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Authors: Klaudia Zielonka, Marcin Jasiński, Krzysztof Jamroziak

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REVIEW ARTICLE

Influence of gut microbiota on efficacy and adverse effects of treatment of lymphoproliferative disorders

Klaudia Zielonka[1*], Marcin Jasiński[2], Krzysztof Jamroziak[1]

[1]Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Warszawa, Poland

[2]Doctoral School, Medical University of Warsaw, Warszawa, Poland

*Address for correspondence: Klaudia Zielonka, Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Banacha 1A, 02–091 Warsaw, Poland, e-mail: klaudiazielonka99@gmail.com

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Abstract

Gut microbiota has aroused great interest because of its influence on the human body's homeostasis. In addition, multiple reports have indicated its role in the pathogenesis of various diseases. Interestingly, gut microbiota can affect hematological disorders by participating in lymphomagenesis. Patients with lymphoproliferative disorders undergo many procedures that alter their unique microbiota composition and lead to dysbiosis. However, this can have a biased effect as many studies have highlighted gut microbiota's activity in chemotherapy efficacy, for instance by either enhancing the anti-malignant effects of cyclophosphamide or by diminishing the activity of doxorubicin or cladribine. This review aimed to summarize gut microbiota's influence on chemotherapy's outcomes on treatment-related side effects in lymphoproliferative disorders, antimicrobial regimens, and possible gut microbiota modifications to enhance treatment outcomes.

Key words: microbiota, chemotherapy, lymphoproliferative disorders

Introduction

The term ‘gut microbiota’ (GMB) refers to a composition of microbes, including bacteria, viruses, yeast, protozoa, fungi, and archaea, that exist within the human gastrointestinal (GI) tract [1]. Acquired at birth, GMB plays a fundamental role in the development of the immune system and its further homeostasis. The GI tract is the biggest lymphoid organ and the most extensive surface in touch with an external environment [2]. As much as 70% of human immune cells are there, and every day they identify a variety of new antigens. Therefore, a relationship between the GMB and the immune system is required to balance excessive responses to antigen and infectious complications. Furthermore, protective activities to combat pathogens, vitamins and amino acid synthesis, and the structure of the GI tract barrier, are influenced by GMB [3]. One thousand or more species inhabit the GI tract, with the exact composition unique to each individual and appearing to remain stable throughout life [4].

The main phyla in the GI tract are *Firmicutes* and *Bacteroidetes*, which are dominant; less abundant are *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia* [5]. Nevertheless, lifestyle, diet, xenobiotics, physical injury, and disease can alter its composition and lead to dysbiosis, so the state of disruption in the composition and functions of microbiota is triggered by a host of external factors [6].

Hematological patients are especially prone to develop dysbiosis due to hospitalization, infection, malnutrition, treatment, and eventually hematopoietic stem cell transplantation (HSCT).

Interestingly, multiple studies have demonstrated substantial crosstalk between the GMB and the innate immune system in influencing response to tumors, therapy outcome, and patients’ overall survival (OS) [7]. Therefore, this review aimed to highlight the implications of GMB on the efficacy and adverse effects of therapy for lymphoproliferative malignancies.

The composition of GMB in the human body is set out in Table I.

Table I. Composition of gut microbiota in healthy humans (based on [5, 95–97])

Microorganism of human GMB	**Dominant phyla of GMB**	**Most abundant genus of GMB**	**Additional information**
Bacteria	*Bacteroidetes*	Bacteroides Tanarella	Phyla dominate in human GMB

		Parabacteroides Allstipes Prevotella	and represent 90% of GMB Each phylum comprises ~30% of bacteria in feces and mucus overlying intestinal epithelium Substantial numbers of *Firmicutes* are related to known butyrate-producing bacteria [5, 97].
	Firmicutes	Clostridium (represents 95% of *Firmicutes* phyla) Lactobacillus Bacillus Enterococcus Ruminicoccus	
	Actinobacteria	Bifidobacterium Corynebacterium Atobium	Phylum is mainly represented by *Bifidobacterium* genus [97]
	Proteobacteria	Escherichia Shigella Helicobacter	Less abundant phylum which may comprise ~0.1% of bacteria in strict anerobic environment of colon Increase of phylum is observed in GMB of people aged over 70 [95]
	Fusobacteria	Fusobacterium	
	Verrucomicrobia	Akkermansia	
Methanogenic archaea	Mainly single phylotype *Methanobrevibacter smithii*		
Eukarya	Mainly yeasts		
Viruses	Primarily phage		

