxa, favouring the expansion of opportunistic pathogens. In contrast, chemotherapeutic agents may exert both direct and indirect effects, including mucosal damage and immune modulation, leading to long-lasting alterations in microbial communities.

Moreover, it was also demonstrated that the oral microbial composition is different in children with ALL receiving chemotherapy from healthy controls, with a high caries risk for the dysbiosis of the oral microbiota [22].

4. Gut Microbiota and Genetic Predisposition

Recent evidence indicates that more than 5% of healthy newborns harbour preleukaemic clones arising in utero, most commonly driven by early somatic genetic events such as chromosomal aneuploidies or structural rearrangements [23,24]. Among these, the t(12;21)(p13;q22) translocation, resulting in the ETV6-RUNX1 fusion gene, represents one of the most frequent initiating lesions in paediatric B-cell ALL. This fusion can be detected in a small fraction of healthy neonates; however, only a minority of carriers will eventually develop overt leukaemia, indicating that additional postnatal events are required for disease progression [25].

In this context, it is important to distinguish between inherited (germline) genetic susceptibility and acquired (somatic) alterations. Germline variants in genes such as ETV6 have been identified in a subset of patients and may confer increased susceptibility to ALL, whereas somatic alterations—including gene fusions, copy number alterations, and secondary mutations—drive clonal expansion and transformation. The progression from a clinically silent preleukaemic state to overt disease is therefore considered a multistep process [26].

Emerging evidence suggests that environmental and immunological factors may contribute to this transition. In particular, exposure to infections and immune perturbations has been proposed as a trigger for secondary genetic events or for the expansion of pre-existing preleukaemic clones. In this framework, the gut microbiota may play a modulatory role through its impact on immune system development and inflammatory responses [27].

Experimental models support this hypothesis. Vicente et al. demonstrated that mice with a genetic predisposition to precursor B-ALL (as PAX-5 heterozygosity or ETV6-RUNX1 fusion) presented a distinct gut microbiome. They detected a big difference

between the microbiomes of wild-type (WT) and PAX-5+/− mice due to the lack of commensal microbiota in the PAX-5+/− mice. In particular, members of the family *Rikenellaceae* and of the genus *Oscillospira* detected in WT mice were not present in the PAX5 +/− mice. Moreover, they showed that depletion of the gut microbiota after antibiotic treatment supports pB-ALL development in these predisposed mice even when they were not exposed to common infections [28]. It is not easy to translate this study to humans, but it would be interesting to investigate whether the Pax51/− model can reproduce this condition in children where an increased number of paediatric pB-ALL developed in association with a parallel broad use of antibiotics.

In addition, the bone marrow microenvironment plays a critical role in disease evolution [29].

Stromal cells, inflammatory cytokines (including TNF-α, IL-6, and IL-1β), and immune signalling pathways contribute to the survival and expansion of preleukaemic clones. The interplay between systemic immune regulation—potentially influenced by the gut microbiota—and local bone marrow niche dynamics represents a key area for future investigation [30]. Overall, paediatric ALL appears to arise from a complex interaction between early somatic genetic events, inherited susceptibility, and postnatal environmental influences. While the microbiota is unlikely to represent a primary oncogenic driver, it may act as a modulator of immune and inflammatory pathways that influence disease initiation and progression.

5. Gut Microbiota and Trained Immunity

A pivotal driver of the evolution from preleukaemic to leukaemic clones is the exposure to immune disturbance. Therefore, trained immunity, which represents a memory-like property of innate immunity, could be a protective factor in the prevention of B-ALL, as described by Hauer et al. [10]. This metabolic and epigenetic rewiring that involves macrophages, monocytes, and natural killer (NK) cells is related to exposure to infection, vaccination and other early-life epidemiological factors such as the mode of birth, social contacts and breastfeeding. This process is largely mediated by epigenetic modifications, including histone marks such as H3K4me3 and H3K27ac, which regulate chromatin accessibility and gene transcription in monocytes and macrophages [31]. In parallel, metabolic rewiring—particularly shifts toward glycolysis and altered mitochondrial function—supports the persistence of this activated state [32]. These epigenetic changes give innate immune cells a functional memory, which subsequently modulates their response to a second biological event later in life (Figure 1). An altered DNA methylation may be a mediating mechanism of immune cell training, and there are gene methylation signatures specific to ALL and infection exposure. Langie et al. proved the hygiene hypothesis, assuming that a lack of infection in early life suppresses immune system development and is related to ALL risk. They compared disease-associated methylation signatures with those related to infection exposure and demonstrated significant overlap between the two [33].

Early-life microbial exposures, including those shaping the gut microbiota, are critical in establishing trained immunity. Perturbations in microbiota composition (e.g., due to caesarean delivery, reduced microbial exposure, or antibiotic use) may lead to inadequate or dysregulated immune training. This has been hypothesized to contribute to abnormal immune response, chronic low-grade inflammation, and impaired immune surveillance [34].

