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Review Article

Antibiotic-Induced Obesity in Childhood Acute Lymphoblastic Leukemia: An Intricate Network of Antibiotic-Microbiome-Obesity

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Abstract

Acute Lymphoblastic Leukemia (ALL) is the most prevalent cancer among children, necessitating an investigation of its associated complications and comorbidities. Of particular concern is the frequent occurrence of obesity in patients undergoing treatment for childhood leukemia. Obesity is recognized as a risk factor for various cardiovascular conditions, venous thromboembolism (VTE), hypertension, hyperglycemia, diabetes mellitus and non-insulin-dependent diabetes mellitus (NIDDM). Consequently, a comprehensive examination of this issue from multiple perspectives is essential. The disturbance in gut microbiota diversity, resulting from the administration of Chemotherapy drugs and Antibiotics to these patients, may contribute to the development of obesity. Given the heightened risk of obesity in children with ALL, it is imperative to explore the relationship between obesity and factors such as antibiotic usage in this population. This review aims to synthesize and analyze the most recent published evidence concerning the association of obesity and antibiotics in pediatric ALL. Through this comprehensive analysis, we seek to shed light on the intricate interplay between antibiotics, obesity, and childhood ALL, with the ultimate goal of guiding future research and clinical interventions.

1. INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) stands as the most prevalent form of childhood leukemia, with a higher incidence observed among patients aged 2 to 5 years. Remarkably, ALL boasts a high cure and survival rate, nearing 90% (1). Both chemotherapy and antibiotic administration have been identified as instigators of microbiota alteration and dysbiosis. Dysbiosis entails an imbalance in microbial taxa and reduced diversity within the gut microbiota. This disruption of microbiota equilibrium commences in children with ALL and renders them more susceptible to chronic diseases during adulthood. Notably, adult survivors of childhood ALL face an increased risk of chronic diseases, including metabolic syndrome and obesity (2).

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Gut microbes can contribute to adipose tissue accumulation in the host, potentially leading to weight gain. Consequently, overweight and obesity may emerge as side effects of cancer treatment, quantified using the Body Mass Index (BMI) as an indicator. According to references, a BMI≥30.0 denotes obesity, while a BMI ranging from 25 to 29.9 is considered overweight. Late side effects are frequently observed among childhood ALL survivors, intensifying their risk of morbidity. Such survivors face an augmented predisposition to chronic diseases, metabolic syndrome, and obesity during adulthood (2). Furthermore, decreased secretion of endogenous growth hormone (GH) following cranial radiation therapy (CRT) disrupts lipid metabolism and increases total body fat in adult survivors of childhood ALL (3). Additionally, obesity during the pre-maintenance phase of chemotherapy in ALL patients heightens their susceptibility to Hypertension, Hyperglycemia, and Febrile Neutropenia (4). Moreover, obesity has been associated with a threefold increase in the risk of venous thromboembolism (VTE), underscoring the significance of studying obesity in these patients to enhance disease management (5). The primary objective of this study is to comprehensively review various factors, such as obesity, antibiotic use, and the composition of microbial flora in childhood ALL patients, investigating their interrelationships (**Figure 1**).

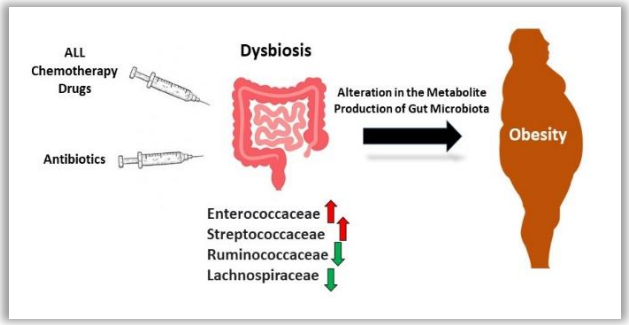

Figure 1. The Association of Chemotherapy Drugs and Antibiotics with Obesity in Childhood ALL.

