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Recent insights into the role of the microbiome in malignant and benign hematologic diseases

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ABSTRACT

Growing evidence suggests the impact of microbiome alteration, named dysbiosis, on the development of neoplasms, infections, inflammatory diseases, and immuno-mediated disorders. Regarding hematologic diseases, most data regard hematopoietic stem cell transplant (HSCT). In this review, we systematically evaluate the studies concerning microbiome in malignant and benign hematologic disorders beyond HSCT. A permissive microbiota is associated to the development of hematologic malignancies (including acute leukemia, lymphoma, and multiple myeloma), as well as of iron deficiency anemia, autoimmune cytopenias, and aplastic anemia. This happens through various mechanisms; chronic inflammatory triggering, epithelial barrier alteration, antigen dissequestration, and molecular mimicry. Hematologic therapies (chemo and immunosuppression) may induce/worsen dysbiosis and favour disease progression and infectious complications. Antibiotics may also induce dysbiosis with possible long-term consequences. Finally, novel target therapies are likely to alter microbiome, inducing gut inflammation (i.e. small molecules such as tyrosine-kinase-inhibitors) or enhancing host's immune system (as observed with CAR-T cells and checkpoint inhibitors).

1. Introduction

The role of environmental factors in the development of hematologic diseases has been clearly recognized and a number of evidences exist for both chemical and physical factors such as chemotherapies and radiations. Infectious agents also emerged as a possible trigger for both oncologic and benign hematologic diseases. Regarding the former, some lymphomas and leukemias have been associated with viral infections (i.e. EBV (Brady et al., 2007), HCV (Tasleem and Sood, 2015), HIV (Grogg et al., 2007), and HTLV (Longo et al., 1984)), but even with bacterial ones (i.e. Chlamydia spp. and Helicobacter pylori (Ponzoni and Ferreri, 2017)). Suggested pathogenic mechanisms include chronic inflammatory triggers (as typically observed for mucosa associated lymphoid tissue lymphoma and Chlamydia or Helicobacter infections) or the presence of specific cancerogenity (as observed for some viral species that produce transactivating proteins able to interfere with cellular cycle). As regards benign conditions, autoimmune cytopenias and aplastic anemia have largely been associated with infections including Parvovirus B19 (Tyrrell, 1984), hepatotropic viruses (Cudillo, 2009), Mycoplasma spp. (Stéphan et al., 1999) and Mycobacterium tuberculosis (Coburn et al., 1973). The pathogenic mechanisms involved encompass molecular mimicry, antigen dissequestration, and, again, a chronic inflammatory trigger that may favor the emergence of the prohibited autoreactive clones. There is growing attention on the microbiota, the totality of commensal, symbiontic and pathogenic microorganisms that colonize human body. The role of the microbiota in cancerogenesis and autoimmunity is largely unknown, but it is unlikely to be a silent spectator. In fact, it is thought to participate to both host defense, tolerance maturation, and immunosurveillance (Samuelson et al., 2015). Most studies in the context of hematological diseases focused on the alteration of the microbiome in bone marrow transplant and have been revised elsewhere (Andermann et al., 2018; Staffas et al., 2017). However, as shown by Severyn and colleagues in a recent study, there is an increasing interest concerning microbiome composition/alteration in hematological diseases and their therapies besides the transplant setting (Severyn et al., 2019). In this review we provide a short overview of microbiome definition and analysis, and then discuss the studies that evaluated its role in malignant and benign hematologic disorders.

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2. Microbiome: an overview

The term microbiota refers to an ecological community of commensal, symbiotic and pathogenic microorganisms that colonize various districts within the human body (Peterson et al., 2009), including the gastointestinal tract, respiratory system, oral cavity, skin and female reproductive system. These communities encompass more than a trillion microbial cells such as bacteria, fungi, viruses and archaea (Gill et al., 2006). The whole genetic asset of these microorganisms, defined microbiome, comprehends approximately 3.3 million genes, an extraordinary greater number compared with the 23,000 genes included in the human genome (Qin et al., 2010). The microbiota and its products exert major influence on many host homeostatic processes, such as the regulation of metabolic pathways, synthesis of vitamins and fat storage, energy metabolism through the production of short-chain fatty acids (O'Hara and Shanahan, 2006), defense against pathogens (Buffie and Pamer, 2013), immune system development, regulation of the immune response, and inflammation (Samuelson et al., 2015; Actis, 2014).

The microbiome is dynamic and changes throughout life, but infancy and early childhood represent the critical period in shaping its composition. In addition to genetic influence, the most important environmental factors intervening in early life are antibiotic use and disease status (Lozupone et al., 2012), gestational age, delivery mode, and diet (Meropol and Edwards, 2015): all these factors are able to impair the homeostatic functions mediated by the microbiota, potentially leading to immediate consequences or impacting health status later in life (Charbonneau et al., 2016).

Many sites in the human body have been considered sterile until recently, since presence of bacteria has been classically investigated with culture-dependent techniques.

However, the advent of modern high-throughput sequencing methods has allowed to study entire microbial communities and to deepen our knowledge from an ecological point of view. The introduction of these techniques has defined the beginning of the Human Microbiome Project (HMP), with the aim to better characterize the human microbiota and to describe microbial communities in five different body sites: oropharynx, skin, vagina, gut and nasal cavity, with major efforts given to the intestinal microbiome (Turnbaugh et al., 2007). This campaign determined deep changes in the approach on microbiological studies: focus is not centered on the single bacteria, yet on describing entire communities, investigating their relationship with the host.

Most of the modern molecular techniques are based on a broad-range PCR, which employs primers that target the 16S ribosomal RNA (rRNA) gene, a highly conserved region contained in bacterial genomes, allowing amplification of all bacterial genetic material present in the sample (Patel et al., 2017). After amplification, the use of next-generation sequencing (NGS) technologies permits the simultaneous characterization of an entire community, with a great reduction of time needed for the analysis and important advantages in terms of cost-effectiveness (Schuster, 2008). Sequences are then grouped by similarity to each other in a process termed operational taxonomic unit (OTU) picking, in which sequences with more than 97 % similarity are clustered in a single OTU. Relative abundances of different OTUs in study groups and diversity analysis are then used to report data. Definitions of the most common terms used in microbiome studies are reported in Table 1.

Other modern molecular approaches include metagenomic sequencing, in which all the microbial genome is included in the analysis in addition to the bacterial one, and transcriptome analysis, based on RNA sequencing to profile the whole microbiome transcription. These two techniques guarantee more detailed information than marker gene sequencing, but are quite expensive and complex to prepare, hence their use is less common (Knight et al., 2018).

Table 1
Glossary.

Microbiota	Ecological community of commensal, symbiotic and pathogenic microorganisms that colonize various districts within the human body
Microbiome	Genetic asset of an entire microbial community
Metabolome	The totality of metabolites produced by a microbial community
Keystone Species	Microorganisms considered extremely important in maintaining organization and function within a community
Operational Taxonomic Unit (OTU)	Cluster of sequences closely related (usually with with 97 % or more similarity), intended to represent a taxonomic unit of a microorganism
Biodiversity	Number of OTUs in a community and their relative abundance. It is influenced by richness (number of OTUs in a sample) and evenness (how equal relative abundances are distributed in a sample)
Alpha-diversity	Within-sample-diversity: measure of how abundant OTUs are in relation to others in the same sample
Beta-diversity	Measure that compares different microbial communities

3. Microbiome in malignant hematology

Tables 2 and 3 summarize available microbiome studies in acute leukemias, lymphoproliferative disorders, and multiple myeloma. Common features of these diseases are neoplastic proliferation, cytokine inflammatory storm, and acquired immunodeficiency (due to both disease itself and chemotherapy) with increased infectious risk.