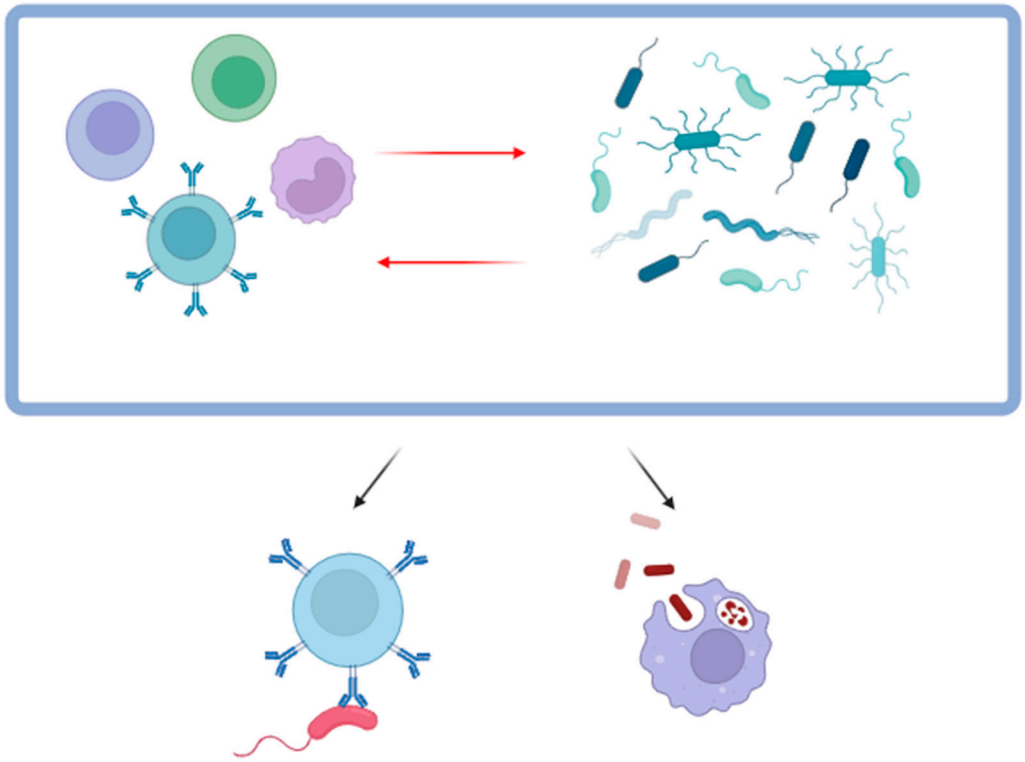

Figure 1. Crosstalk between immune cells and gut microbiota: their connection leads to the activation of immune cells and development of immunomodulation with an adequate memory reaction for further infections.

All these aspects could affect gut microbiome maturation, contributing to the onset of leukaemia (Figure 2). In particular, the immaturity of microbiota leads to a lack of SCFA produced by bacterial taxa in children with ALL, fostering a dysregulated immune response and increasing the risk of conversion of preleukaemic clones in overt leukaemia [35]. The first source of the neonatal microbiome is the maternal gut, colonizing the newborn baby with maternal skin and vaginal microbiota.

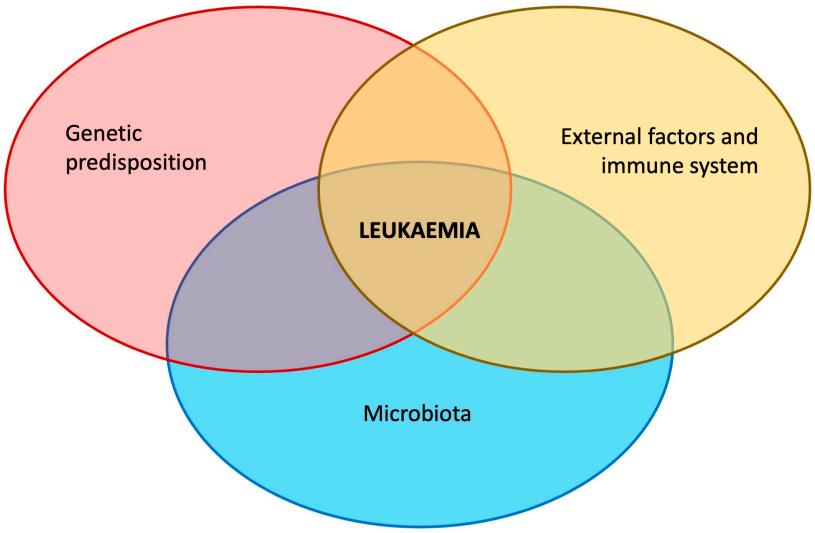

Figure 2. A schematic representation of factors contributing to developing leukaemia.

The correlation between the main three factors—genetic predisposition, alteration in immune system and microbiota—leading to the evolution from preleukaemic clones to overt leukaemia.