GMB — gut microbiota

Chronic lymphocytic leukemia

Despite the introduction of novel targeted therapies in chronic lymphocytic leukemia (CLL), such as BCl-2 antagonists and Bruton's tyrosine kinase (BTK) inhibitors, the FCR protocol combining an anti-CD20 monoclonal antibody with chemotherapeutic agents (fludarabine, cyclophosphamide, and rituximab) is still widely used in fit patients without *TP53* gene abnormalities [8]. It has been revealed that the clinical activity of FCR is due to the drugs' pleiotropic effects. Interestingly, the efficacy and toxicity of FCR components may also be

influenced by GMB. For instance, the antineoplastic activity of cyclophosphamide is enhanced by a potent immunomodulatory effect [9]. High doses used in CLL treatment induce intestinal epithelium damage and mucositis. However, a study by Viaud et al. [10] demonstrated that the event is essential for the proper activity of cyclophosphamide. The disrupted barrier resulted in the translocation of commensal Gram-positive bacteria into the secondary lymphoid organs. Subsequently, the commensals enhanced T helper 17 (Th17) cells and memory Th1 immune response, which promoted antitumor activity. Conversely, germ-free mice with tumors were resistant to cyclophosphamide, indicating microbiota's significant role in the antitumor activity of cyclophosphamide [10]. Furthermore, the analysis outlined *Enterococcus hirae* and *Barnesiella intestinihominis* as being responsible for the anti-malignant feature of cyclophosphamide [11].

This finding was assessed in a clinical study by Pflug et al. [12]. A group of patients with CLL treated with anti-Gram-positive antibiotics developed a response to the treatment, progressed significantly earlier (median progression-free survival (PFS) 14.1 vs. 44.1 months, p <0.001), and had reduced OS (median OS 56.1 vs. 91.7 months, p <0.001) [12]. Independent multivariate analysis confirmed a direct correlation between anti-Gram-positive antibiotics administration and PFS, suggesting the beneficial role of GMB in the antitumor effect of cyclophosphamide [12]. Furthermore, it has been postulated that fludarabine cytotoxicity could also be altered due to dysbiosis, although the mechanism is different [13]. This comprises enzymatic modification of the drug by Gram-negative non-pathogenic *Escherichia coli* and gram-positive *Listeria welshimeri*, resulting in increased antineoplastic activity [13]. Hence, bacterial infections might lead to biotransformation of the fludarabine and enhance its anticancer effect and toxicity.

It is common knowledge that bacteria and viruses participate in lymphomagenesis. However, a study by Hoogeboom et al. [14] presented an influence of fungi on the development of a subtype of CLL with mutated immunoglobulin heavy chain variable gene (IGHV). In the subtype, the IGHV gene encodes B-cell receptors (BCRs), which are significantly specific for β-(1-6)-glucan, an antigen of yeasts and filamentous fungi [14]. Significantly, CLL cells derived from patients with no known history of fungal infection proliferated in response to the β-(1-6)-glucan [14]. This suggests the possible participation of fungi in the pathogenesis of CLL, similar to that observed in *Helicobacter pylori* responsible for gastric mucosa-associated lymphoid tissue (MALT) lymphoma [15]. It would also be interesting to verify whether the fungi infection or the antifungal treatment affects the future outcomes of chemotherapy.

Multiple myeloma

Multiple myeloma (MM) is linked to a state of immunosuppression and immune impairment, and it is assumed that dysbiosis and chronic antigen stimulation could be crucial for the pathogenesis of MM [16]. In addition, the abovementioned studies presented the influence of GMB on response to immunotherapies in CLL. In MM, immunomodulatory drugs are a mainstay of therapy; therefore there was a clear need to determine the effects of GMB on the treatment outcome.

It was recently shown that the composition of harvested microbiota of newly diagnosed patients with MM differs from healthy individuals. Compared to a control group, fecal species were abundant with nitrogen-recycling bacteria such as *Klebsiella* and *Streptococcus* [17]. The mechanism of dysbiosis in some MM patients is a result of renal insufficiency, which is one of the symptoms of MM [17]. Impaired renal function leads to the accumulation of metabolites in serum, such as ammonium, which cannot be converted into urea, and hinder its excretion with urine. In MM, ammonium enters the GI tract and stimulates the outgrowth of nitrogen-recycling bacteria. The bacteria prevent ammonium accumulation by hydrolysis of urea and uric acid in the GI tract and *de novo* synthesis of L-glutamine promoted by *Klebsiella* [17]. In addition, glutamine is essential for the growth of MM cells and is known for its effect on tumorigenesis [18]. To assess the influence of nitrogen-recycling bacteria on the course of MM, fecal microbiota transplantation (FMT) of MM patients was performed on mice. Those mice which underwent FMT presented severe progression of the disease [17].

Infections in MM are the leading cause of death and may significantly accelerate progression and reduce survival [19]. These findings suggest the potential role of antimicrobial strategies in MM, which could slow progression. The suggestion that GMB influences the progression of MM was confirmed by Calcinotto et al. [20]. In this study, commensal bacteria contributed to the accumulation of cells producing IL-17 in the bone marrow and led to MM's progression. *Prevotella heparinolytica*, a GMB component, significantly enhanced the tumor and gut inflammation. Additionally, activation of T cells resulted in their migration to the MM environment, and bone marrow ensued with eosinophil, which enhanced inflammation and consequently resulted in tumor progression. This event can be considered one of the factors responsible for the progression of smoldering MM to MM [20].