2. SEARCH STRATEGY AND ELIGIBILITY CRITERIA AGE GENES

A literature search of PubMed, Scopus, and Google Scholar databases was performed for publications up to August 1, 2022, using the following search terms in various combinations: 'acute lymphoblastic leukemia', 'ALL', 'childhood acute lymphoblastic leukemia', 'childhood ALL', 'pediatric', 'obesity', 'antibiotics', 'gut microbiota', 'chemotherapy regiment'. The initial results were then screened by two independent authors based on inclusion and exclusion criteria. We included papers if they investigate: (a) pediatric patients (< 18 years old) with ALL, (b) obese patients with childhood ALL, (c) patients receiving antibiotics during chemotherapy, and (d) only papers written in English. We exclude all articles regarding adult patients with ALL. To strengthen our search, the reference list of included papers was screened to identify possible eligible articles.

3. GUT MICROBIOTA AND ITS ROLE IN HUMAN HEALTH

Intestine microorganisms that live symbiotically with the host are called Gut Microbiota. The gut microbiota composition varies in inter-individuals and in different parts of the intestine (6). The *Bifidobacterium/Lactobacillus* and the *firmicutes/bacteroidetes* are the predominant bacterial genera in the infant and adults' intestines respectively (7, 8). A healthy gut microbiota has a key role in immune homeostasis through the induction of Th17 and regulatory T cells. A study conducted on adult survivors of childhood ALL showed that there is a positive correlation between phyla *Actinobacteria* and HLA-DR+CD4+CD8+ cells. The increase in these CD markers accompanied by an increase in inflammatory biomarkers such as CRP and IL-6 indicates the elevated activity of the immune system in these patients. Furthermore, a decrease in *F. praunitzii was detected. F. praunitzii induces* IL-10 which is an anti-inflammatory cytokine.

So, disrupting the microbiota of ALL patients disturbs the homeostasis of the immune system. A healthy gut microbiota is the most important factor in guaranteeing immune homeostasis (9) (**Figure 2**).

Firmicutes and *bacteroidetes* break down indigestible carbohydrates into metabolic products that contribute to regulating immune function. Some other bacterial species like *Bifidobacteria* also help in this process. One of these metabolic products is butyrate which plays an anti-inflammatory role by the inhibition of histone deacetylase activity (10). Disruption of the usual gut microbiota composition results in interference with immune hemostasis and subsequently elevates the risk of susceptibility to various diseases including metabolic syndrome, diabetes mellitus, gastrointestinal disorders, and obesity (11).

The microbiome composition may also correlate with leukemogenesis. A study was conducted on mice with a genetic predisposition to pre-B-ALL (Pax5 heterozygosity or ETV6-RUNX1 fusion) which showed that the lack of commensal microbiota may increase the risk of pre-B-ALL (12).

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Gut microbiota has an essential role in human health. According to investigations, a healthy diet is considered a necessary way to have a balanced gut microbiota composition. Using a low-fat diet with high fiber content plus probiotics can optimize gut microbiota with the purpose of preventing different kinds of diseases (13).

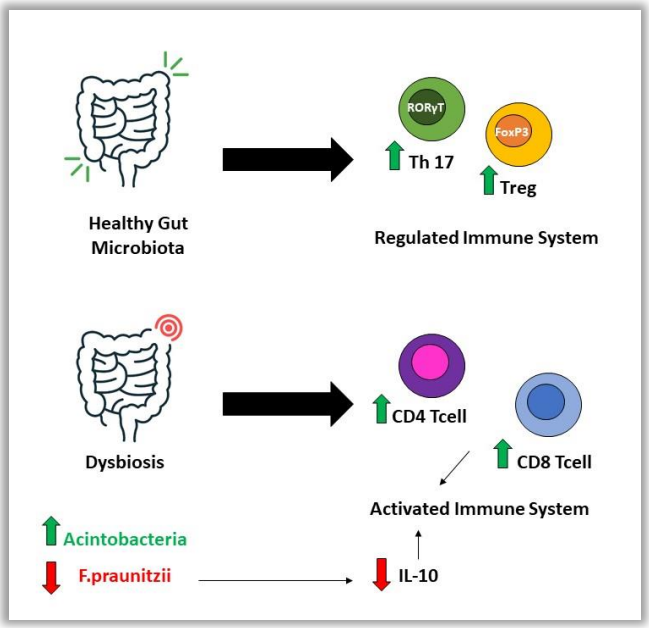

Figure 2. The Association of gut microbiota and immune system homeostasis.