Neonates delivered by caesarean section present a low *Bacteroides* profile leading to reduced stability and delayed maturation of the gut microbiome and diminished stool level of SCFAs (especially acetate) during the first period of life [36]. The microbiota is also stabilized by maternal IgA transferred through breastfeeding. Moreover, human milk oligosaccharides (HMOs) promote the expansion of *Bifidobacterium* species, which have an important role in the development of T-cell-dependent IgA response, and lead to increasing number of memory B cells during childhood. Indeed, a lack of exclusive breastfeeding is linked to reduced abundance of *Bifidobacterium* spp. [37]. Paucity of social contacts due to a lack of older siblings is associated with delayed maturation and diminished gut microbiome α-diversity and less abundance of *Faecalibacterium* spp. Delayed entry into daycare is related as well to reduced relative abundance of *Lachnospiraceae*, *Ruminococcaceae* and *Prevotella* spp. [38]. In addition, contact with livestock and pets in early life may train the immune system, reducing the ALL development risk [39]. In contrast with our findings, few earlier studies described significant positive associations between paediatric leukaemia and regular contact with pets during childhood or between ALL and cat ownership [40,41]. However, the limited literature indicates a lower risk of paediatric ALL with farm residence in the first year of life, any time during childhood or with frequent farm visits during the first year of life. These immune challenges also lead to an altered cytokine response [42]. ALL children showed high levels of CXCL9, CXCL10, IL-6, and IL-10 at the time of diagnosis, while at the end of induction therapy, a decrease in the levels of these immunological molecules and an increase in CCL5, interferon-γ (IFN-γ), and IL-17A levels were detected [43]. Indeed, it is demonstrated that B-ALL patients have an alteration in chemokine and cytokine profiles in the bone marrow microenvironment that contributes to suppressing the immune response. The anti-tumour activity depends on IFN-1 signalling, and evidence showed that the IFN-α/β pathway and IRF3 expression are suppressed in ETV6-RUNX1 cells [44]. The intestinal microbiota maintains a constitutive type I interferon expression [45] thanks to SCFAs produced by some bacteria species that increase the activity of CD8+ cytotoxic cells by inhibiting histone deacetylases and enhancing IL-12 responses, leading to the production of IFN-γ and tumour necrosis factor (TNF) [46,47]. In the context of paediatric ALL, such dysregulation of trained immunity could represent a mechanistic link between early-life environmental factors and leukaemogenesis [24]. Although direct evidence remains limited, it is plausible that altered immune education may influence the expansion of preleukaemic clones or the response to secondary oncogenic hits. Therefore, trained immunity provides a conceptual framework linking microbiota composition, immune system development, and leukaemia risk, although further longitudinal studies are needed to validate this hypothesis. Given the impact of the microbiome on the immune system, recent studies evaluated the influence of the gut microbial community on the treatment response of immunotherapies such as immune checkpoints (ICs) (e.g., anti-PD1). Sivan et al. described commensal *Bifidobacteria* as having a positive association with anti-tumour T-cell response, with Bifidobacterium longum, *Collinsella aerofaciens*, and *Enterococcus faecium* more abundant in stool samples of IC responders [48]. Furthermore, the anti-PD-1 responders showed greater levels of α-diversity and abundance of *Ruminococcaceae*, *Faecalibacterium*, and *Bifidobacterium* species [49]. Microbiome composition impairs anti-PD1 response, with *Akkermansia*, *Ruminococcus* spp., *Alistipes* spp., and *Eubacterium* spp. being high represented in drug responders, while under-representation was found for *Bifidobacterium adolescentis*, *B. long* and *Parabacteroids distasonis* in drug responders [50]. Moreover, not using antibiotics during anti-PD-1 treatment could increase patients' positive response from 25% up to 40%. However, these studies concern mostly adult solid tumours.