Proteasome inhibitors (PIs) are potent agents in the treatment of MM. Nevertheless, they present gastrointestinal adverse effects provoked by dysregulation of the NF-κB pathway. Therefore, it is vital to assess whether microbiota, which also influences the NF-κB pathway, may alleviate the side effects of PIs [21, 22]. Another side effect of PIs, mainly bortezomib, is severe peripheral neuropathy characterized by paraesthesia and reduced sensitization. Unfortunately, there is no prevention to PIs-induced neuropathy, and aggravation of the symptoms often leads to tapering off or even withdrawal of PIs [23]. Little is known about the possible mechanism of PI-dependent polyneuropathy; however, activation of astrocytes seems to induce hypersensitivity. Astrocyte activation may be initiated by various factors, including those outside the central nervous system such as bacterial lipopolysaccharides (LPS), contributing to the activation of toll-like receptor 2 (TLR2) and then production of proinflammatory cytokines and chemokines. Interestingly, modulation of the process may be done by activating aryl hydrocarbon receptors located in astrocytes with tryptophan-derived ligand synthesized by *Lactobacillus*, *Clostridium sporogenes*, and *Peptostreptococcus* [24]. However, this is only a hypothesis, and experimental studies are essential to verify if targeting GMB may actually alleviate PIs-induced peripheral neuropathy.

Minimal residual disease (MRD) status after autologous HSCT (auto-HSCT) in MM patients is the principal factor indicative of outcome after the treatment. Intriguingly, *Eubacterium halli* has been found to be present in higher amounts among MRD(–) patients after auto-HSCT [25]. Therefore, it is clinically relevant to perform additional tests on larger groups to define more species associated with MRD, which could assess treatment efficacy during therapy [25].

Non-Hodgkin lymphoma

This heterogeneous group of diseases is influenced by microbiota in various manners. Manifold organisms may contribute to lymphomagenesis. Persistent inflammation induced by *Delftia*, *Chlamydophila psittaci*, and *Helicobacter pylori* — commensal of approximately half of the human population, may be associated with MALT lymphoma in the conjunctiva, ocular region, and stomach respectively [15, 26, 27]. Eradication of *Helicobacter pylori* and *Chlamydophila psittaci* with an antibacterial regimen results in regression of the lymphomas without chemotherapeutic agents [28, 29]. Interestingly, *Helicobacter heilmannii* induced lymphoma development in mouse models by the formation of infiltration of lymphocytes in the gastric mucosa [30]. Single reports have mentioned *Borrelia burgdorferi* infection

preceding lymphomas [31, 32]. Ataxia–telangiectasia mice exposed to a more sterile environment had a reduced risk of lymphoma [33].

GMB influences not only lymphomagenesis but is essential for anti-malignant effects of chemotherapeutics. Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma. DLBCL is linked to substantially poor outcomes; consequently, 40% of patients who develop complete response will relapse. Great efforts have been made to understand the resistance to the treatment. There are hypotheses concerning altered tumor microenvironment, deficiency in immune cells, and upregulation of inhibitory checkpoint molecules [34]. Studies have revealed that the GMB of patients with DLBCL differed significantly before treatment completion [35]. Furthermore, aggressive DLBCL was characterized by more aberrant and reduced diversity than was indolent lymphoma [36]. Interestingly, the patients who responded to immunotherapy tend to have higher pre-treatment diversity with a distinct composition of GMB and an abundance of *Dorea formicigenerans* (associated with indolent lymphoma) and *Faecalibacterium prausnitzii*, known for being related to the better response of melanoma to anti-PD1 (programmed-cell death 1) immunotherapy [36]. The whole GMB composition has been considered a predictor of treatment response. The diversity of GMB has been altered by chemotherapy compared to baseline diversity before treatment, with a marked increase in *Bacteroidetes* and a concomitant decrease in *Firmicutes* at the phylum level [36]. The group was small; however, similar studies performed on mouse models revealed that *Bifidobacterium* upregulated the level of tumor-specific CD8+ T cell and interferon γ secretion and, consequently, increased the sensitivity to anti-PD1 and antibody CTLA4 [37]. Conversely, antibiotics used one month prior to anti-PD1 therapy for epithelial tumors resulted in lower OS (median 20.6 vs. 11.5 months, p <0.001) and PFS (median 4.1 vs. 3.5 months, p = 0.017) [38]. This needs to be further studied in a larger group of patients with lymphoma, as resistance to immunotherapy in melanoma patients has been overcome with probiotics and FMT [37, 38].

Attenuation of the efficacy of chemotherapy comprising platinum salts observed in mouse models has been assessed clinically [39]. Accordingly, earlier use of anti-Gram-positive antibiotics was associated with reduced PFS (median 2.3 vs. 11.5 months, p = 0.001) and OS (median 5.6 vs. 96.8 months, p <0.001) in a group of patients with relapsed lymphoma treated with platinum-based chemotherapy [12]. Platinum genotoxicity needs reactive oxygen species produced by tumor-associated inflammatory cells stimulated by commensals [39]. Additionally, dysbiosis guides chemoresistance to oxaliplatin, although in an unknown manner. On the contrary, in tumor cell lines infected with *Mycoplasma hyorhinis*,

degradation of gemcitabine and a decrease in the antitumoral efficacy induced by mycoplasma thymidine phosphorylase have been observed [40, 41]. Intra-tumor Gammaproteobacteria exerted the same effect, and ciprofloxacin's administration reversed this effect and elicited anti-malignant activity of the drug [41]. There are more examples of other chemotherapeutics affected by bacteria; for instance, doxorubicin and cladribine activity were significantly decreased by *Escherichia coli* [13]. However, there has been a lack of clinical studies investigating the correlation of GMB composition with treatment outcomes in hematological patients.