4. GUT MICROBIOTA IN CHILDHOOD ALL

Chemotherapy and antibiotic usage in childhood ALL patients can induce changes in the gut microbiota, leading to dysbiosis. Dysbiosis refers to an imbalance in microbial taxa and a reduction in diversity. Dysbiosis often involves decreased diversity in the phyla Firmicutes and Bacteroidetes, along with an increased presence of Enterobacteriaceae (6). Interestingly, in a study conducted on adult survivors of childhood ALL showed an increase in both phyla Firmicutes and Bacteroidetes in anal specimen of these group compared to the healthy group (9).

The microbiome study holds significant diagnostic potential in the approach to certain cancer types (14, 15). At the onset of ALL, a notable decrease in the diversity of oral and gut microbiome is detected (16). For instance, ALL patients exhibit an increase in the Phylum Firmicutes, particularly Granulicatella and Veillonella subspecies, accompanied by a decrease in Fusobacteria in their oral microbiota (17). So although the decreased diversity in the phyla Firmicutes is one of the indicators of dysbiosis, some studies show a rise in Firmicutes in ALL patients (18, 19). To assess the microbiome composition in ALL patients who had been treated for at least one year, stool samples were subjected to 16S rRNA gene sequencing, enabling the determination of microbiome composition due to the uniqueness of variable gene regions in different bacteria. This analysis revealed reduced gene expression of Ruminococcaceae and Lachnospiraceae bacteria, particularly Ruminococcaceae Faecalibacterium, in these patients (2) (**Table 1**).

5. THE ANTIBIOTIC-MICROBIOME-OBESITY AXIS IN ALL

Sometimes, ALL patients receive antibiotic treatment in the initial disease phase as a prophylactic measure against infections (21). Consequently, in addition to chemotherapy, antibiotic usage alters the patients' microbial flora (16). Antibiotic treatment can lead to long-term gut microbiota changes, resulting in dysbiosis and a subsequent loss of specific taxonomy and functional diversity (6).

Post-antibiotic dysbiosis may cause an increase in Clostridium difficile as an example (22). Hospitalized children diagnosed with ALL are at a greater risk of infection due to the immunosuppressive therapies and antibiotics usage (23). gut dysbiosis can facilitate the transfer of resistance genes and lead to antibiotic resistance (24). Antibiotic-resistant organisms can be a cause of recurrent Clostridium difficile infections and thus provide more difficulties for the ALL patient (25). In addition, these patients are predisposed to antibiotic-resistance Enterobacteriaceae too (26). Therefore, antibiotics by affecting the gut microbiome and causing dysbiosis, increase the susceptibility of ALL patients to Clostridium difficile and Enterobacteriaceae infection (27).

A study conducted by Yassour et al. evaluated the impact of antibiotic treatment on bacterial strain diversity and stability in the infant gut microbiome. By analyzing whole-genome shotgun sequencing of monthly stool samples over 36 months from 39 children, half of whom received multiple courses of antibiotics during the first 3 years of life, it was observed that antibiotic-treated children had reduced bacterial strain diversity and a less stable gut microbiome following antibiotic treatment (28)

Diet in childhood has a very important role in intestinal microbiome formation and the microbiome change might cause overweight/obesity. Eventually, obesity is one of the antibiotic's long-term side effects but the exact mechanism of microbiome changes due to antibiotics, which ultimately causes obesity, is still unknown and requires further investigations (29, 30).