Focusing on acute leukemias (Table 2), microbiome changes have been related not only to the microenvironmental alterations induced by leukemia itself, but also to chemotherapy or antibiotics administration (Ford et al., 2019; Nearing et al., 2019; Rajagopala et al., 2016; Wen et al., 2019; Song and Gyarmati, 2019). Patients undergoing intensive chemotherapy may develop severe dysbiosis, which leads to gastrointestinal adverse effects and a higher risk of infectious complications (such as bloodstream infections) by multi-resistant microbes as *Enterococcus*. (Rashidi et al. (2019a)) analyzed the bacterial microbiome profile of consecutive stool samples from 20 leukemic patients undergoing intensive chemotherapy and demonstrated that repeated courses favored the expansion of *Enterococci*, with increased frequency of systemic infections. In a recent report, (Rashidi et al. (2019b)) underlines again the importance of dysbiosis in this setting, comparing gut microbiome of a cohort of AL patients and a cohort of HSCT patients and describing microbiome changing in both cohorts (marked loss of diversity and domination of low-diversity communities by Enterococcus). In a pilot study by (Reyna-Figueroa et al. (2019)), the administration of probiotics was able to improve the outcomes of gastrointestinal side effects of chemotherapy in children with acute leukemias.

Concerning acute lymphoblastic leukemia (ALL), the development of bloodstream infections following bacterial translocation is one of the major causes of death. Normally, the mucosa associated-immune system contributes to microbiota homeostasis. In ALL, the loss of normal mucosal lymphatic cells and possibly the infiltration of malignant blasts leads to an impairment of host immune system, microbiome imbalance and outbreak of systemic infections (Song and Gyarmati, 2019; Bai et al., 2017). It was indeed shown by (Wang et al. (2014)) that the oral bacterial flora of 13 ALL patients displayed lower richness and remarkable differences, as compared to healthy controls. In particular, the phyla *Firmicutes* was more abundant and *Fusobacteria* less abundant. Furthermore, (Hakim et al. (2018)) analyzed fecal samples from 199 ALL patients at diagnosis and after three initial chemotherapy cycles and demonstrated that the predominance of certain bacterial taxa in gut microbiome (e.g. *Proteobacteria* before chemo or *Streptococcaceae* at any time during chemo) can predict infections occurrence. More recently, Liu X et al. reported differentially abundant taxa in the gut of pediatric ALL patients (e.g., *Roseburia faecis, Edwardsiella tarda,* and *Fusobacterium naviforme*), that also correlated with the level of interleukin-10, a known

Table 2
Microbiome studies in leukemias.

Type of study	Study title	Significance	N° of patients	Type of microbiome	Ref
Clinical study	Decrease in vancomycin-resistant Enterococcus colonization associated with a reduction in carbapenem use as empiric therapy for febrile neutropenia in patients with acute leukemia	Antimicrobial prophylaxis may induce dysbiosis in patients with acute leukemia	342	Gut	(Ford et al., 2019)
Clinical study	Infectious Complications Are Associated With Alterations in the Gut Microbiome in Pediatric Patients With Acute Lymphoblastic Leukemia	Infections may induce dysbiosis in patients with acute lymphoblastic leukemia	16	Gut	(Nearing et al., 2019)
Clinical study	Gastrointestinal microbial populations can distinguish pediatric and adolescent Acute Lymphoblastic Leukemia (ALL) at the time of disease diagnosis	Microbiome composition differs in pediatric and adolescents with acute lymphoblastic leukemia	51	Gut	(Rajagopala et al., 2016)
Clinical study	Pediatric Acute Lymphoblastic Leukemia Patients Exhibit Distinctive Alterations in the Gut Microbiota.	Microbiome differs from healthy controls in pediatric ALL patients	58	Gut	Liu et al., 2020a
Review	Interactions Between Gut Microbiota and Acute Childhood Leukemia	Microbiota changes through life and dysbiosis may be cause and consequance of leukemia development and therapy, respectively	–	Gut	(Wen et al., 2019)
Preclinical study	Bacterial translocation in acute lymphocytic leukemia	Leukemia treatment may alter the epithelium and favor bacterial translocation	Murine model	Gut	(Song and Gyarmati, 2019)
Clinical study	Dysbiosis patterns during re-induction/salvage versus induction chemotherapy for acute leukemia	The different steps of leukemia therapies may induce heterogeneous dysbiosis	20	Gut	(Rashidi et al., 2019a)
Clinical study	Gut dysbiosis during antileukemia chemotherapy versus allogeneic hematopoietic cell transplantation	Microbiome alteration may occur either after leukemia chemotherapy and following stem cell transplant	–	Gut	(Rashidi et al., 2019b)
Clinical study	Probiotic Supplementation Decreases Chemotherapy-induced Gastrointestinal Side Effects in Patients With Acute Leukemia	Probiotic supplementation may reduce dysbiosis and prevent gut side effects of leukemia therapy	60	Gut	(Reyna-Figueroa et al., 2019)
Clinical study	Changes in the gastrointestinal microbiota of children with acute lymphoblastic leukaemia and its association with antibiotics in the short term	Microbioma may be altered by antibiotics prophylaxis and treatment in acute leukemia patients	63	Gut	(Bai et al., 2017)
Clinical study	Oral microbiota distinguishes acute lymphoblastic leukemia pediatric hosts from healthy populations	Leukemia patients show different oral microbiome composition as compared to healthy controls	26	Oral	(Wang et al., 2014)
Clinical study	Gut Microbiome Composition Predicts Infection Risk During Chemotherapy in Children With Acute Lymphoblastic Leukemia	Microbiome composition is associated with infections complications in leukemia patients	199	Gut	(Hakim et al., 2018)
Clinical study	Gut microbiota profiles of treatment-naïve adult acute myeloid leukemia (AML) patients with neutropenic fever during intensive chemotherapy	Adult AML with a first episode of febrile neutropenia after induction chemotherapy demonstrated a significant decrease in gut microbiota diversity that remained constant despite recovery	10	Gut	Rattanathammethee T 2020
Clinical study	Prospective evaluation of HSV, Candida spp., and oral bacteria on the severity of oral mucositis in pediatric acute lymphoblastic leukemia	Microbiome composition is associated with mucositis in leukemia patients	71	Oral	(de Mendonça et al., 2012)
Clinical study	Oral Mucositis in Pediatric Acute Lymphoblastic Leukemia Patients: Evaluation of Microbiological and Hematological Factors	Microbiome composition is associated with infections complications in leukemia patients	71	Oral	(Mendonça et al., 2015)
Clinical study	Reduced microbial diversity in adult survivors of childhood acute lymphoblastic leukemia and microbial associations with increased immune activation	Microbiome alteration may occur in adult leukemia survivors and associate with immune activation	134	Gut	(Chua et al., 2017)
Clinical study	The role of the gastrointestinal microbiome in infectious complications during induction chemotherapy for acute myeloid leukemia.	Microbiome composition is associated with infections complications in leukemia patients	34	Gut and oral	(Galloway-Peña et al., 2016)
Clinical study	Microbiome Signatures are Predictive of Infectious Risk Following Induction Therapy for Acute Myeloid Leukemia	Microbiome composition is associated with infections complications in leukemia patients	97	Gut	(Galloway-Peña et al., 2019)

immunosuppressive cytokine [Liu et al., 2020a]. Even mucositis seems to be affected by oral microbiome alterations, and de Mendonça RM et al. demonstrated that the presence of HSV and Candida represent risk factor for the development of mucositis in two different studies (de Mendonça et al., 2012; Mendonça et al., 2015).

Microbiome alteration may also favor long term side effects in leukemia survivors: (Chua et al. (2017)) compared the anal microbiota of adult survivors of childhood ALL with that of healthy controls, and found microbiota alterations, such as reduction of microbial diversity, higher abundance of *Actinobacteria* and depletion of *Corynebacterium*. Moreover, these abnormalities showed a relationship with late-onset chronic inflammatory complications, such as obesity and type 2 diabetes.