6. Gut Microbiota in Children with ALL

6.1. Leukaemia Onset and Microbiota Composition

ALL patients showed, at the onset of disease, significant change in gastrointestinal microbiota and microbial profile, differing from those of healthy controls [51], as Gao et al. described 15 species significantly higher in their ALL group [19]. In particular, the diversity of intestinal flora in paediatric ALL is sufficiently lower than that in healthy children [52]. ALL can induce structural changes in gut microbiota, with the alpha diversity being significantly reduced compared to siblings and weakened by antibiotics. *Bacteroidales* and *Enterococcaceae* can be considered as biomarkers for ALL, with a marked loss of diversity and domination of low-diversity communities by *Enterococcus* [53,54]. Chen et al. studied the causal relationship between gut microbiota and onset of haematologic malignancy and showed that the risk of ALL was greatly associated with the abundance of the phylum *Cyanobacteria*, the order *Methanobacteriales*, the class *Methanobacteria*, the family *Peptococcaceae*, the family *Methanobacteriaceae*, and the genera *Lachnospiraceae UCG010*, *Methanobrevibacter*, *Eubacterium brachy* group, and *Butyrivibrio* [55]. These findings suggest that pre-existing dysbiosis may be associated with disease onset; however, a direct causal role of the microbiota in leukaemogenesis has not been definitively established. In addition, these changes in gut microbiome could be linked to the above-mentioned factors such as caesarean delivery, breastfeeding and infections that can drive its maturation and association with ALL [56]. During intensive treatment, including chemotherapy and antibiotic exposure, microbiota alterations become more pronounced. Rajagopala et al. studied the gut microbiota of paediatric ALL patients using 16S rRNA marker gene sequences before and after chemotherapy treatment, showing a microbiota diversity of the ALL group significantly lower than the control group [57]. The study of 16S rRNA sequences of bacteria was amplified using primers that targeted the V1–V3 regions of the ribosomal gene sequence, giving phylogenetic information comparable with that obtained from nearly full-length 16S rRNA reads [58]. Although numerous taxa have been proposed as potential biomarkers of ALL (e.g., *Bacteroidales*, *Enterococcaceae*, *Methanobacteriales*, and *Lachnospiraceae*), the overall evidence remains heterogeneous, and consistent meta-analytic trends are still lacking. This variability is partly explained by methodological difference between studies as well as by heterogeneity in study design, population characteristics, and analytical approaches. Comparative evaluation across studies highlights both converging findings—such as reduced microbial diversity—and contrasting results regarding specific taxa. Most investigations rely on 16S rRNA gene sequencing, which enables taxonomic profiling (generally at the genus level) but provides limited resolution and functional insight. In contrast, shotgun metagenomic sequencing allows species- and strain-level characterization as well as functional analysis, but it is less frequently applied due to higher cost and complexity. Reproducibility across studies is further challenged by differences in cohort characteristics (e.g., age, treatment phase, and antibiotic exposure), sample collection protocols, and bioinformatic pipelines. In addition, many studies are limited by relatively small sample sizes, cross-sectional design, and inconsistent control for confounding factors such as antibiotic exposure, diet, and treatment phase, which further complicates the interpretation and reproducibility of findings. Despite these limitations, the convergence of findings on reduced microbial diversity and gut dysbiosis supports a potential role of the microbiome in ALL pathogenesis.

The role of the gut microbiota gained increasing attention not only in solid tumours and ALL but also in other haematologic malignancies such as acute myeloid leukaemia. Like ALL, significantly lower gut microbiota diversity prevails in AML patients compared to healthy control community. At the gate level, AML patients had a reduced relative abundance of *Firmicutes* and a higher relative abundance of *Bacteroidota*; at the genus level,

they presented a higher relative abundance of *Bacteroides* and a lower relative abundance of *Faecalibacterium*, *Roseburia*, *Subdoligranulum*, and *Bifidobacterium*. Moreover, the relative abundance of *Faecalibacterium* and *Roseburia* in faeces is decreased in AML patients compared to controls [59].

6.2. Chemotherapy and Modifications in Gut Microbiota

In paediatric patients with ALL, chemotherapy is associated with a reduction in intestinal flora, including some probiotic bacteria, such as *Bifidobacterium* spp. and *Faecalibacterium* spp., and may increase the abundance of pathogenic bacteria, like *Klebsiella* spp. and *Enterococcus* spp. [60]. The abundance of mucolytic Gram-positive anaerobic bacteria, including *Ruminococcus gnavus* and *Ruminococcus torques*, tended to increase during chemotherapy treatment and remained elevated one year after the initiation of chemotherapy [61]. After induction chemotherapy, several taxa are changed in stool and saliva samples of ALL patients [62]. Indeed, in this type of patient, it was also demonstrated that there was a structural imbalance of the oral microbiota with a prevalence of certain taxa including the phylum *Firmicutes*, the class *Bacilli*, the order *Lactobacillales*, the families *Aerococcaceae* and *Carnobacteriaceae*, as well as the genera *Abiotrophia* and *Granulicatella* [63]. The relative abundance of *Proteobacteria* before chemotherapy initiation predicts development of febrile neutropenia, and domination of *Enterococcaceae* or *Streptococcaceae* at any time during chemotherapy anticipates infection in subsequent phases of chemotherapy [64]. The gut microbiota profile in children with ALL remains different from healthy controls even after cessation of chemotherapy [18]. Moreover, Rajagopala et al. showed that in ALL patients *Lachnospiraceae* are consistently increased at diagnosis and during chemotherapy, contributing to the development of gastrointestinal complications [60]. Prolonged neutropenia and elevated chemokine levels are associated with a decreased abundance of the specific intestinal genera from the *Ruminococcaceae* families due to *Enterococcus* spp. overgrowth, which is associated with delayed neutrophil reconstitution and increased chemokine signalling, and possibly more significant infective complications [65].

6.3. Drug Metabolism and Gut Microbiota

The metabolic effects of specific gut bacteria on drugs have a significant influence on chemotherapy. Drug-metabolizing activity of human gut bacteria has emerged as an interesting function, and the intestinal flora composition is considered an important factor in individual variability of pharmacokinetics, response to therapy and adverse event rate [66]. Gut microbiota dysregulation can influence the absorption and metabolism of chemotherapeutic drugs, and the damage to the intestinal epithelial cells, destroying the intestinal barrier, resulted in intestinal dysbiosis and increased risk of infection. Therefore, the gut microbiome influences the response to chemotherapeutic drugs altering bioavailability, bioactivity, or toxicity [67], although the underlying mechanism and causal relationship are still under investigation.