The concept of a potential association between gut microbiota and obesity has spurred investigations into the gut microbiomes of obese individuals. Studies involving germ-

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Table 1. **The gut microbiota composition in childhood acute lymphoblastic leukemia.**

Microbial taxa	Variation	Specimen	References
Phyla *Firmicutes*	Increased	Anal swab	(9)
subspecies of *Granulicatella* and *Veillonella*	Increased	Fecal sample	(17)
subspecies of *Ruminococcaceae* and *Lachnospiraceae*	Decreased	Fecal sample	(2)
Phyla *Bacteroidetes*	Increased	Anal swab	(9)
Phyla *Fusobacteria*	Decreased	Oral swab	(17)
Phyla *Actinobacteria*	Increased	Fecal sample	(9)
F. *praunitzii*	Decreased	Fecal sample	(9)
Phyla *Enterococcaceae*	Increased	Fecal sample	(20)
Phyla *Streptococcaceae*	Increased	Fecal sample	(20)

free mice have provided initial evidence supporting a link between gut microbiota and obesity. By transferring gut microbes from conventionally raised mice into germ-free mice, researchers observed an increase in fat content and insulin resistance levels in the transplanted mice, despite reduced food intake. This experiment highlighted the role of gut microbes in promoting adipose tissue accumulation in the host. Obese mice exhibited a significant decline of 50% in the abundance of Bacteroidetes within their gut microbiota, accompanied by a proportional rise in Firmicutes (18). Turnbaugh et al. further corroborated these findings by showing a significant increase in the ratio of Firmicutes to Bacteroidetes in obese mice, suggesting an enhanced energy-harvesting capacity of the microbiota from the diet (19). Similar observations have been made in humans, where the gut composition of obese children revealed an elevated proportion of Firmicutes and a decreased proportion of Bacteroidetes (18). Moreover, transferring microbiota via fecal transplant from adult mice twin pairs discordant for obesity into germ-free mice fed a low-fat diet resulted in weight gain and obesity-associated metabolic phenotypes (31).

Other studies have identified specific bacterial groups, such as the Christensenellaceae family and the genera Methanobacteriales, Lactobacillus, Bifidobacteria, and Akkermansia, as potentially linked to obesity. These findings suggest that obesity-associated microorganisms are species-specific, and bacteria within the same genus may exert contrasting effects, possibly owing to the intricate metabolic mechanisms underlying obesity (18).

5.1. Antibiotics in Chemotherapy Regiment in Childhood ALL

A systematic review by McDonnel et al. provided recent evidence on gut microbiome dysbiosis in children after antibiotic treatment. This review included twelve studies that met eligibility criteria, comprising five cohort studies, five randomized controlled trials and two cross-sectional studies. Among these studies, five reported a substantial reduction in microbiome diversity, and three reported a significant reduction in its richness. Moreover, antibiotic exposure was associated with reduced microbiome diversity and richness, alterations in bacterial abundance, Bifidobacteria and Lactobacillus decrease, and Proteobacteria increase, including E. coli (32).

Chemotherapy may lead to an imbalance in gastrointestinal microbial flora, causing a significant decrease in bacterial diversity during the intensive induction and re-induction phases of chemotherapy in childhood ALL patients. A population-based study on children with ALL identified *Enterococcaceae* or *Streptococcaceae* as the predominant gut microbiota during chemotherapy (20) , with the predominance of the Enterococcaceae population serving as a predictor of infection (16).

5.2. Childhood ALL and Obesity

Various factors can cause overweight/obesity in ALL patients. In summary, these factors can include ALL treatments which are chemotherapy, especially cranial radiation therapy (CRT), corticosteroids, and asparaginase. In addition, microbiome composition changes in ALL patients with obesity. Studies indicate an increase in some bacterial strains such as Lachnospiraceae spp., Fusobacterium spp., and Firmicutes in overweight/obese children without cancer (33).

Gut dysbiosis is a potential pathogenic factor for developing childhood disorders (34). Throughout ALL onset and cancer therapy, changes occur in the microbiome. In a study, it was shown that at the time of diagnosis of pediatric ALL, we face a late maturation of the gut microbiome. In other

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words, the lack of specific SCFA-producing taxa can compromise the immune system, predispose to chronic inflammation, or trigger ALL (35). Extensive evidence from animal models and human studies supports the notion that obesity and related diseases are associated with significant gut dysbiosis, leading to alterations in microbiota-derived metabolite production. This dysbiosis disrupts host homeostasis, contributing to increased adiposity, inflammation, oxidative stress, and metabolic dysfunction. Gut microbes generate various metabolites derived from dietary substrates and host compounds, including short-chain fatty acids (SCFAs), indole derivatives, and polyamines (such as putrescine, spermidine, and spermine). Additionally, gut bacteria biochemically modify various host-produced metabolites, including secondary bile acids, ATP, and other metabolites (36).