Regarding acute myeloid leukemia (AML), fewer studies investigated the predictive value of microbiome composition on the development of infections during therapy (Galloway-Peña et al., 2016). (Galloway-Peña et al. (2019)) showed that a lower baseline stool α-diversity and the loss of microbial diversity during induction chemotherapy were associated with infectious complications either during or after chemo. More recently, Rattanathammethee T and Colleagues demonstrated a significant decrease in gut microbiota diversity in AML patients experiencing febrile neutropenia after induction chemotherapy [Rattanathammethee et al., 2020]. Even in this setting, the unscrupulous use of prophylactic antibiotics can contribute to the dysbiosis and to the consequent increased risk of translocation and systemic infection.

Also some lymphomas (Table 3) have been pathogenically associated to certain microorganisms, including pathogenic virus (EBV (Brady et al., 2007; Henle and Henle, 1970; Pannone et al., 2014), HTLV1

Table 3
Microbiome studies in lymphomas and multiple myeloma.

Disease	Type of study	Study title	Significance	N° of patients	Type of microbiome	Ref
Lymphoma	Review	Helicobacter pylori infection and gastric cancer biology: tempering a double-edged sword.	Chronic bacterial infections may favor the emergence of neoplastic clones through various mechanisms. This is particularly clear for gastrointestinal lymphomas and mucosal associated lymphoid tissue lymphomas	–	Gut	(Mentis et al., 2019)
	Review	Gastric microbiota: An emerging player in Helicobacter pylori-induced gastric malignancies.		–	Gut	(Espinoza et al., 2018)
	Preclinical study	Intestinal bacteria modify lymphoma incidence and latency by affecting systemic inflammatory state, oxidative stress, and leukocyte genotoxicity		–	Gut	(Yamamoto et al., 2013)
	Review	Intestinal microbiome and lymphoma development.		–	Gut	(Yamamoto and Schiestl, 2014a)
	Review	Lymphoma caused by intestinal microbiota		–	Gut	(Yamamoto and Schiestl, 2014b)
	Clinical study	Conjunctival dysbiosis in mucosa-associated lymphoid tissue lymphoma.		50	Conjunctival	(Asao et al., 2019)
	Clinical study	Fecal microbiota diversity in survivors of adolescent/young adult Hodgkin lymphoma: a study of twins.	Dysbiosis induced by lymphoma and its treatment may have long-term consequences	342	Gut	(Cozen et al., 2013)
	Review	Gut microbiome and CAR-T cells therapy	Microbiome composition is likely to be influenced/altered by novel targeting therapies including CAR-T cells	–	Gut	(Abid et al., 2019)
Multiple Myeloma	Preclinical study	Microbiota-driven interleukin-17-producing cells and eosinophils synergize to accelerate multiple myeloma progression	Gut symbionts may favor myeloma progression through altered cytokine signalling	–	Gut	(Calcinotto et al., 2018)
	Clinical study	Microbiota Taxonomic Shifts in Chinese Multiple Myeloma Patients Analyzed by Quantitative Polimerase Chain Reaction (QPCR) and 16S rRNA High-Throughput Sequencing	Distinct myeloma composition may be observed in myeloma patients	57	Gut	(Zhang et al., 2019)
	Clinical study	Minimal residual disease negativity in multiple myeloma is associated with intestinal microbiota composition.	Microbiota composition may be associated with deeper disease remission	34	Gut	(Pianko et al., 2019)

(Longo et al., 1984), HHV8 (Chang et al., 1994), HIV (Grogg et al., 2007; Mylona et al., 2008; Re et al., 2019), HBV (Li et al., 2018), HCV (Tasleem and Sood, 2015; Zuckerman et al., 1997)), and normal residents of the microbiome or their metabolites, such as Helicobacter pylori (Stolte et al., 2002), (Pereira and Medeiros, 2014), (Mentis et al., 2019), (Espinoza et al., 2018). In animal models, it has been shown that intestinal microbiota contributes to the penetrance, latency, oxidative stress and genotoxicity of some microorganisms, being a possible modifiable factor of lymphomagenesis (Yamamoto et al., 2013; Yamamoto and Schiestl, 2014a, b). In humans, (Asao et al. (2019)) reported an increased abundance of genus *Delftia* and a lower abundance of *Bacteroides* and *Clostridium* in conjunctival microbioma of MALT lymphoma patients, suggesting that *Delftia* may have a pathogenetic role in this rare lymphoma. Furthermore, the effect of therapy in inducing dysbiosis has been reported also in adult survivors of Hodgkin's lymphoma where the deficiency of certain intestinal microbes has been found (Cozen et al., 2013). Of note, the role of microbiome is now under active investigation even in more innovative therapies, such as chimeric antigen receptor (CAR) T-cells, although results are still speculative so far (Abid et al., 2019).

Finally, in multiple myeloma (MM), gut microbiome imbalance may play a role in the stimulation of plasma cells and has been implicated in clonal selection and oncogenesis. In preclinical models, *Prevotella heparinolytica* was shown able to stimulate T-helper 17 cells in gut, which migrate to bone marrow and promote myeloma progression (Calcinotto et al., 2018). A recent report by Zhang et al. showed that, at the time of the diagnosis, MM patients display imbalanced composition and diversity of gut microbiome compared with healthy controls; in particular, MM group showed higher abundances of *Proteobacteria* and lower abundances of *Actinobacteria* at the phylum level and higher proportions of *Bacterioides*, *Facealibacterium* and *Roseburia* at the genus level (Zhang et al., 2019). Finally, (Pianko et al. (2019)) showed that certain microbes are associated with the depth of response to therapy, with *Eubacterium hallii* and *Faecalibacterium prausnitzii* being more abundant in minimal residual disease negative patients.

4. Microbiome in benign hematologic conditions

Tables 4 and 5 show available literature on microbiome status in benign hematologic conditions including iron deficiency anemia, sickle cell anemia (SCD), aplastic anemia (AA), immune thrombocytopenia (ITP), and congenital neutropenia. Regarding the first, it is known that iron is essential for both the growth of pathogens and the host immune activation/inflammation against them. Several studies have focused on iron deficiency, which has been recognized to cause major shifts in microbiota composition by favoring the growth of species that do not need iron (e.g., Lactobacillaceae) or of good iron scavengers bacteria (e.g. the health-promoting bifidobacteria, or potentially entero-pathogenic Enterobacteriaceae) (Kortman et al., 2014; Balamurugan et al., 2010). These data have been confirmed in in vitro colonic fermentation models inoculated with children fecal microbiota: iron deficiency resulted in decreased relative abundance of short-chain fatty acid producers (*Lachnospiraceae, Ruminococcaceae,* and *Bacteroidaceae*), and increased proportions of *Bifidobacteriaceae*, *Enterobacteriaceae,* and *Lactobacillaceae* (Dostal et al., 2015, 2013; Dostal et al., 2012). Muleviciene et al. (2018) compared the gut microbiota of patients with iron deficiency anemia and healthy controls aged 6–34 months. They described in the former an increased relative abundance of certain microbes (e.g. *Enterobacteriaceae* or *Veillonellaceae*), a reduced abundance of others (e.g. *Coriobacteriaceae*) and a decreased ratio of

Table 4
Microbiome studies in congenital and acquired anemias.