This correlation concerns various type of drugs, from antibiotics to chemotherapy [65] (Figure 3) (Table 1). β-lactams are commonly used as first-line antibiotic therapy for neutropenic fever in paediatric patients with cancer. Amoxicillin treatment leads to increasing abundance of the *Enterobacteriacee* family of and pathogenic genera such as *Enterococcus* spp., *Staphylococcus* spp., and *Streptococcus* spp. However, other health-promoting genera have been described as reduced in abundance: *Blautia* spp., *Collinsella* spp., *Oscillospira* spp. and *Roseburia* spp. [68]. Cephalosporins are also used in children as first-line treatment for febrile neutropenia. After their administration, an increase in *Enterococcus* spp. (associated with negative clinical outcomes in leukaemia) has been shown in many studies [69]. The mechanism is related to changes in gene expression, protein activity and

overall metabolism of the gut microbiota. In particular, the microbiota of patients treated with β-lactams presents enzymatic activities for carbohydrate degradation, resulting in an unbalanced sugar metabolism, and there is an abundance of cells with damaged membranes and increased expression of genes involved in antibiotic resistance, stress response and phage induction [70] (Figure 4).

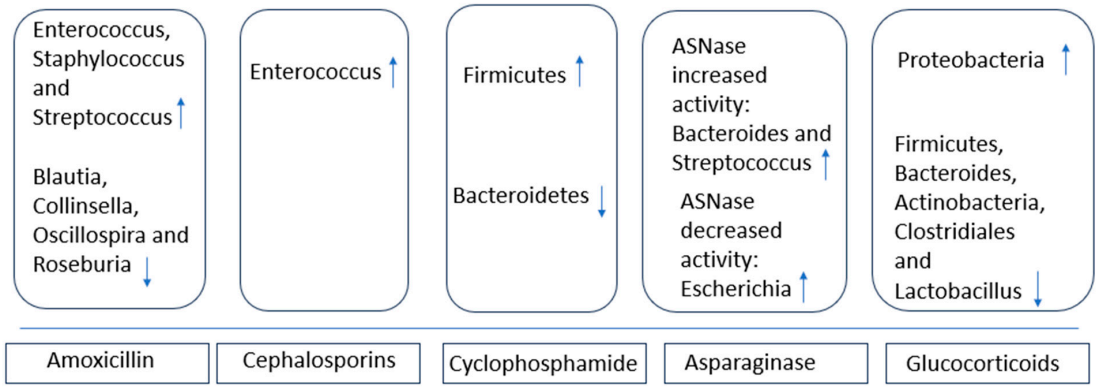

Figure 3. Drug metabolism and gut microbiota: many drugs used in ALL treatment are associated with increased or decreased abundance of various microorganism that can affect patient drug response and outcome.

Table 1. Summary of distinct effects of cytotoxic and anti-infectious drugs upon microbiota during therapy.

Drug	Increased Microorganisms	Reduced Microorganisms	Study
Amoxicillin	*Enterococcus*, *Staphylococcus* and *Streptococcus*	*Blautia* *Collinsella*, *Oscillospira* and *Roseburia*	Pallav et al. 2014 [68]
Cephalosporins	*Enterococcus*		Rashid et al. 2015 [69]
Cyclophosphamide	*Firmicutes*	*Bacteroidetes*	Xu et al. 2015 [71]
Asparaginase	*Bacteroides* and *Streptococcus* when drug increased activity *Escherichia* when drug reduced activity		Dunn et al. 2021 [72]
Glucocorticoids	*Proteobacteria*	*Firmicutes*, *Bacteroides*, *Actinobacteria*, and decreased *Clostridiales* and *Lactobacillus*	He et al. 2019 [73]

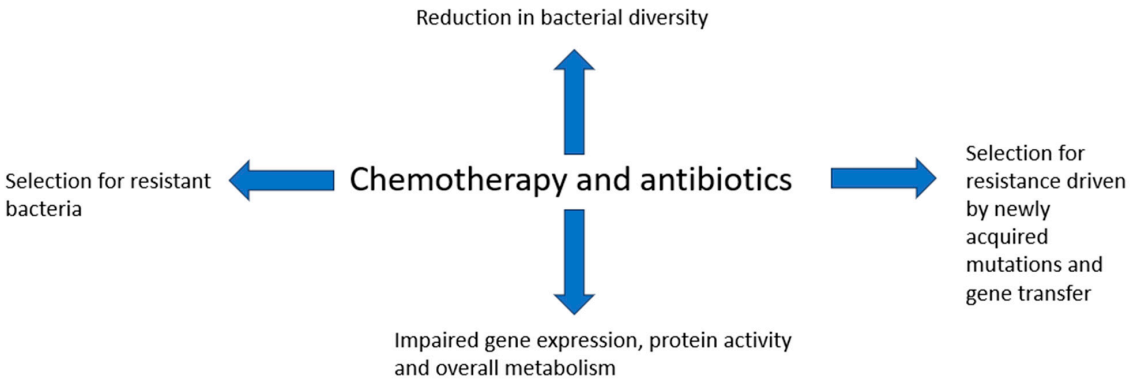

Figure 4. Pathway scheme of the effect of chemotherapy and antibiotics on gut microbiota.