A comprehensive study involving 1451 adult survivors of childhood ALL treated with CRT demonstrated a significant increase in BMI (37). A BMI-based investigation of adult survivors of childhood ALL further revealed that patients treated with cranial radiotherapy ≥ 20 Gy were more susceptible to obesity (38). Despite the replacement of CRT with intrathecal and systemic chemotherapy in recent decades, it is evident that obesity remains common among pediatric ALL survivors, regardless of CRT receipt (39). Weight gain commences during ALL treatment and persists in 40-50% of adult survivors of childhood ALL (40, 41). Chemotherapy often leads to an increase in serum cholesterol and triglyceride levels. Hyperlipidemia, particularly an elevation in total cholesterol, can result from ALL treatments involving Corticosteroids and Asparaginase (42). Dyslipidemia, with a predominance of decreased HDL levels and mild Hypertriglyceridemia, is observed in 99% of ALL patients. Treatment efficiency appears to be lower in ALL patients with overweight/obesity. Additionally, T-ALL patients exhibit a higher prevalence of Hypercholesterolemia compared to B-ALL patients (43). Notably, obesity at the time of ALL diagnosis can predict the possibility of relapse and the likelihood of cure in a study encompassing 4,260 patients.

Obese patients face an elevated risk of liver and pancreatic toxicity in comparison to non-obese patients (22). Glucocorticoid treatment, such as Dexamethasone or Prednisone, can induce overweight/obesity in childhood ALL due to a significant increase in energy intake and decreased physical activity during hospitalization (22, 23). Furthermore, a reverse relationship exists between weight and plasma levels of drugs like Mercaptopurine and Dactinomycin. In female survivors of childhood ALL treated with cranial radiation, polymorphisms in the leptin receptor (LEPR) gene itself may contribute to obesity (24). ACP1-SH3YL1 gene locus polymorphisms have also been linked to an increased risk of Osteonecrosis and higher cholesterol levels in ALL patients (25).

5.3. Antibiotic-induced obesity via alteration of gut microbiota

Several studies have demonstrated that the use of antibiotics can have diverse effects. For instance, a study conducted on malnourished Malawian children revealed that prescribing Amoxicillin or Cefdinir helped them gain weight due to compromised intestinal mucosa. The addition of antibiotics to the diet of malnourished individuals reduced their mortality rate (44). Therefore, in this case, not only the obesity caused by the use of antibiotics did not have a destructive effect by altering the intestinal microbiota, but it was also healing.

Extensive and intricate networks of neurons and hormones operate bidirectionally between the gastrointestinal system and the brain, with their receptors responsible for regulating appetite, food intake, and obesity. Nutrients in the gastrointestinal tract can trigger complex hormonal and neural signaling pathways to the brain, with the vagus nerve playing a key role in mediating this signaling. The gut signals transmitted to the nucleus tractus solitarius (NTS), which then communicates with the smooth muscles of the gut via effector fibers. Subsequently, the NTS transmits information to the hypothalamus, a brain region responsible for regulating appetite, food intake and energy balance, particularly in the arcuate nucleus (ARC) neurons. The ARC comprises various types of neurons, including agouti-related protein, orexigenic neuropeptide Y, cocaine- and amphetamine-regulated transcript, anorexigenic peptides (such as Leptin), and pro-opiomelanocortin neurons. Research studies have demonstrated that vagotomy in animal models leads to increased food intake and weight gain by reducing the signaling of anorexigenic hormones. The gut microbiota associated with obesity enhances the efficiency of calorie extraction from ingested foods. As a result, an obesity-associated microbiota, enables the host to extract more energy from indigestible carbohydrates and proteins by increasing the production of primary fermentation enzymes and nutrient transporters, compared to a lean-associated gut microbiota (45).