Moreover, doxorubicin is responsible for dysbiosis and affects the integrity of intestinal mucosa, which can lead to fatal infections [42]. Stimulation of NOD2, a critical part of the immune response, by bacterial muramyl dipeptide may have a protective role in mucosal damage induced by doxorubicin [42, 43]. Furthermore, GMB has alleviated the adverse effect of cisplatin. D-methionine, a prebiotic, has antioxidative and anti-inflammatory features and, by promoting the growth of *Lachnospiracae* and *Lactobacillus*, can regulate microbiota and reverse cisplatin-induced ototoxicity [44, 45]. Therefore, a hypothesis arises that supplementation could help to avoid cardiac dysfunction and the ototoxic effect of cisplatin. A mouse-performed study showed that *Lactobacillus* supplementation alleviated weight loss and cardiotoxicity evoked by cisplatin and reduced inflammation [46]. Moreover, in mouse models, an increase of *Lactobacillus johnsonii* was coherent with delayed development of B-cell lymphoma and oral supplementation was linked to decreased systemic inflammation and genotoxicity [47].

Further interesting findings concerned the accumulation of one of the short-chain fatty acids (SCFAs) — butyrate [48]. Mice fed with a high-fiber diet presented a raised level of butyrate and consequently had a significantly lower risk of lymphoma. Additionally, there was a correlation with tumor growth, as it may lead to apoptosis of lymphoma cells [48]. However, this finding must be treated with caution. Humans have altered the metabolism of SCFAs, and due to degradation in the liver it is undetectable in serum, so the anti-lymphoma effect might not be revealed [49].

Rituximab, an anti-CD20 antibody, markedly affects intestinal microbiota in mice. It is important to emphasize that after treatment with rituximab, GMB composition was reduced in *Lactobacillus reuteri* [50]. Consequently, the absence of *Lactobacillus reuteri* may be related to intestinal damage, a severe adverse event of rituximab administration, and inflammatory cell infiltration in the gut mucosa. As a result, administration of antibiotics can lead to

rituximab-induced mucositis, and oral supplementation of *Lactobacillus reuteri* could restore the alleviating effect on gut inflammation [50].

A possible mechanism suggests hampering inflammatory reactions by *Lactobacillus reuteri*. However, this *in vitro* observation needs further confirmation via *in vivo* and clinical studies [50].

Hodgkin lymphoma

Undoubtedly, childhood plays a crucial role in determining GMB diversity because that is when the transition of Th2 response to Th1 takes place. Notably, a study performed on adolescent/young adult Hodgkin lymphoma (HL) patients revealed that their total assemblage of microorganisms was less diverse than that of a healthy population [51]. Moreover, their Th1 response was suppressed while Th2 was enhanced. This suggests that this immunological shift did not happen. Considering possible causes of this condition, less early-childhood fecal-oral exposure due to a more hygienic environment has been postulated as the primary cause [51]. First, however, it is vital to determine whether the less diverse microbiota is not an effect of previous therapy, which is a common cause of the impoverishment of commensals in an oncological patient [51].

Doxorubicin is one of the anthracyclines with a potent antitumor effect. However, its use is limited due to the induction of cardiomyopathy. Additionally, the agent leads to dysbiosis. Interesting findings suggest that dysbiosis contributes to cardiotoxicity. In the analysis, antibiotics administered to mice resulted in depletion of the altered GMB, thus contributing to the alleviation of cardiac failure, inhibition of cardiac cell apoptosis, and decrease in cardiac enzymes activity [52]. FMT obtained a similar effect implemented a day after doxorubicin administration. Then attenuation of doxorubicin-induced dysbiosis and heart function improvement were assessed by left ventricular ejection fraction, and loss of cardiac fibrosis was observed [53]. This must be evaluated in clinical practice, as it raises the possibility of dealing with anthracycline-induced cardiotoxicity.

Programmed death-ligand 1 (PD-L1) blockade presents a highly remarkable outcome in classical HL [54]. Interestingly, the responsiveness and effectiveness of anti-PD1 immunotherapy are significantly determined by GMB [55, 56]. This has been assessed clinically in patients with refractory melanoma, in whom FMT from responders to anti-PD1 therapy to non-responders reprogrammed the resistance to anti-PD1 [56]. Activated and differentiated CD8+ cells, more abundant in the tumor microenvironment of the responders,

were the result of both immunotherapy of anti-PD-L1 and FMT, which combated myeloid-induced immunosuppression [56]. An extensive analysis performed on humans revealed that prior use of antibiotics was linked to a poorer outcome of immunotherapy [57]. There raises the question as to which moment is the most appropriate to implement antibiotics. One study indicated that one month prior was enough to diminish the effect of immunotherapy [58]. Hence, similar studies should be performed in a population with HL to establish antimicrobial management in immunotherapy.