Disease	Type of study	Study title	Significance	N° of patients	Type of microbiome	Ref
Iron deficiency anemia/chronic inflammation	Clinical study	Low levels of faecal lactobacilli in women with iron-deficiency anaemia in South India.	Iron deficiency anemia/ low iron status may be associated with altered composition of microbiome both in preclinical models and in patients	34	Gut	(Balamurugan et al., 2010)
	Preclinical study	Low iron availability in continuous *in vitro* colonic fermentations induces strong dysbiosis of the child gut microbial consortium and a decrease in main metabolites.		–	Gut	(Dostal et al., 2013)
	Preclinical study	Iron depletion and repletion with ferrous sulfate or electrolytic iron modifies the composition and metabolic activity of the gut microbiota in rats		–	Gut	(Dostal et al., 2012)
	Clinical study	Iron deficiency anemia-related gut microbiota dysbiosis in infants and young children: A pilot study.		20	Gut	(Muleviciene et al., 2018)
	Review	The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review.	Iron supplementation and iron excess may impact on gut microbiome composition	–	Gut	(Paganini and Zimmermann, 2017)
	Preclinical study	Commensal Bacteria-induced Interleukin 1β (IL-1β) Secreted by Macrophages Up-regulates Hepcidin Expression in Hepatocytes by Activating the Bone Morphogenetic Protein Signaling Pathway.	Commensal bacteria modulate iron absorption through cytokine signaling and hepcidin levels regulation	–	Gut	(Shanmugam et al., 2015)
	Preclinical study	Intestinal inflammation modulates expression of the iron-regulating hormone hepcidin depending on erythropoietic activity and the commensal microbiota.		–	Gut	(Shanmugam et al., 2014)
Sickle cell anemia	Preclinical study	Depletion of Intestinal Microbiome Partially Rescues Bone Loss in Sickle Cell Disease Male Mice	bacteria load leads to increased inflammatory cytokines, impaired osteoblast function, and bone loss in SCD mice	–	Gut	Tavakoli and Xiao, 2019
Aplastic anemia	Commentary	An altered gut microbiota may trigger autoimmune-mediated acquired bone marrow failure syndromes.	Microbiome may be associated with the development of aplasti anemia	–	Gut	(Espinoza et al., 2016)
	Clinical case	Excellent response of severe aplastic anemia to treatment of gut inflammation: A case report and review of the literature	Gut dysbiosis correction may contribute to aplastic anemia recovery	–	Gut	(Zhao et al., 2020)
	Clinical study	The oral microbiome of patients undergoing treatment for severe aplastic anemia: a pilot study.	Immunosuppressive therapy and stem cell transplant for aplastic anemia may induce dysbiosis	24	Oral	(Ames et al., 2019)

Table 5
Microbiome studies in immune thrombocytopenia and congenital neutropenia.

Disease	Type of study	Study title	Significance	N° of patients	Type of microbiome	Ref
Immune thrombocytopenia (ITP)	Clinical	Intestinal microbiota dysbiosis play a role in pathogenesis of patients with primary immune thrombocytopenia	alterations in biodiversity and composition of microbiota in ITP. Possible implications of diet therapy and fecal microbiota transplantation treatment	94	Oral	Liu et al 2020
	Clinical	Gut Microbiome and Metabolome Were Altered and Strongly Associated With Platelet Count in Adult Patients With Primary Immune Thrombocytopenia	Several ITP-altered gut bacteria and metabolites can be diagnostic biomarkers for ITP, and are highly correlated with platelet count, suggesting a pathogenic role	30	Gut	Zhang et al., 2020
	Clinical	Gut microbiome alterations and its link to corticosteroid resistance in immune thrombocytopenia	Dysbiosis distinguished ITP patients from healthy controls. Corticosteroid treatment affected gut microbiome. Corticosteroid-resistant patients displayed a distinct gut microbiome	99	Gut	Wang et al., 2020
Congenital Neutropenia	Clinical study	Oral microbial dysbiosis in patients with Kostmann syndrome.	lower bacterial diversity may contribute to frequent caries and periodonthitis	9	Oral	Topcuoglu et al., 2019
	Clinical study	Dysbiosis of the Oral Ecosystem in Severe Congenital Neutropenia (SCN) Patients.	SCN patients have significantly higher bacterial load with low bacterial diversity in saliva compared to healthy controls	10	Oral	Zaura et al., 2020

Bifidobacteriaceae/Enterobacteriaceae. They also highlighted the impact of iron deficiency on microbiome in infants and its possible long-term consequences, such as altered brain, heart, and skeletal muscles development and functioning, and delayed cognitive and social–emotional development. Finally, also an increase in colonic iron, as observed after dietary supplementation, may alter the microbiome (Dostal et al., 2012; Paganini and Zimmermann, 2017), with reduction of beneficial bacteria (e.g. *Bifidobacteria* and *Lactobacilli*) and an increase in *Enterobacteriaceae*, including *Escherichia enteropathogenic coli* (Balamurugan et al., 2010; Paganini and Zimmermann, 2017). Whether iron intake has an

impact on gut microbiome or the microbiome itself interacts with iron absorption mechanisms is still a matter of study: Shanmugam et al., showed that two gut commensal bacteria (*Bifidobacterium longum* and *Bacteroides fragilis*) may upregulate hepcidin expression, inducing IL1-beta and activating bone morphogenetic protein pathway (Shanmugam et al., 2015, 2014). Altogether these findings highlight that there is a mutual interaction among microbioma, iron metabolism, chronic inflammation, and immune activation against infections. In keeping with an interference of the microbiome with metabolic homeostasis, Tavakoli et al. recently reported that increased gut bacteria augmented antigenic load traversing the impaired intestinal barrier, lead to increased inflammatory cytokines, impaired osteoblast function, and bone loss in mice models of SCD; of note this was partially rescued by depletion of intestinal microbiome through antibiotic therapy [Tavakoli and Xiao, 2019].

The relationship between the microbiome and the immune system is even more intriguing for autoimmune cytopenias. In this setting, some bacterial infections/colonizations have been associated with disease development (Kurtzman and Young, 1989; Espinoza et al., 2016). Although it cannot be considered a microbiome alteration, Helicobacter pylori colonization has been found in a proportion of patients with autoimmune thrombocytopenia (Frydman et al., 2015; Kim et al., 2018) and chronic idiopathic neutropenia (Papadaki et al., 2005), with some cases being cured after bacteria eradication. Similar results have been reported for aplastic anemia (AA), a rare hematologic condition characterized by an autoimmune attack against bone marrow precursors mainly caused by self-reactive T-cells, which induces apoptosis of marrow stem cells through direct attack (FAS/FASL) and soluble mediators (IFN-gamma and TNF-alfa). In a proportion of cases, AA may be secondary to Parvovirus B19 (Tyrrell, 1984) or hepatitis viruses (Cudillo, 2009), possibly due to molecular mimicry, antigen dis-sequestration, or chronic immune system stimulation. Regarding molecular mimicry, a high correlation among the genetic sequence of T-cells receptors variable regions and the molecular structure of CMV, EBV and Influenza A virus, has been recently reported, suggesting their role in AA pathogenesis (Lundegren et al., 2018). Consistently with this hypothesis, the treatment of gut infection with antibiotics resulted in good hematologic response in a patient with AA (Zhao et al., 2020). On the other hand, immunosuppressive therapy (IST) as well as HSCT, the main therapeutic approaches indicated for AA patients, may alter the microbiome and concur to increase infectious risk, which represents one of the major causes of mortality and morbidity in AA. (Ames et al. (2019)) examined the oral microbiome of 24 severe AA patients who underwent IST plus the thrombopoietin analogue eltrombopag (N = 20) or HSCT (N = 4) and found that patients displayed unique bacterial identifiers as compared to healthy controls. Moreover, changes of relative abundance of *Prevotella histicola* in IST-treated cases, and of *Haemophilus parainfluenzae* and *Rothia mucilaginosa* in the HSCT group, were observed. Of note, the Authors claimed that their experimental approach using tongue brushings may have been less influenced by antibiotic therapy, compared with gut studies.

Altogether, data on AA show that microbiome composition differs in patients compared to healthy controls, might have a pathogenic role, and may be influenced by therapy, particularly HSCT.