The treatment with Cyclophosphamide reduced faecal bacterial diversity, with a shift toward higher *Firmicutes* and lower *Bacteroidetes* proportion [71]. Specific bacteria species seem to be related to different ASNase activity levels in treated children. *Escherichia* spp. are higher in the decreased-activity group, while *Bacteroides* and *Streptococcus* spp. prevailed in the increased-activity one [72]. Glucocorticoids, which are the mainstays in leukaemia treatment, influence the microbiome as well. They lead to decreased gut microbiota richness and diversity, diminished relative abundance of *Firmicutes*, *Bacteroides*, and *Actinobacteria*, and decreased *Clostridiales* and *Lactobacillus* spp. In contrast, steroids increased the abundance of *Proteobacteria* [73].

6.4. Gut Microbiota and Haematopoietic Stem Cell Transplantation

Patients who underwent HSCT present an altered gut microbiota [74]. The post-HSCT microbiota frequently shows reduced diversity, low abundance of commensals, and an increased frequency of *Enterococcus*, *Streptococcus*, or *Proteobacteria* colonization [75]. This intestinal microbiome injury is caused by many factors. First, multiple chemotherapy rounds, usually combined with total body irradiation (TBI), are administered to patients undergoing allogeneic HSCT. Due to the toxicity of both therapies, loss of microbial diversity and change in microbiome composition occurs [76]. The exposure to antibiotics, frequent and prolonged in this type of patient, could affect the microbiota as well. A retrospective study reported a reduction in the abundance of *Clostridia* associated with higher transplant-related mortality following the early administration of broad-spectrum antibiotics (between day −7 and day 0 before allogeneic HSCT) [77]. Finally, diet significantly influences the components of the gut microbiome given the reduced oral intake due to the loss of appetite, pain, and nausea caused by mucositis [78]. Overall, these factors can dramatically modify the intestinal microbiome and disturb gut homeostasis.

Microbiota injury is specially marked in allogeneic HSCT patients who develop Graft versus Host Disease (GvHD). Biagi et al. studied 36 paediatric patients undergoing HSCT, collecting stools at three time points: before HSCT, at time of engraftment and >30 days following HSCT. They found that children developing gut acute-GvHD presented an altered gut microbiota composition before undergoing HSCT. It was defined by (i) reduced diversity, (ii) lower *Blautia* content, and (iii) increase in *Fusobacterium* abundance. Therefore, they revealed a specific microbiome signature, before HSCT, predictive of subsequent gut acute-GvHD development [79].

6.5. Microbiota-Based Therapeutic Options

A therapeutic and innovative method permitting the restoration and modulation of the gut microbiota layout in particular in HSCT children is the faecal microbiota transplantation (FMT) [80]. It was shown that in patients with refractory diarrhoea after allo-HSCT, FMT was effective and safe [81]. Moreover, Zeng et al. demonstrated that FMT from young mice rejuvenated aged HSCs, improving short-term and long-term haematopoietic repopulation capacity. Mechanistically, single-cell RNA sequencing showed that FMT from young mice mitigated inflammatory signals and stimulated lymphoid differentiation of HSCs during ageing. They also found that FMT reshaped the gut microbiome composition and metabolite landscape, and *Lachnospiraceae* and tryptophan-associated metabolites fostered the recovery of haematopoiesis and rejuvenated aged HSCs [82]. Therefore, patients who received autologous FMT had a higher number of every lineage of leukocytes, suggesting that FMT is advantageous and revealing consistent associations between the gut microbiota and microbiota-driven modulation of immunity [83]. However, although some previous data demonstrated promising results, the knowledge regarding FMT in HSCT is still highly limited.

Studies described that FMT is safe and effective in immunocompromised (IC) patients. Kelly et al. performed a multicentre retrospective series (75 adult and 5 paediatric patients) on the use of FMT in IC patients with recurrent or severe Clostridium difficile infection and demonstrated an overall cure rate of 89% [84]. Suchman et al. also conducted a retrospective, long-term follow-up study of FMT in IC patients, including those undergoing chemotherapy (range 7–95 years), obtaining an overall cure rate of 86.5% [85].

In addition, the use of personalized precision nutrition based on patient's needs permits the regulation of the balance of gut microbiota and minimizes the adverse effects of drugs. Thus, understanding how diet impacts the structure and function of microbiota during cancer treatment can lead to the development of a precise nutritional approach. Furthermore, conservative dietary patterns can greatly affect the presence of specific bacteria, such as *F. nucleatum*, which has been described to be associated with some genetic characteristics of tumours [86].