Specific bacterial species of *Actinobacteria* and *Firmicutes*, detected in patients with melanoma, have been responsible for improving the efficacy of PD-1 [38, 56]. Interestingly, responders had elevated levels of products of bacterial catabolism, which could be treated as biomarkers of microbiome diversity [59]. Notably, the products of catabolism correlated with the presence of taxa associated with response to anti-PD1 [56]. The establishment of key commensals in HL patients is relevant. Patients who are refractory to anti-PD-1 could be treated with FMT and gain response to immunotherapy [56]. It is worth noting that today's trends for using supplementation probiotics by patients themselves may also lead to worsening response to treatment. Patients anticipating the therapy should be warned about the possible effects of using over-the-counter drugs on their own [60].

Hematopoietic stem cell transplantation

Although its severe complications such as graft-versus-host disease (GvHD) and engraftment syndrome, HSCT including autologous (auto-HSCT), haploidentical, and allogeneic (allo-HSCT) types, remains a powerful method in a variety of hematological malignancies. The source of hematopoietic stem cells may be peripheral blood, bone marrow or umbilical cord [61]. HSCT is preceded by multiple procedures, chemotherapy, anti-infective treatment, and conditioning which can alter the diversity and abundance of GMB, and consequently destroy the beneficial commensals [62]. Interestingly, patients whose diversity or microbiota composition did not change significantly through the process of HSCT (both auto- and allo-) were characterized by fewer complications that contributed to better 2-year OS in contrast to the group with a loss of diversity with a mortality rate of 66.7% [62]. Moreover, antimicrobial prophylaxis is an inevitable part of the event due to the risk of neutropenic fever or infectious complications during the whole HSCT procedure. Nevertheless, studies have had contradictory results on the administration of antibiotics on gut microbial diversity. Kusakabe et al. [62] suggested that carbapenems, cephems, and glycopeptides did not significantly

contribute to the loss of diversity and alterations of GMB. Further studies are essential to evaluate correlations among antibiotics to assess the outcome of HSCT and OS and implement protocols in the course of HSCT. For instance, in allo-HSCT, rifaximin was linked to reduced 1-year transplant-related mortality and increased OS (log-rank = 0.008, $p = 0.008$), unlike ciprofloxacin and metronidazole, due to its protective feature on microbiota diversity, and did not affect the infectious complications at the same time [63]. There is a need to evaluate similar studies for auto-HSCT. The effects of GMB on HSCT are summarized in Table II.

Table II. Summary of known effects of gut microbiota on efficacy and toxicity of cellular therapies used in lymphoproliferative diseases

Auto-HSCT	
Organism	**Mechanism and clinical relevance**
Firmicutes and *Acinetobacter*	Depletion results in loss of butyrate production Butyrate reduces intestinal permeability leading to anti-inflammatory effect and as a result attenuates chemotherapy-induced mucositis in mice Depletion led to enhancing mucositis [69]
Proteobacteria	Increased amount during dysbiosis Increased amount may be considered as a biomarker of dysbiosis [67, 69]
Blautia and *Ruminococcus*	Presence on day +7 was associated with enhancement and severity of emesis after melphalan conditioning, biomarker of emesis after melphalan conditioning [73]
Tenericutes	Presence is considered a protective factor against nausea [73]
Glomerella	Presence negatively correlated with time to neutrophil engraftment, and development of early culture-negative neutropenic fever [73]
Allo-HSCT	
Organism	**Clinical relevance**
Enterococcus	Increased amount associated with development of GvHD and GvHD-related mortality, conditioning protocols, diet, intestinal mucositis, and antimicrobial prophylaxis enhanced amount of *Enterococcus* [62, 75]
Eubacterium limosum	Presence associated with reduced risk of relapse after allo-HSCT [77]
Candida albicans	Higher density was associated with worse outcomes of HSCT [76]
Low diversity of	Increased transplant-related mortality, independent factor of allo-HSCT

microbiota in time of neutrophil engraftment	mortality [74], autologous FMT in time of neutrophil engraftments correlated with better 3-year survival [78]	
Clostridiales	A urinary 3-indoxyl produced by *Clostridiales* was predictive of outcome after HSCT [79]	
	Responsible for production of butyrate, which acts as an energy source for intestinal epithelial cells and mitigates intestinal effects of GvHD [83]	aGvHD
	Butyrate-induced enhancement of Treg cells and restoration of intestinal cells, mitigation of inflammation and GvHD [82], oral supplementation with fructooligosaccharide prebiotics resulted in production of SCAFs, led to proliferation of T regulators, and therefore, decreased risk of GvHD [84]	
	Clostridiaes supplementation was considered to alleviate gastrointestinal symptoms of GvHD [82]	
Actinobacteria and *Firmicutes*	Presence in stool during neutrophil recovery time may serve as a biomarker of development of severe aGvHD [86]	
Blautia	Presence beneficial for OS, associated with reduced GvHD mortality [81]	
CAR-T		
Organism	**Clinical relevance**	
Enterococci	Overgrowth of *Enterococci* leads to direct stimulation of TLR2 receptors, enhancement of IL-2, TNFα, IFNγ and CD8+ T cells production and severe CRS [90, 91]	
Ruminococcus, Bacteroides and Faecalibacterium	Higher amount associated with a complete response at day 100 Implementation of piperacillin/tazobactam, imipenem/cilastatin and meropenem (PIM) four weeks prior to CAR-T CD19 correlated with reduced OS and increased risk of neurotoxicity syndrome; no correlations with CRS were seen [89]	
Veillonellales	Higher abundance associated with a decreased complete response at day 100 [89]	