Interesting results have emerged also from the study of microbiome in ITP: Liu et al. evaluated 94 newly diagnosed ITP patients and identified a skewed gut microbiota (increased Proteobacteria, Bacteroidetes and Bacteroidetes/Firmicutes ratio, decreased Firmicutes versus controls), with specific alterations in diversity (Anaerorhabdus, sutterella, Peptostreptococcaceae, Clostridium_XI and carnobacteriaceae) [Liu et al., 2020b]. Another study showed that the proportion and combination of certain fecal bacteria and their metabolites (increased Blautia, Streptococcus, and Lactobacillus, decreased Bacteroides) could provide diagnostic markers and are highly correlated with platelet count, suggesting a role in ITP pathogenesis [Zhang et al. 2020]. Furthermore, Wang and Colleagues demonstrated a different microbiome composition in treatment naïve, steroid responsive and steroid refractory ITP patients, indicating a possible utility in the prediction of response to immunosuppression [Wang et al. 2020].

Finally, in two studies in patients with severe congenital neutropenia, higher bacterial load with low diversity in saliva, compared to healthy controls (*Firmicutes* was higher while *Proteobacteria* lower), were reported, with an association with increased cytokine levels; this finding suggest a contribution to the increased rate of dental caries and periodontitis observed in these patients [Topcuoglu et al. 2019; Zaura et al. 2020].

5. Discussion

The role of the environmental factors in the development of hematologic diseases has been established by a number of evidences. However, the complexity of this environment inside and outside the host makes it difficult to show a clear-cut cause/effect flow in most cases. Imbalances of microbiome composition, defined dysbiosis, are linked to several pathologic conditions including neoplasms, infections (Honda and Littman, 2012), inflammatory diseases (Haag and Siegmund, 2015), and immuno-mediated disorders (Hevia et al., 2014; Kostic et al., 2015; Chen et al., 2016). The use of NGS techniques improves our ability to analyze the microorganisms inhabiting host's cavities and skin and paved the way to several studies exploring the possible correlations with disease pathogenesis, complications, and therapy outcome (Schuster, 2008) (Fig. 1).

Concerning pathogenesis, gut (Yamamoto et al., 2013) and conjunctival (Asao et al., 2019) microbiota have been implicated in lymphomagenesis through continuous inflammatory triggering and have also shown to elicit autoimmune-mediated acquired bone marrow failure typical of aplastic anemia (Espinoza et al., 2016). Among disease complications, infections are one of the primary causes of morbidity and mortality in hematologic patients, particularly in the transplant setting. Most efforts have been made to disclose the correlations between patients' microbiome and infectious risk, and showed a relationship with specific variation of gut or oral microbiome (Rashidi et al., 2019a; de Mendonça et al., 2012; Mendonça et al., 2015). Moreover, the use of chemotherapy may impact the composition of patients' microbiome by selecting specific bacteria and killing the others (Rashidi et al., 2019b). Similarly, strong immunosuppression, that is part of many hematologic treatments, may alter the immune system surveillance on commensal microbes again leading to selective pressures. In this regard, it is likely to exist an ecologic balance: the immune system controls bacterial overgrowth and commensal flora participates to immune system development and maturation. A better knowledge of this "*micro(b)environment*" would help to avoid excess of immunosuppression in patients with dysbiosis. Moreover, the development of specific probiotics may help the reconstitution of a healthier microbiota. In this view, the use of fecal microbiota transplant is under active investigation to restore microbial equilibrium after chemotherapy and antibiotics (Severyn et al., 2019). Furthermore, therapy induced dysbiosis may have some correlations with late onset complications in cancer survivors (Cozen et al., 2013). Since long term toxicities are difficult to predict and may impact life expectancy, particularly in young patients, microbiome studies and dysbiosis prevention will aid to improve clinical care.

Finally, the impact of the microbiome on therapy outcome is a fascinating issue. Far beyond chemotherapy, biologic treatments are enriching the treatment of both benign and malignant hematologic diseases in the modern era. Some of these drugs are oral (tyrosine kinase inhibitors) and most of them cause diarrhoea as common adverse events, likely impacting on gut microbiome. This may result in dysbiosis, and in an increased infectious risk, again worsening microbiota alteration.

Other drugs are designed to enhance immune system activity against the tumor (i.e. checkpoint inhibitors, chimeric antigen T cells (Abid et al., 2019), bispecific antibodies) and may conversely induce autoimmunity, cytokine production, and inflammatory reactions.

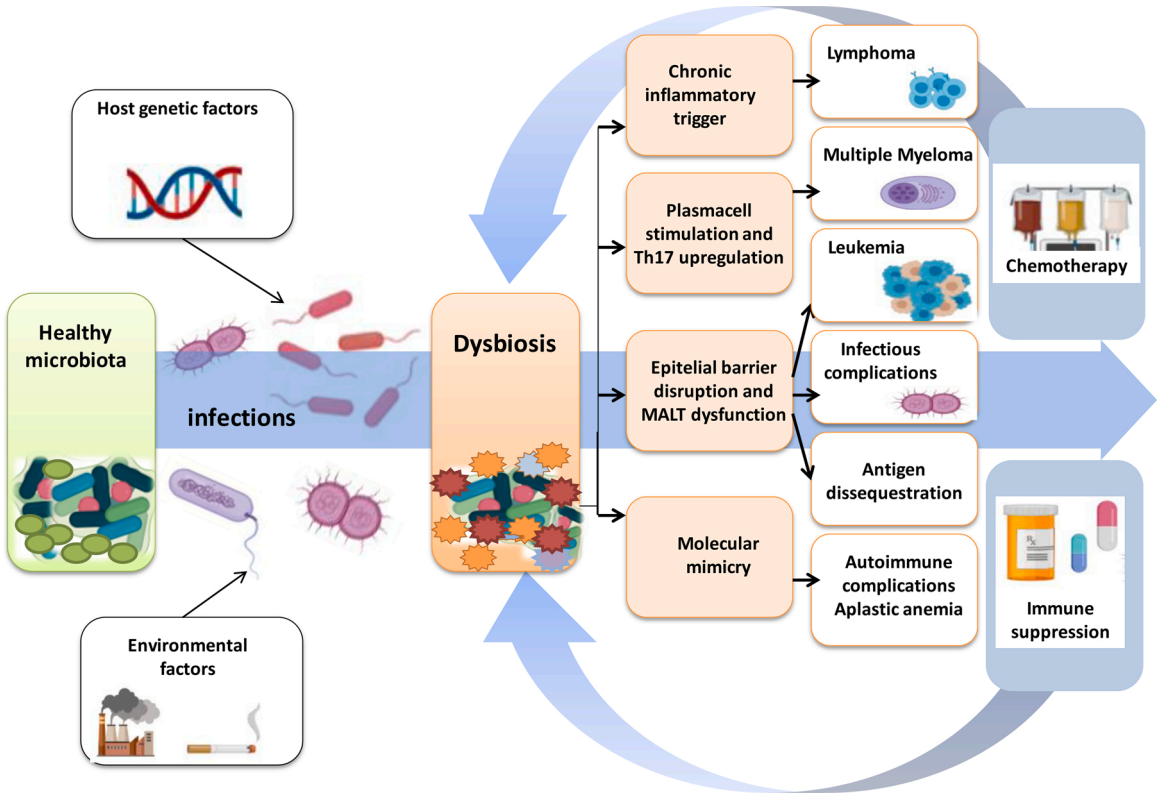

Fig. 1. Microbiome alteration and its impact on hematologic diseases.
Host's genetic predisposition and environmental factors may favour microbiome alteration, namely dysbiosis. The latter may be associated with the development of neoplastic and autoimmune disorders through various mechanisms including chronic inflammatory triggering, epithelial barriers alteration with antigen dissequestration, and molecular mimicry. The treatment of hematologic diseases (chemotherapy and immunosuppression) may further worsen dysbiosis and favour disease progression. Infections may be either a cause or a consequence of dysbiosis. MALT mucose associated lymphoproliferative tissue.