Also, probiotics demonstrated effectiveness in fighting various cancers and maintaining the balance of gut microbiota, thus improving drug efficacy and reducing toxicity. During ALL treatment, probiotics may help manage the side effects of chemotherapy and radiotherapy, especially in reducing the infection risk and promoting intestinal recovery after treatment-induced injury [87,88]. Ekert et al. performed a study in paediatric patients with leukaemia treated with antibiotics in comparison to ALL patients treated with antibiotics and supplemented with *Lactobacilli*. In the group administered *Lactobacilli*, side effects such as vomiting and nausea were reduced [89]. Figueroa et al. examined paediatric patients with ALL after 30 days of chemotherapy, dividing them into two groups, with half of them receiving *Lactobacillus rhamnosus* GG probiotic during the chemotherapy. Only 30% of patients had gastrointestinal symptoms in the group who used probiotics during chemotherapy. In contrast, 63% of patients from the group without probiotics complained of several adverse effects of chemotherapy [90]. Furthermore, Huang et al. demonstrated that probiotics could affect the production of anti-inflammatory cytokines, activate phagocytosis, and regulate tumour cell proliferation and apoptosis in the treatment of haematological tumours [91]. Probiotics also contribute to maintaining the immune stabilization of the gut microbiota and attenuating the effects of leukaemia complications. Thus, modifying diet, using probiotics, FMT, and antibiotic stewardship may improve the gut microbiome; however, their therapeutic benefits in cancer patients remain promising but not yet conclusively established and require further validation in controlled clinical studies.

6.6. Gut Microbiota and Prognosis of ALL

In the last few years, a dynamic change in the intestinal microbiome and its functional pathways in children with ALL has emerged, from different studies, as a clear event that could be used as a prognostic factor. Indeed, the altered gut microbiota is associated with complications after chemotherapy or HSCT, influencing prognosis in leukaemic patients. The prevalence of *Enterococcaceae* or *Streptococcaceae* predicted a higher risk of infection in ALL patients [63], and the relative abundance of *Bifidobacterium longum* at onset can predict infection during induction chemotherapy [92]. A decrease in alpha and beta diversities has been correlated with a growing risk of infection within 6 months after therapy [93]. Furthermore, the gut microbiota diversity is associated with different survival after HSCT (Table 2).

Masetti et al. studied stool samples of 90 paediatric allo-HSCT patients using 16S ribosomal RNA amplicon sequencing to characterize the gut microbiota. They found that children with a higher-diversity microbiome before transplantation presented a higher incidence of overall survival and lower probability of grade 2 to 4 and grade 3 to 4 acute-

GVHD. In particular, the higher-diversity group showed increased relative abundances of health-related microbial families, such as *Ruminococcaceae* and *Oscillospiraceae*. Instead, a great abundance of *Enterococcaceae* and *Enterobacteriaceae* was detected in the lower-diversity patients [94]. Margolis et al. analysed faecal samples from 74 children before conditioning HSCT and after neutrophil recovery. A unique microbiota signature was identified linking with different infections or acute-GvHD. Some facultative anaerobes (e.g., *Lachnoclostridium* and *Parabacteroides*) defining gut microbiota prior conditioning predicted bacteraemia risk. In contrast, a different ratio of oral (e.g., *Rothia* and *Veillonella*) to intestinal anaerobes (e.g., *Anaerobutyricum* and *Romboutsia*) at neutrophil recovery anticipated bacterial infections and viral enterocolitis [95]. Elgarten et al. performed shotgun metagenomic sequencing on pre-transplant stool samples of 88 paediatric allo-HSCT patients. These samples presented lower alpha diversity and less abundance of specific taxa and bacterial genes than healthy controls. Particularly, children showed a decreased proportion of *Bacteroides*, *Ruminococcaeae* and genes involved in butyrate production but higher gammaproteobacterial species. They found that this significant dysbiosis early in the transplant course was associated with poor clinical outcome [96]. Ingham et al. studied immunological markers, immune reconstitution and gut microbiota composition relating to clinical outcomes in children undergoing HSCT. They identified three group: (i) significant concentrations of the antimicrobial peptide human beta-defensin 2 (hBD2) before the transplantation in patients with a high number of *Lactobacillaceae*, who later suffered from moderate or severe acute-GvHD and presented high mortality; (ii) rapid recovery of NK and B cells in patients with elevated obligate anaerobes such as *Ruminococcaceae*, who manifested no or mild acute-GvHD and showed low mortality; and (iii) high inflammation, supported by high levels of C-reactive protein, in children with great abundances of facultative anaerobic bacteria such as *Enterobacteriaceae* [97].

Table 2. Clinical outcome related to microbiota composition in HSCT paediatric patients. HSCT: Haematopoietic Stem Cell Transplantation; seq: sequencing; GvHD: Graft versus Host Disease. ↑ = *increased* and ↓ = *decreased*.

Study	Patients	Sequencing	Timing	Microbiota Composition	Outcome
Ingham et al. 2019 [97]	30	16s rRNA seq	Before HSCT	(1) *Lactobacillaceae* ↑ (2) *Ruminococcaceae* ↑ (3) *Enterobacteriaceae* ↑	(1) GvHD and ↑ mortality (2) ↑ KN and B cells ↓ Mortality (3) ↑ Inflammation
Biagi et al. 2019 [79]	36	16s rRNA seq	Before HSCT, at time of engraftment and >30 days following HSCT	*Blautia* ↓ *Fusobacterium* ↑	↑ GvHD
Elgarten et al. 2021 [96]	88	Shallow shotgun	Before HSCT	*Bacteroides* ↓ *Ruminococcaeae* ↓	Dysbiosis and poor clinical outcome
Margolis et al. 2023 [95]	74	16s rRNA seq and metagenomic shotgun seq	Before HSCT After neutrophil recovery	*Lachnoclostridium* ↑ *Parabacteroides* ↑ *Anaerobutyricum* ↑ *Romboutsia* ↑	↑ Bacteriemia ↑ Bacterial infections and viral enterocolitis
Masetti et al. 2023 [94]	90	16s rRNA seq	Before HSCT	*Ruminococcaceae* ↑ *Oscillospiraceae* ↑ *Enterococcaceae* ↓ *Enterobacteriaceae* ↓	↑ Overall survival ↓ GvHD ↑ GvHD