HSCT — hematopoietic stem cell transplant; auto-HSCT — autologous hematopoietic stem cell transplantation; allo-HSCT — allogeneic hematopoietic stem cell transplantation; GvHD — graft-versus-host disease; FMT — fecal microbiota transplant; SCFAs — short-chain fatty acids; Treg cells — regulatory T cells; aGvHD — acute graft-versus-host disease; OS —

overall survival; CAR-T therapy — chimeric antigen T-cell receptor-modified therapy; TLR2 — toll-like receptor 2; IL-2 — interleukin 2; TNFα — tumor necrosis factor alpha; IFNγ — interferon gamma; CRS — cytokine release syndrome

Autologous HSCT

Auto-HSCT accounts for approximately half of transplants in Europe. Nowadays, the main indications of auto-HSCT concern lymphoproliferative disorders. The recipient is simultaneously the donor of the stem cells, and the infusion of stem cells is preceded by high-dose conditioning chemotherapy [61]. Unlike allo-HSCT, an association of GMB on auto-HSCT has not been fully elucidated. One of the most common complications of auto-HSCT is mucositis [64]. Intestinal barrier disruption leads to translocation and may induce bloodstream infections [65], which are the main cause of mortality and morbidity in HSCT patients [66, 67].

For a long time, scientists have tried to elucidate the pathogenesis of mucositis. However, few hypotheses postulated the importance of GMB due to its inhibitory effect on the NF-κB pathway and diminishing inflammatory cytokines levels [66]. This was further confirmed in a group of patients with NHL receiving carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning. Furthermore, depletion in *Firmicutes* members, influencing NF-κB pathway and *Acinetobacter* members inhibiting inflammation were observed [68, 69]. Both species are responsible for butyrate production, which causes an anti-inflammatory effect by reducing intestinal permeability and attenuating chemotherapy-induced mucositis in mice [49, 70, 71]. On the other hand, Proteobacteria species were elevated and considered a biomarker of dysbiosis [69, 72]. This led to intestinal barrier disruption and the translocation of bacteria.

Interestingly, there is a correlation between bacteria diversity and complications related to auto-HSCT. High dose melphalan conditioning in plasmatic cell disorders affects the intestinal microbiota variety, and the detection of *Blautia* and *Ruminococcus* on day +7 is associated with enhancement and severity of emesis after melphalan conditioning [73]. On the other hand, oral bacteriome at baseline was predictive of nausea, especially the presence of phyla *Tenericutes* which was regarded as a protective factor [73]. Additionally, bacterial composition at baseline correlated with time to neutrophil engraftment [73]. Development of early culture-negative neutropenic fever was linked to oral fungal genus with the emphasis on

Glomerella, whose presence negatively correlated with time to neutrophil engraftment (p = 0.03) [73]. The evaluation of diversity GMB through total procedure auto-HSCT showed only subtle changes of butyrate-producing bacteria and other commensals after auto-HSCT, apart from *Lachnospiraceae*, of which amounts substantially decreased [58]. Further studies on a larger group are essential to evaluate the possibility of species as a biomarker of complications due to auto-HSCT.

Allogeneic HSCT

In allo-HSCT, stem cells are harvested from related or unrelated donors. It is mainly used to treat acute leukemias and plays a minor role in lymphoproliferative disorders.

Multiple studies have indicated an unquestionable impact of GMB diversity on allo-HSCT [74]. Loss of diversity in GBM is an inevitable event during allo-HSCT. Conditioning protocols, diet, intestinal mucositis, and antimicrobial prophylaxis lead to the impoverishment of beneficial species and the enhancement of *Enterococcus*, associated with developing GvHD and GvHD-related mortality [62, 75]. A few independent studies have suggested that pre-HSCT microbiota seems to have no significant impact on the future outcome of HSCT, whereas GMB after HSCT is important from the very first day of transplant [62, 75, 76].