Microbiome may actively participate to these processes in two opposite ways, either enhancing tumor progression (Calcinotto et al., 2018), or ameliorating response to therapy (Pianko et al., 2019).

In conclusion, future studies on microbiome composition pre- and post-specific treatments, will add hints on the pathogenesis of benign and malignant hematologic diseases. These new insights will ideally help to predict the infectious risk, to assess and adapt the need of anti-infective prophylaxis, and to modulate the depth of immunosuppression and cytotoxicity preventing both short- and long-term complications.

Authorship contributions

Bruno Fattizzo, Francesca Cavallaro and Francesco Folino designed the review, wrote the paper and revised it for important intellectual content. Wilma Barcellini revised the paper for important intellectual content.

Declaration of Competing Interest

All Authors declare that they have no financial nor personal relationships with other people or organisations that could inappropriately influence (bias) their work.

References

Abid, M.B., Shah, N.N., Maatman, T.C., Hari, P.N., 2019. Gut microbiome and CAR-T therapy. Exp. Hematol. Oncol. 8, 31.
Actis, G.C., 2014. The gut microbiome. Inflamm. Allergy - Drug Targets. 13, 217–223.
Ames, N.J., Barb, J.J., Ranucci, A., Kim, H., Mudra, S.E., Cashion, A.K., et al., 2019. The oral microbiome of patients undergoing treatment for severe aplastic anemia: a pilot study. Ann. Hematol. 98, 1351–1365.
Andermann, T.M., Peled, J.U., Ho, C., Reddy, P., Riches, M., Storb, R., et al., 2018. The microbiome and hematopoietic cell transplantation: past, present, and future. Biol. Blood Marrow Transplant. 7, 1322–1340.
Asao, K., Hashida, N., Ando, S., Motooka, D., Kurakami, H., Nakamura, S., et al., 2019. Conjunctival dysbiosis in mucosa-associated lymphoid tissue lymphoma. Sci. Rep. 9, 8424.
Bai, L., Zhou, P., Li, D., Ju, X., 2017. Changes in the gastrointestinal microbiota of children with acute lymphoblastic leukaemia and its association with antibiotics in the short term. J. Med. Microbiol. 66, 1297–1307.
Balamurugan, R., Mary, R.R., Chittaranjan, S., Jancy, H., Shobana Devi, R., Ramakrishna, B.S., 2010. Low levels of faecal lactobacilli in women with iron-deficiency anaemia in South India. Br. J. Nutr. 104, 931–934.
Brady, G., MacArthur, G.J., Farrell, P.J., 2007. Epstein-Barr virus and Burkitt lymphoma. J. Clin. Pathol. 60, 1397–1402.
Buffie, C.G., Pamer, E.G., 2013. Microbiota-mediated colonization resistance against intestinal pathogens. Nat. Rev. Immunol. 13, 790–801.
Calcinotto, A., Brevi, A., Chesi, M., Ferrarese, R., Garcia Perez, L., Grioni, M., et al., 2018. Microbiota-driven interleukin-17-producing cells and eosinophils synergize to accelerate multiple myeloma progression. Nat. Commun. 9, 4832.
Chang, Y., Cesarman, E., Pessin, M.S., Lee, F., Culpepper, J., Knowles, D.M., et al., 1994. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 266, 1865–1869.
Charbonneau, M.R., Blanton, L.V., DiGiulio, D.B., Relman, D.A., Lebrilla, C.B., Mills, D. A., Gordon, J.I., 2016. A microbial perspective of human developmental biology. Nature. 535, 48–55.
Chen, J., et al., 2016. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Sci. Rep. 6, 28484.
Chua, L.L., Rajasuriar, R., Azanan, M.S., Abdullah, N.K., Tang, M.S., Lee, S.C., et al., 2017. Reduced microbial diversity in adult survivors of childhood acute lymphoblastic leukemia and microbial associations with increased immune activation. Microbiome. 5, 35.
Coburn, R.J., England, J.M., Samson, D.M., Walford, D.M., Blowers, R., Chanarin, I., A.J, et al., 1973. Tuberculosis and blood disorders. Br. J. Haematol. 25, 793–799.
Cozen, W., Yu, G., Gail, M.H., Ridaura, V.K., Nathwani, B.N., Hwang, A.E., et al., 2013. Fecal microbiota diversity in survivors of adolescent/young adult Hodgkin lymphoma: a study of twins. Br. J. Cancer 108, 1163–1167.
Cudillo, L., 2009. Aplastica anemia and viral hepatitis. Mediterr. J. Hematol. Infect. Dis. 1, 2009026.
de Mendonça, R.M., de Araújo, M., Levy, C.E., Morari, J., Silva, R.A., Yunes, J.A., et al., 2012. Prospective evaluation of HSV, Candida spp., and oral bacteria on the severity