6. POTENTIAL STRATEGIES TO IMPROVE ALL SURVIVAL THROUGH MODULATION OF THE ANTIBIOTIC-MICROBIOME-OBESITY AXIS

Various studies are being done to prevent the destructive impact of antibiotics on the gut microbiota. In a randomized

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controlled trial, antibiotics were injected into a number of participants with BMI <30 kg/m2 with and without DAV132. DAV132 mostly contains activated charcoal as an adsorbing ingredient which is able to absorb Mixifloxacin as an antibiotic. The result was that the gut microbiota composition was significantly preserved in the group that was injected with DAV132 (46). Therefore, not only antibiotic-microbiome-obesity axis studies are valuable, but they can lead to the design of new drugs that preserve the gut microbiota in order to prevent the long-term side effects of antibiotics such as obesity in adult survivors of pediatric ALL.

7. CONCLUSION AND FUTURE PERSPECTIVE

During chemotherapy, one of the dominant populations of gut microbiota becomes Enterococcaceae, which may predispose ALL patients to infection. The prescription of antibiotics to ALL patients for prophylaxis potentially alters and disrupts the intestinal microbiota by reducing its microbial diversity. A state of dysbiosis could be a result of antibiotics prescription which is a widely used medical intervention in childhood ALL.

Obesity can stem from various complex mechanisms, one of which is dysbiosis. Dysbiosis can contribute to obesity and obesity-related diseases due to its influence on metabolite production. An increase in Lachnospiraceae spp., Fusobacterium spp., and Firmicutes and the reduction of Faecalibacterium has been observed in obesity, suggesting that the imbalance of beneficial bacteria like Faecalibacterium might have a role in the development of obesity in adult survivors of childhood ALL (2, 33).

Previous studies have extensively discussed issues related to gut microbiota imbalance in childhood ALL, driven by the effects of antibiotics and chemotherapy drugs on the composition of intestinal flora. Investigations have also explored the role of altered gut microbiota composition in causing overweight/obesity in childhood ALL. In this study, we comprehensively reviewed the relevance of these contributing factors in the population of children diagnosed with ALL. In conclusion, along with ALL treatments such as corticosteroids which can be a cause of overweight/obesity, chemotherapy and antibiotics can cause dysbiosis in childhood ALL that might have long-lasting effects and predispose childhood ALL patients to obesity and obesity-related diseases in adulthood. Perhaps it is very important to emphasize studies based on the maintenance of gut microbiota in children diagnosed with ALL because these patients take a variety of gut microbiota-unbalancing drugs for a long time more than any other patient. The future perspective of our studies should be in line with maintaining the intestinal microbiome of childhood ALL through the design of drugs that balance the gut microbiota specifically.

Acknowledgment

None.

Conflict of interest

The authors declare that there is no conflict of interest in this paper.

Data availability

All data generated or analyzed during this study are included in this published article. The corresponding author can be contacted for more information.

References

1. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet. 2013;381(9881):1943-55.

2. Thomas R, Wong WSW, Saadon R, Vilboux T, Deeken J, Niederhuber J, et al. Gut microbial composition difference between pediatric ALL survivors and siblings. Pediatr Hematol Oncol. 2020;37(6):475-88.

3. Jarfelt M, Lannering B, Bosaeus I, Johannsson G, Bjarnason R. Body composition in young adult survivors of childhood acute lymphoblastic leukaemia. Eur J Endocrinol. 2005;153(1):81-9.

4. Meenan CK, Kelly JA, Wang L, Ritchey AK, Maurer SH. Obesity in pediatric patients with acute lymphoblastic leukemia increases the risk of adverse events during pre-maintenance chemotherapy. Pediatr Blood Cancer. 2019;66(2):e27515.

5. Prasca S, Carmona R, Ji L, Ko RH, Bhojwani D, Rawlins YA, et al. Obesity and risk for venous thromboembolism from contemporary therapy for pediatric acute lymphoblastic leukemia. Thromb Res. 2018;165:44-50.