There is robust evidence that enhanced microbiota variability correlates with increased overall survival after HSCT, with a 3-year survival of 67% in a high diversity group as opposed to 36% for a low diversity group [74]. Peled et al. [77] indicated that the presence of *Eubacterium limosum* was associated with a reduced risk of relapse [hazard ratio (HR) 0.82 per 10-fold increase in abundance; 95% confidence interval (CI), 0.71 to 0.95, p = 0.009]. Fungal commensals did not determine the efficacy of HSCT, although a higher density *of Candida albicans* was associated with a worse outcome depicted in lower OS (p = 0.0008), disease-free survival (p = 0.0064), and GvHD-free (p = 0.026) [76]. Low microbiota diversity, especially during the time of neutrophil engraftment, is significantly linked to worse outcomes contributing to increased transplant-related mortality, and can be considered an independent factor of allo-HSCT mortality (transplant-related mortality: adjusted HR 5.25, p = 0.014) [74]. One analysis indicated that correlation in neutrophil, lymphocyte and monocyte populations during hematological recovery and microbiota dynamics, with reconstitution of GMB, may have beneficial effects on white blood cell (WBCs) counts. Observation of patients who received autologous FMT at the time of neutrophil engraftments showed higher WBCs up to 100 days after FMT and further correlated with better survival. The striking effect of

Staphylococcus on lymphocytes and *Faecalibacterium* on neutrophils has been observed; nevertheless, evaluation of species responsible for the better efficacy of HSCT is relevant for clinical practice [78].

There is a need for better predictive biomarkers for the outcome of HSCT. Notably, increased urinary 3-indoxyl sulphate (3-IS), a fermented product of commensal colonic *Clostridiales*, and predicts outcomes after HSCT. Studies by Weber at al. revealed that low 3-IS levels within the first 10 days after HSCT correlated with substantially increased transplant-related mortality (p = 5.017) and decreased OS (p = 5.05) one year after HSCT [63, 79] This may suggest that microbiota elements after HSCT could serve as biomarkers of survival after HSCT.

Acute GvHD (aGvHD) is a severe complication of allo-HSCT. Intestinal GvHD affects 54% of patients who developed aGvHD and significantly contributes to increased mortality among patients [80]. There are a few postulated mechanisms of aGvHD regarding microbiota disturbance as a possible factor [81]. Animal models of GvHD showed monodominance of *Entereobacteriales* with a concomitant decrease of *Clostridiales*. Interestingly, *Clostridiales* are important producers of SCFAs, including butyrate. Therefore, *Clostridiales* supplementation has been considered to alleviate gastrointestinal symptoms of GvHD [82]. In addition, butyrate serves as an energy source for intestinal epithelial cells, and it raises protected intestinal cells and mitigates intestinal effects of GvHD [83]. Another mechanism involving the protective role of butyrate in intestinal aGvHD outlined butyrate-induced enhancement of Treg cells and subsequent restoration of intestinal cells. This resulted in the mitigation of both inflammation and GvHD [82]. Moreover, oral supplementation with fructooligosaccharide prebiotics resulted in the production of SCAFs, led to a proliferation of Tregs, and decreased the risk of GvHD [84].

Considering the mortality rate in aGvHD, biomarkers indicative of aGvHD may help stratify risk in patients. Furthermore, it could be a key in the differential diagnosis between aGvHD and other HSCT complications [85]. Additionally, the neutrophil recovery time is significant for predicting aGvHD and the presence of *Actinobacteria* and oral *Firmicutes* in the stool during neutrophil recovery time may serve as a biomarker of the development of severe aGvHD [86].

Intestinal mucositis leads to difficulties with oral intake, something which requires the implementation of parenteral nutrition. Consequently, this may contribute to malnourishment of intestinal cells and reduction in GMB diversity compared to enteral nourishment, eventually triggering aGvHD [87]. Additionally, parenteral nutrition leads to the

replenishment of *Blautia*, which has been associated with reduced GvHD mortality [HR (95% CI) 0.18 (0.05–0.63), $p = 0.007$] and beneficial for OS ($p < 0.001$) [88].

Chimeric antigen receptor T-cell

CD19-targeted chimeric antigen receptor-modified (CAR) T-cell is a novel therapy registered in lymphoproliferative disorders that is revolutionizing current management. In the long term, CD19-targeted CAR T-cell therapy is inefficacious in most patients who relapse or develop CAR-T-related toxicity [89]. Considering bacterial effects on other immunotherapy mentioned in HL [56–58], it seems highly probable that there is a correlation between CAR-T and GMB. GMB may be one of the determinants responsible for the failure of CAR-T therapy, although little is known yet on this subject. Nevertheless, recent articles have suggested that microbiota and antibiotics do influence CAR-T therapy. Schubert et al. [90] put forward an interesting hypothesis suggesting that overgrowth of *Enterococci* in intestines may lead to severe cytokine release syndrome (CRS) induced by CAR-T. Direct stimulation of *Enterococci* to TLR2 receptors, which enables co-stimulatory signal enhancing the production of IL-2, TNFα and IFNγ in murine and human CD8+ T cells, contributed to an increase in polyfunctional T cells against tumor cells and the possibility of CRS [90, 91]. Investigations performed on mice suggested that long-term broad-spectrum antibiotics therapy contributing to loss in bacterial diversity did not influence the outcome of CD19-CAR-T. This is only partially consistent with a retrospective study concerning the use of antibiotics on the efficacy of CD19 CAR-T [92]. Implementation of piperacillin/tazobactam, imipenem/cilastatin and meropenem therapy four weeks prior to CAR-T CD19 correlated with reduced OS in patients with NHL (HR = 1.71, $p = 0.011$) [89]. Significantly, antibiotics seemed to have no impact on PFS in that cohort. Besides the influence on OS, exposure to these antibiotics was associated with increased immune effector cell-associated neurotoxicity syndrome; however, no correlations with CRS were seen [89]. The impact of GMB on CAR-T is set out in Table II. Further studies concerning microbiota's influence on CAR-T efficacy are essential.