7. Discussion

The interplay between the gut microbiota, immune system development, and paediatric ALL represents a complex and still incompletely understood biological network. The present review highlights how microbial composition, early-life environmental exposures, and host genetic predisposition converge in shaping both disease risk and clinical evolution.

A central emerging concept is that microbiota alterations may occur early in life, during critical windows of immune system maturation. Factors such as mode of delivery, breastfeeding, antibiotic exposure, infections, and social interactions influence gut microbiome development and, consequently, the establishment of trained immunity. In this context, inadequate microbial stimulation may impair immune education, leading to dysregulated inflammatory responses and reduced immune surveillance. This framework is consistent with the "delayed infection" or hygiene hypothesis and supports the idea that altered microbiota composition may contribute to the progression from preleukaemic clones to overt ALL in genetically predisposed children.

However, a key unresolved question concerns the direction of this association. Two non-mutually exclusive hypotheses can be considered. On one hand, early-life dysbiosis may represent a contributing factor to leukaemogenesis by affecting immune maturation, cytokine balance, and epigenetic programming of innate immune cells. On the other hand, microbiota alterations observed at diagnosis may reflect a consequence of preclinical immune dysregulation of the disease itself. This distinction is further complicated by the impact of chemotherapy, antibiotics, and supportive care, all of which profoundly reshape microbial communities. Currently, most available studies are observational and cross-sectional, limiting the ability to establish causality.

Despite these uncertainties, some consistent patterns emerge across studies. Reduced microbial diversity is one of the most reproducible findings in children with ALL, both at diagnosis and during treatment. In contrast, the identification of specific microbial taxa associated with disease onset or progression remains heterogeneous. This variability likely reflects differences in study design, cohort characteristics, treatment phases, and methodological approaches, including the use of 16S rRNA sequencing versus shotgun metagenomics. The limited functional resolution of many studies further constrains the interpretation of microbiota–host interactions.

Importantly, the role of the microbiota extends beyond disease onset to influence treatment response and clinical outcomes. Chemotherapy and antibiotic exposure contribute to profound and long-lasting dysbiosis, favouring the expansion of opportunistic pathogens and increasing the risk of infections and treatment-related complications. In addition, microbiota composition appears to modulate drug metabolism and toxicity, representing a potential source of interindividual variability in therapeutic response. These findings suggest that the gut microbiome may serve not only as a biomarker but also as a modifiable factor in the management of paediatric ALL.

The interaction between microbiota and host genetics represents another critical dimension. Experimental models indicate that genetic predisposition to ALL may be associated with distinct microbial profiles, and that microbiota perturbations—such as antibiotic-induced depletion—can promote disease development in susceptible hosts. Although translation to human populations remains challenging, these observations reinforce the concept of a bidirectional relationship between host biology and microbial ecology.

From a clinical perspective, microbiota-based interventions—including dietary modulation, probiotics, and faecal microbiota transplantation—are gaining increasing attention. While preliminary data suggest potential benefits in reducing treatment-related toxicity and improving immune recovery, current evidence remains limited and largely derived

from small or heterogeneous studies. Safety concerns, particularly in immunocompromised paediatric patients, and the lack of standardized protocols further limit their routine clinical application.

Overall, the available evidence supports a significant association between gut microbiota and paediatric ALL across different stages of the disease. Nevertheless, major limitations persist, including small sample sizes, a lack of longitudinal designs, and insufficient control of confounding factors such as antibiotic exposure and diet. Future research should prioritize prospective, multi-centre studies integrating microbiome, immunological, and genomic data to better define causal relationships and identify clinically actionable targets.

Clarifying whether microbiota alterations represent drivers of leukaemogenesis or secondary epiphenomena remains a fundamental challenge. Addressing this question will be essential to translate microbiome research into effective preventive and therapeutic strategies in paediatric ALL.

8. Conclusions

The relationship between gut microbiota and paediatric acute lymphoblastic leukaemia (ALL) represents an emerging and promising field of research. Current evidence consistently shows an association between microbial dysbiosis and disease onset, treatment-related complications, and clinical outcomes.

However, most available data are observational, and a causal link between microbiota alterations and leukaemogenesis has not yet been established.

Microbiome-based approaches, including microbial profiling and targeted interventions, may contribute in the future to risk stratification and personalized therapeutic strategies in paediatric ALL.

Further longitudinal and mechanistic studies are required to clarify the role of gut microbiota and to translate these findings into clinical practice.

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