6. Lange K, Buerger M, Stallmach A, Bruns T. Effects of Antibiotics on Gut Microbiota. Dig Dis. 2016;34(3):260-8.

7. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007;449(7164):804-10.

8. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. science. 2005;308(5728):1635-8.

9. Chua LL, Rajasuriar R, Azanan MS, Abdullah NK, Tang MS, Lee SC, et al. Reduced microbial diversity in adult survivors of childhood acute lymphoblastic leukemia and microbial associations with increased immune activation. Microbiome. 2017;5(1):35.

10. Andoh A. Physiological role of gut microbiota for maintaining human health. Digestion. 1960;93(3):176-81.

11. Kc D, Sumner R, Lippmann S. Gut microbiota and health. Postgrad Med. 2020;132(3):274.

[DOI: 10.61186/ijbc.16.1.35]

12. Vicente-Dueñas C, Janssen S, Oldenburg M, Auer F, González-Herrero I, Casado-García A, et al. An intact gut microbiome protects genetically predisposed mice against leukemia. Blood. 2020;136(18):2003-17.

13. Armet AM, Deehan EC, O'Sullivan AF, Mota JF, Field CJ, Prado CM, et al. Rethinking healthy eating in light of the gut microbiome. Cell Host Microbe. 2022;30(6):764-85.

14. Poore GD, Kopylova E, Zhu Q, Carpenter C, Fraraccio S, Wandro S, et al. Microbiome analyses of blood and tissues suggest cancer diagnostic approach. Nature. 2020;579(7800):567-74.

15. Nycz BT, Dominguez SR, Friedman D, Hilden JM, Ir D, Robertson CE, et al. Evaluation of bloodstream infections, Clostridium difficile infections, and gut microbiota in pediatric oncology patients. PLoS One. 2018;13(1):e0191232.

16. Oldenburg M, Rüchel N, Janssen S, Borkhardt A, Gössling KL. The Microbiome in Childhood Acute Lymphoblastic Leukemia. Cancers (Basel). 2021;13(19).

17. Wang Y, Xue J, Zhou X, You M, Du Q, Yang X, et al. Oral microbiota distinguishes acute lymphoblastic leukemia pediatric hosts from healthy populations. PLoS One. 2014;9(7):e102116.

18. Liu BN, Liu XT, Liang ZH, Wang JH. Gut microbiota in obesity. World J Gastroenterol. 2021;27(25):3837-50.

19. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027-31.

20. Hakim H, Dallas R, Wolf J, Tang L, Schultz-Cherry S, Darling V, et al. Gut Microbiome Composition Predicts Infection Risk During Chemotherapy in Children With Acute Lymphoblastic Leukemia. Clin Infect Dis. 2018;67(4):541-8.

21. Alexander S, Fisher BT, Gaur AH, Dvorak CC, Villa Luna D, Dang H, et al. Effect of Levofloxacin Prophylaxis on Bacteremia in Children With Acute Leukemia or Undergoing Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. Jama. 2018;320(10):995-1004.

22. Schubert AM, Sinani H, Schloss PD. Antibiotic-Induced Alterations of the Murine Gut Microbiota and Subsequent Effects on Colonization Resistance against Clostridium difficile. mBio. 2015;6(4):e00974.

23. Tai E, Richardson LC, Townsend J, Howard E, McDonald LC. Clostridium difficile infection among children with cancer. Pediatr Infect Dis J. 2011;30(7):610-2.

24. Stecher B, Maier L, Hardt WD. 'Blooming' in the gut: how dysbiosis might contribute to pathogen evolution. Nat Rev Microbiol. 2013;11(4):277-84.

25. Ramirez J, Guarner F, Bustos Fernandez L, Maruy A, Sdepanian VL, Cohen H. Antibiotics as Major Disruptors of Gut Microbiota. Front Cell Infect Microbiol. 2020;10:572912.

26. Simona Z, Ondřej H, Jana P, Patrik M, Jana V, Magdaléna R, et al. Occurrence and Antibiotic Resistance of Enterobacteriaceae in Acute Leukemia Patients. Klin Onkol. 2018;31(4):282-8.