Conclusions and perspectives for future

GMB is thought to have tremendous effects on chemotherapy efficacy and outcomes by cooperating with the immune system [10, 12, 56]. However, since many of these results have been obtained from *in vitro* or *in vivo* experiments or retrospective patient cohorts, it would be

essential to confirm and quantify the influence of GMB on the effects of chemotherapeutic agents, immunotherapy, and HSCT in prospective clinical trials.

In the future, determining the composition of GMB prior to and during treatment may be helpful in further management. Moreover, GMB can serve as a biomarker for patients especially at risk of poor outcomes, and may lead to modifications in their treatment protocol or antimicrobial prophylaxis [36, 59].

Therefore, every effort should be made to maintain microbiota's primary composition and abundance. However, therapeutic interventions with modifications to reestablish baseline GMB composition such as FMT should be considered in situations resulting in dysbiosis.

By way of illustration, FMT augmented anti-PD-1 immunotherapy and had excellent outcomes in patients with steroid-refractory or dependent type aGvHD as a second-line treatment with or without ruxolitinib [93, 94].

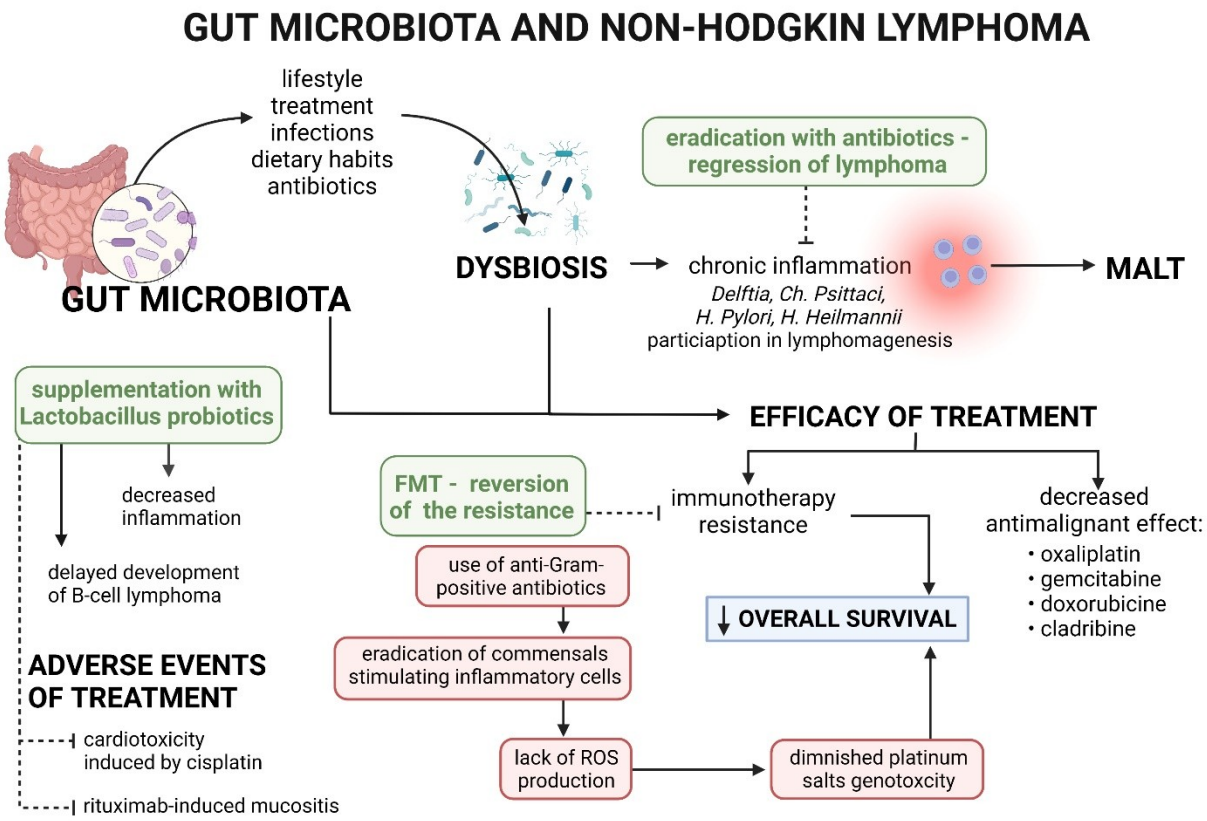

Figure 1. Gut microbiota and non-Hodgkin lymphoma (created with BioRender.com); MALT — mucosa-associated lymphoid tissue; FMT — fecal microbiota transplant; ROS — reactive oxygen species

Authors' contributions

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Conflicts of interest

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to Biomedical journals.

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