of oral mucositis in pediatric acute lymphoblastic leukemia. Support. Care Cancer 20, 1101–1107.
Dostal, A., Chassard, C., Hilty, F.M., Zimmermann, M.B., Jaeggi, T., Rossi, S., et al., 2012. Iron depletion and repletion with ferrous sulfate or electrolytic iron modifies the composition and metabolic activity of the gut microbiota in rats. J. Nutr. 142, 271–277.
Dostal, A., Fehlbaum, S., Chassard, C., Zimmermann, W.B., Lacroix, C., 2013. Low iron availability in continuous in vitro colonic fermentations induces strong dysbiosis of the child gut microbial consortium and a decrease in main metabolites. FEMS Microbiol. Ecol. 83, 161–175.
Dostal, A., Lacroix, C., Bircher, L., Pham, V.T., Follador, R., Zimmermann, M.B., Chassard, C., 2015. Iron modulates butyrate production by a child gut microbiota in vitro. MBio 6, e01453–01415.
Espinoza, J.L., Elbadry, M.I., Nakao, S., 2016. An altered gut microbiota may trigger autoimmune-mediated acquired bone marrow failure syndromes. Clin. Immunol. 171, 62–64.
Espinoza, J.L., Matsumoto, A., Tanaka, H., Matsumura, I., 2018. Gastric microbiota: an emerging player in Helicobacter pylori-induced gastric malignancies. Cancer Lett. 414, 147–152.
Ford, C.D., Coombs, J., Stofer, M.G., Lopansri, B.K., Webb, B.J., Ostronoff, F., et al., 2019. Decrease in vancomycin-resistant Enterococcus colonization associated with a reduction in carbapenem use as empiric therapy for febrile neutropenia in patients with acute leukemia. Infect. Control Hosp. Epidemiol. 40, 774–779.
Frydman, G.H., Davis, N., Beck, P.L., Fox, J.G., 2015. Helicobacter pylori eradication in patients with immune thrombocytopenic Purpura: a review and the role of biogeography. Helicobacter 20, 239–251.
Galloway-Peña, J.R., Smith, D.P., Sahasrabhojane, P., Ajami, N.J., Wadsworth, W.D., Daver, N.G., et al., 2016. The role of the gastrointestinal microbiome in infectious complications during induction chemotherapy for acute myeloid leukemia. Cancer 122, 2186–2196.
Galloway-Peña, J.R., Shi, Y., Peterson, C.B., Sahasrabhojane, P., Gopalakrishnan, V., Brumlow, C.E., et al., 2019. Microbiome signatures are predictive of infectious risk following induction therapy for acute myeloid leukemia. Clin. Infect. Dis. [Epub ahead of print].
Gill, S.R., Pop, M., Deboy, R.T., Eckburg, P.B., Turnbaugh, P.J., B.S, et al., 2006. Metagenomic analysis of the human distal gut microbiome. Science 312, 1355–1359.
Grogg, K.L., Miller, R.F., Dogan, A., 2007. HIV infection and lymphoma. J. Clin. Pathol. 60, 1365–1372.
Haag, L.M., Siegmund, B., 2015. Intestinal microbiota and the innate immune system - a crosstalk in Crohn's disease pathogenesis. Front. Immunol. 6, 489.
Hakim, H., Dallas, R., Wolf, J., Tang, L., Schultz-Cherry, S., Darling, V., et al., 2018. Gut microbiome composition predicts infection risk during chemotherapy in children with acute lymphoblastic leukemia. Clin. Infect. Dis. 67, 541–548.
Henle, W., Henle, G., 1970. Evidence for a relation of Epstein-Barr virus to Burkitt's lymphoma and nasopharyngeal carcinoma. Bibl. Haematol. 36, 706–713.
Hevia, A., et al., 2014. Intestinal dysbiosis associated with systemic lupus erythematosus. MBio 5, 01548, 14.
Honda, K., Littman, D.R., 2012. The microbiome in infectious disease and inflammation. Annu. Rev. Immunol. 30, 759–795.
Kim, B.J., Kim, H.S., Jang, H.J., Kim, J.H., 2018. Helicobacter pylori eradication in idiopathic thrombocytopenic Purpura: a meta-analysis of randomized trials. Gastroenterol. Res. Pract., 6090878
Knight, R., Vrbanac, A., Taylor, B.C., Aksenov, A., Callewaert, C., Debelius, J., et al., 2018. Best practices for analysing microbiomes. Nat. Rev. Microbiol. 16, 410–422.
Kortman, G.A., Raffatellu, M., Swinkels, D.W., Tjalsma, H., 2014. Nutritional iron turned inside out: intestinal stress from a gut microbial perspective. FEMS Microbiol. Rev. 38, 1202–1234.
Kostic, A.D., et al., 2015. The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. Cell Host Microbe 17, 260–273.
Kurtzman, G., Young, N., 1989. Viruses and bone marrow failure. Baillieres Clin. Haematol. 2, 51–67.
Li, M., Gan, Y., Fan, C., Huan, H., Zhang, X., Shen, Y., et al., 2018. Hepatitis B virus and risk of non-Hodgkin lymphoma: an updated meta-analysis of 58 studies. J. Viral Hepat. 25, 894–903.
Liu, X., Zou, Y., Ruan, M., Chang, L., Chen, X., Wang, S., Yang, W., Zhang, L., Guo, Y., Chen, Y., Zhang, Y., He, H., Gan, Y., Wang, K., Zhu, X., 2020a. Pediatric Acute Lymphoblastic Leukemia Patients Exhibit Distinctive Alterations in the Gut Microbiota. Front Cell Infect Microbiol. 10 (October16), 558799.
Liu, C., Cheng, L., Ji, L., Li, F., Zhan, Y., Wu, B., Ke, Y., Chen, P., Hua, F., Yuan, L., Min, Z., Sun, L., Chen, H., Cheng, Y., 2020b. Intestinal microbiota dysbiosis play a role in pathogenesis of patients with primary immune thrombocytopenia. Thromb Res. 190 (June), 11–19.
Longo, D.L., Gelmann, E.P., Cossman, J., Young, R.A., Gallo, R.C., O'Brien, S.J., Matis, L. A., 1984. Isolation of HTLV-transformed B-lymphocyte clone from a patient with HTLV-associated adult T-cell leukaemia. Nature 310, 505–506.
Lozupone, C.A., Stombaugh, J.I., Gordon, J.I., Jansson, J.K., Knight, R., 2012. Diversity, stability and resilience of the human gut microbiota. Nature 489, 220–230.
Lundegren, S., Huuhtanen, J., Keranen, M.A., Hirsch, C.M., Jokinen, E., Heinonen, M., 2018. Next-generation sequencing reveals a t cell receptor signature characteristic of patients with aplastic Anemia. e al. Blood 132 (Supplement 1), 537.
Mendonça, R.M., Araújo, Md, Levy, C.E., Morari, J., Silva, R.A., Yunes, J.A., et al., 2015. Oral mucositis in pediatric acute lymphoblastic leukemia patients: evaluation of microbiological and hematological factors. Pediatr. Hematol. Oncol. 32, 322–330.
Mentis, A.A., Boziki, M., Grigoriadis, N., Papavassiliou, A.G., 2019. Helicobacter pylori infection and gastric cancer biology: tempering a double-edged sword. Cell. Mol. Life Sci. 76, 2477–2486.
Meropol, S.B., Edwards, A., 2015. Development of the infant intestinal microbiome: a bird's eye view of a complex process. Birth Defects Research Part C - Embryo Today: Reviews. 105, 228–239.
Muleviciene, A., D'Amico, F., Turroni, S., Candela, M., Jankauskiene, A., 2018. Iron deficiency anemia-related gut microbiota dysbiosis in infants and young children: a pilot study. Acta Microbiol. Immunol. Hung. 65, 551–564.
Mylona, E.E., Baraboutis, I.G., Lekakis, L.J., Gergiou, O., Papastamopoulos, V., Skoutelis, A., 2008. Multicentric castleman's disease in HIV infection: a systematic review of the literature. AIDS Rev. 10, 25–35.
Nearing, J.T., Connors, J., Whitehouse, S., Van Limbergen, J., Macdonald, T., Kulkarni, K., et al., 2019. Infectious complications are associated with alterations in the gut microbiome in pediatric patients with acute lymphoblastic leukemia. Front. Cell. Infect. Microbiol. 9, 28.
O'Hara, A.M., Shanahan, F., 2006. The gut flora as a forgotten organ. EMBO Rep. 7, 688–693.
Paganini, D., Zimmermann, M.B., 2017. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review. Am. J. Clin. Nutr. 106 (Suppl 6), 1688S–1693S.
Pannone, G., Zamparese, R., Pace, M., Pedicillo, M.C., Cagiano, S., Somma, P., et al., 2014. The role of EBV in the pathogenesis of Burkitt's Lymphoma: an Italian hospital based survey. Infect Agent Cancer. 9, 34.
Papadaki, H.A., Pontikoglou, C., Stavroulaki, E., Minadakis, G., Eliopoulos, D.A., Pyrovolaki, K., et al., 2005. High prevalence of Helicobacter pylori infection and monoclonal gammopathy of undetermined significance in patients with chronic idiopathic neutropenia. Ann. Hematol. 84, 317–320.
Patel, A., Harris, K.A., Fitzgerald, F., 2017. What is broad-range 16S rDNA PCR? Arch. Dis. Child. Educ. Pract. Ed. 102, 261–264.
Pereira, M.I., Medeiros, J.A., 2014. Role of Helicobacter pylori in gastric mucosa-associated lymphoid tissue lymphomas. World J. Gastroenterol. 20, 684–698.
Peterson, J., Garges, S., Giovanni, M., McInnes, P., Wang, L., Schloss, J.A., et al., 2009. The NIH human microbiome project. Genome Res. 19, 2317–2323.
Pianko, M.J., Devlin, S.M., Littmann, E.R., Chansakul, A., Mastey, D., Salcedo, M., et al., 2019. Minimal residual disease negativity in multiple myeloma is associated with intestinal microbiota composition. Blood Adv. 3, 2040–2044.
Ponzoni, M., Ferreri, A.J., 2017. Bacteria associated with marginal zone lymphomas. Best Pract. Res. Clin. Haematol. 30, 32–40.
Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., et al., 2010. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65.
Rajagopala, S.V., Yooseph, S., Harkins, D.M., Moncera, K.J., Zabokrtsky, K.B., Torralba, M.G., et al., 2016. Gastrointestinal microbial populations can distinguish pediatric and adolescent Acute Lymphoblastic Leukemia (ALL) at the time of disease diagnosis. BMC Genomics 17, 635.
Rashidi, A., Kaiser, T., Shields-Cutler, R., Graiziger, C., Holtan, S.G., Rehman, T.U., et al., 2019a. Dysbiosis patterns during re-induction/salvage versus induction chemotherapy for acute leukemia. Sci. Rep. 9, 6083.
Rashidi, A., Kaiser, T., Graiziger, C., Holtan, S.G., Rehman, T.U., Weisdorf, D.J., et al., 2019b. Gut dysbiosis during antileukemia chemotherapy versus allogeneic hematopoietic cell transplantation. Cancer [Epub ahead of print].
Rattanathammethee, T., Tuitemwong, P., Thiennimitr, P., Sarichai, P., Na Pombejra, S., Piriyakhuntorn, P., Hantrakool, S., Chai-Adisaksopha, C., Rattarittamrong, E., Tantiworawit, A., Norasetthada, L., 2020. Gut microbiota profiles of treatment-naïve adult acute myeloid leukemia patients with neutropenic fever during intensive chemotherapy. PLoS One. 15 (October 28 (10)), e0236460.
Re, A., Cattaneo, C., Rossi, G., 2019. Hiv and lymphoma: from epidemiology to clinical management. Mediterr. J. Hematol. Infect. Dis. 11, 2019004.
Reyna-Figueroa, J., Barrón-Calvillo, E., García-Parra, C., Galindo-Delgado, P., Contreras-Ochoa, C., Lagunas-Martínez, A., et al., 2019. Probiotic supplementation decreases chemotherapy-induced gastrointestinal side effects in patients with acute leukemia. J. Pediatr. Hematol. Oncol. 41, 468–472.
Samuelson, D.R., Welsh, D.A., Shellito, J.E., 2015. Regulation of lung immunity and host defense by the intestinal microbiota. Front. Microbiol. 6, 1085.
Schuster, S.C., 2008. Next-generation sequencing transforms today's biology. Nat. Methods 5, 16–18.
Severyn, C.J., Brewster, R., Andermann, T.M., 2019. Microbiota modification in hematology: still at the bench or ready for the bedside? Blood Adv. 3, 3461–3472.
Shanmugam, N.K., Trebicka, E., Fu, L.L., Shi, H.N., Cherayil, B.J., 2014. Intestinal inflammation modulates expression of the iron-regulating hormone hepcidin depending on erythropoietic activity and the commensal microbiota. J. Immunol. 193, 1398–1407.
Shanmugam, N.K., Chen, K., Cherayil, B.J., 2015. Commensal bacteria-induced interleukin 1β (IL-1β) secreted by macrophages up-regulates hepcidin expression in hepatocytes by activating the bone morphogenetic protein signaling pathway. J. Biol. Chem. 290, 30637–30647.
Song, Y., Gyarmati, P., 2019. Bacterial translocation in acute lymphocytic leukemia. PLoS One 14, 0214526.
Staffas, A., Burgos da Silva, M., van den Brink, M.R., 2017. The intestinal microbiota in allogeneic hematopoietic cell transplant and graft-versus-host disease. Blood 129, 927–933.
Stéphan, J.L., Galambrun, C., Pozzetto, B., Grattard, F., Bordigoni, P., 1999. Aplastic anemia after Mycoplasma pneumoniae infection: a report of two cases. J. Pediatr. Hematol. Oncol. 21, 299–302.