27. Fisher BT, Sammons JS, Li Y, de Blank P, Seif AE, Huang YS, et al. Variation in Risk of Hospital-Onset Clostridium difficile Infection Across β-Lactam Antibiotics in Children With New-Onset Acute Lymphoblastic Leukemia. J Pediatric Infect Dis Soc. 2014;3(4):329-35.

28. Yassour M, Vatanen T, Siljander H, Hämäläinen AM, Härkönen T, Ryhänen SJ, et al. Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. Sci Transl Med. 2016;8(343):343ra81.

29. Singer-Englar T, Barlow G, Mathur R. Obesity, diabetes, and the gut microbiome: an updated review. Expert Rev Gastroenterol Hepatol. 2019;13(1):3-15.

30. Abenavoli L, Scarpellini E, Colica C, Boccuto L, Salehi B, Sharifi-Rad J, et al. Gut Microbiota and Obesity: A Role for Probiotics. Nutrients. 2019;11(11).

31. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150):1241214.

32. McDonnell L, Gilkes A, Ashworth M, Rowland V, Harries TH, Armstrong D, et al. Association between antibiotics and gut microbiome dysbiosis in children: systematic review and meta-analysis. Gut Microbes. 2021;13(1):1-18.

33. Park H, Uhlemann AC, Jacobs SS, Mowbray C, Jubelirer T, Kelly KM, et al. Title: Obesogenic microbial signatures and the development of obesity in childhood acute lymphoblastic leukemia. Leuk Res. 2023;126:107017.

34. Saeed NK, Al-Beltagi M, Bediwy AS, El-Sawaf Y, Toema O. Gut microbiota in various childhood disorders: Implication and indications. World J Gastroenterol. 2022;28(18):1875-901.

35. Peppas I, Ford AM, Furness CL, Greaves MF. Gut microbiome immaturity and childhood acute lymphoblastic leukaemia. Nat Rev Cancer. 2023;23(8):565-76.

36. Geng J, Ni Q, Sun W, Li L, Feng X. The links between gut microbiota and obesity and obesity related diseases. Biomed Pharmacother. 2022;147:112678.

37. Garmey EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, et al. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2008;26(28):4639-45.

38. Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2003;21(7):1359-65.

39. Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in pediatric ALL survivors: a meta-analysis. Pediatrics. 2014;133(3):e704-15.

40. Odame I, Reilly JJ, Gibson BE, Donaldson MD. Patterns of obesity in boys and girls after treatment for acute lymphoblastic leukaemia. Arch Dis Child. 1994;71(2):147-9.

41. Breene RA, Williams RM, Hartle J, Gattens M, Acerini CL, Murray MJ. Auxological changes in UK survivors of childhood acute lymphoblastic leukaemia treated without cranial irradiation. Br J Cancer. 2011;104(5):746-9.

42. Schmiegelow K, Müller K, Mogensen SS, Mogensen PR, Wolthers BO, Stoltze UK, et al. Non-infectious chemotherapy-associated acute toxicities during childhood acute lymphoblastic leukemia therapy. F1000Res. 2017;6:444.

43. Mogensen PR, Grell K, Schmiegelow K, Overgaard UM, Wolthers BO, Mogensen SS, et al. Dyslipidemia at diagnosis of

[DOI: 10.61186/ijbc.16.1.35]

childhood acute lymphoblastic leukemia. PLoS One. 2020;15(4):e0231209.

44. Trehan I, Goldbach HS, LaGrone LN, Meuli GJ, Wang RJ, Maleta KM, et al. Antibiotics as part of the management of severe acute malnutrition. Malawi Med J. 2016;28(3):123-30.

45. Asadi A, Shadab Mehr N, Mohamadi MH, Shokri F, Heidary M, Sadeghifard N, et al. Obesity and gut-microbiota-brain axis: A narrative review. J Clin Lab Anal. 2022;36(5):e24420.

46. de Gunzburg J, Ghozlane A, Ducher A, Le Chatelier E, Duval X, Ruppé E, et al. Protection of the Human Gut Microbiome From Antibiotics. J Infect Dis. 2018;217(4):628-36.

[DOI: 10.61186/ijbc.16.1.35]