Stolte, M., Bayerdörffer, E., Morgner, A., Alpen, B., Wündisch, T., Thiede, C., et al., 2002. Helicobacter and gastric MALT lymphoma. Gut 50 (Suppl 3).
Tasleem, S., Sood, G.K., 2015. Hepatitis C associated B-cell non-hodgkin lymphoma: clinical features and the role of antiviral therapy. J. Clin. Transl. Hepatol. 3, 134–139.
Tavakoli, S., Xiao, L., 2019. Depletion of Intestinal Microbiome Partially Rescues Bone Loss in Sickle Cell Disease Male Mice. Sci Rep. 9 (June 17 (1)), 8659.
Topcuoglu, N., Erdem, A.P., Karacan, I., Kulekci, G., 2019. Oral microbial dysbiosis in patients with Kostmann syndrome. J Med Microbiol. 68 (April(4)), 609–615.
Turnbaugh, P.J., Ley, R.E., Hamady, M., Fraser-Ligget, C.M., Knight, R., Gordon, J.I., 2007. The human microbiome project. Nature. 449, 804–810.
Tyrrell, D.A., 1984. Human parvovirus, fifth disease, and marrow aplasia. Arch. Dis. Child. 59, 197–198.
Wang, Y., Xue, J., Zhou, X., You, M., Du, Q., Yang, X., et al., 2014. Oral microbiota distinguishes acute lymphoblastic leukemia pediatric hosts from healthy populations. PLoS One 9, 102116.
Wang, Y., Liu, F., Zhang, G., Su, Y., Sun, X., Chen, Q., Wang, C., Fu, H., He, Y., Zhu, X., Liu, X., Lv, M., Zhao, X., Zhao, X., Li, Y., Wang, Q., Huang, X., Zhang, X., 2020. Gut microbiome alterations and its link to corticosteroid resistance in immune thrombocytopenia. Sci China Life Sci. (August 25) https://doi.org/10.1007/s11427−020-1788−2. Online ahead of print.
Wen, Y., Jin, R., Chen, H., 2019. Interactions between gut microbiota and acute childhood leukemia. Front. Microbiol. 10, 1300.
Yamamoto, M.L., Schiestl, R.H., 2014a. Intestinal microbiome and lymphoma development. Cancer J. 20, 190–194.
Yamamoto, M.L., Schiestl, R.H., 2014b. Lymphoma caused by intestinal microbiota. Int. J. Environ. Res. Public Health 11, 9038–9049.
Yamamoto, M.L., Maier, I., Dang, A.T., Berry, D., Liu, J., Ruegger, R.M., et al., 2013. Intestinal bacteria modify lymphoma incidence and latency by affecting systemic inflammatory state, oxidative stress, and leukocyte genotoxicity. Cancer Res. 14, 4222–4232.
Zaura, E., Brandt, B.W., Buijs, M.J., Emingil, G., Ergüz, M., Karapinar, D.Y., Pekpinarli, B., Bao, K., Belibasakis, G.N., Bostanci, N., 2020. Dysbiosis of the Oral Ecosystem in Severe Congenital Neutropenia Patients. Proteomics Clin Appl. 14 (May (3)), e1900058.
Zhang, B., Gu, J., Liu, J., Huang, B., Li, J., 2019. Fecal microbiota taxonomic shifts in chinese multiple myeloma patients analyzed by quantitative polimerase chain reaction (QPCR) and 16S rRNA high-throughput sequencing. Med. Sci. Monit. 25, 8269–8280.
Zhang, X., Gu, S., You, L., Xu, Y., Zhou, D., Chen, Y., Yan, R., Jiang, H., Li, Y., Lv, L., Qian, W., 2020. Gut Microbiome and Metabolome Were Altered and Strongly Associated With Platelet Count in Adult Patients With Primary Immune Thrombocytopenia. Front Microbiol. 11 (July 8), 1550.
Zhao, X.C., Zhao, L., Sun, X.Y., Xu, Z.S., Ju, B., Meng, F.J., Zao, H.G., 2020. Excellent response of severe aplastic anemia to treatment of gut inflammation: a case report and review of the literature. World J. Clin. Cases 8, 425–435.
Zuckerman, E., Zuckerman, T., Levine, A.M., Douer, D., Gutekunst, K., Mizokami, M., et al., 1997. Hepatitis C virus infection in patients with B-cell non-hodgkin lymphoma. Ann. Intern. Med. 127, 423–428.

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