The Gut Microbiota and Immune System Relationship in Human Graft-versus-Host Disease

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Abstract. Gut microbiota has gained increasing interest in the pathogenesis of immune-related diseases. In this context, graft-versus-host disease is a condition characterized by an immune response which frequently complicates and limits the outcomes of hematopoietic stem cell transplantations. Past studies, carried mostly in animals, already supported a relationship between gut microbiota and graft-versus-host disease. However, the possible mechanisms underlying this connection remain elusive. Moreover, strategies to prevent graft-versus-host disease are of great interest as well as the potential role of gut microbiota modulation. We reviewed the role of gut microbiota in the development of immune system and its involvement in the graft-versus-host disease, focusing on data available on humans.

Introduction. Microbiota is the complex system of bacteria, archaea, viruses and fungi living in several body niches, such as skin, vagina, nose and mouth. However, the majority of microorganisms live in the digestive tract. Gut microbiota should be considered a real organ, accounting 100 times more genes than the host and being responsible for multiple functions and in particular of the metabolic and immune homeostasis.¹

Recent studies demonstrated that gut microbiota is only the first layer of a multilayer barrier separating our organism from the content of intestinal lumen and, thus, from the external environment: the so-called “gut barrier”. This barrier is composed, beyond microbiota, by the mucus layer on the epithelial cells, the epithelial cells themselves, the immune cells harboring in the submucosa and by the bidirectional interactions between all these layers (Figure 1). Its integrity is essential to maintain the homeostasis, and its disruption has been associated with many gastrointestinal and extragastrointestinal diseases. Whereas the role of gut barrier disruption appears clear in gastrointestinal disorders, its role in extragastrointestinal diseases could be harder to understand. The basis of this role should be searched in the complex function of immune stimulation/tolerance that gut microbiota exerts.

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many diseases, mostly hematological, otherwise associated with a poor prognosis. Unfortunately, the widespread use of this treatment is often restricted by the development of graft-versus-host disease (GVHD) a condition in which immunocompetent donor T cells attack host tissues in immunocompromised patients, constituting one of the leading causes of non-relapse mortality.² GVHD depends on several factors, such as age, conditioning regimen, hematopoietic graft source and prophylaxis. The traditional classification of GVHD is based on the timing of onset: acute (aGVHD), within the first 100 days after HSCT, and chronic (cGVHD), after the first
Figure 1. The gut barrier and its alterations during the pathogenesis of GVHD. The healthy gut barrier is essential to maintain the immune homeostasis. Total body irradiation and/or chemotherapy, used as conditioning regimen, lead to gut barrier disruption, damaging the mucus layer and the epithelium. Thus, bacteria and bacterial products such as lipopolysaccharide translocate in the lamina propria where, together with endogenous danger molecules released from damaged epithelial cells, activate host and/or donor antigen-presenting cells (APCs) which prime alloreactive donor-derived T cells, triggering the damage to target organs. Modified from Heidegger.

100 days. However, beyond the temporal criterion, aGVHD and cGVHD are different diseases, with characteristic clinical presentation, diagnostic criteria, and tissue pathology. Systemic inflammation and tissue disruption predominate in aGVHD, whereas the immune dysregulation leading to several infections is the prevalent presentation in cGVHD. Thus, the characteristic clinical manifestations became the diagnostic features instead of the time of the onset, based on National Institutes of Health (NIH) consensus criteria.

In particular, in this review we discuss the role of gut microbiota in the GVHD, focusing on data on humans.

The Healthy Gut Microbiota. In the last years, the increasing interest on human gut microbiota led to large-scale attempts to characterize it. The association of traditional cultural techniques with new molecular techniques based on the analysis of the small subunit ribosomal RNA (SSU rRNA) gene sequences as phylogenetic markers made bacteria the most known components of gut microbiota, identifying more than 1000 species. Bacteria together with Archaea and Eukarya constitute the three kingdoms in which life is classified. Bacteria are subclassified in many phyla (plural of phylum, major taxonomic division that contains one or more classes, Box 1), but only a few phyla are mostly represented, accounting for more than 160 species, and, among them, Firmicutes (consisting mainly of Gram-positive clostridia) and Bacteroidetes (consisting mainly of Gram-negative bacteria) are prevalent. These two phyla, together with the less represented Actinobacteria and Proteobacteria are not only the most abundant, but also include the most diverse microorganisms in the adult gastrointestinal tract. Other represented phyla are Verrucomicrobia, Lentisphaerae, Synergistetes, Planctomycetes, Tenericutes and the Deinococcus-Thermus group, Melainabacteria, and Gemmatimonacete. Regarding the other two kingdoms, the Euryarchaeota, including the highly represented methanogens, are the most represented Archaea, whereas, among the Eukarya, some Candida spp are the most prevalent.
The earliest years of life are essential for the development of individual microbiota that depends on several factors, such as maternal and family members microbiota, kind of delivery, breastfeeding and early exposure to antibiotics. After this phase, individual microbiota composition is stable in the adult life for decades, and it may be the same also for the entire lifetime unless perturbing factors occur, such as antibiotic therapies or infections.6

The Role of Gut Microbiota in the Immune Regulation. The correct development of gut microbiota is strictly related to the healthy maturation of the immune system, and both develop in the first 2 years of life. In fact gut microbiota constitutes a stimulus that drives the development of the immune system in its capacity to react to pathogens and in the induction and maintenance of the tolerance process. On the other side, immune dysregulation can induce an alteration in gut microbiota.7,8 The importance of this bidirectional relationship has been highlighted by data from germ-free (GF) animals that showed reduced development of both innate and adaptive immunity with increased susceptibility to microbial infections.9,10

The integrity of the gut barrier is the basis of the healthy stimulation of the immune system by microbiota.

In fact, the continuous stimulation by luminal commensal antigens should be regulated to avoid the over-stimulation of the immune system. This is warranted by the presence of a physical barrier between gut microbiota and host immune cells, composed of epithelial cells and the mucus layer above them. In particular, the mucus layer consists of an inner and an outer layer, but whereas the outer one is colonized by large numbers of bacteria, the inner one, thicker than the outer one, constitutes a barrier for them.11,12 Furthermore, even innate lymphoid cells13,14 and IgAs15 contribute to reduce the penetration of microorganisms through the epithelial cells and their presentation to the immune system. Microbiota is essential for the correct development of both innate and adaptive immune response.

Conversely, microbiota needs a healthy immune system to correct its development. In fact, for example, the deficit in IgA response alters the composition of microbiota.16-18

Microbiota and the Innate Immune Response. Gut microbiota could regulate lamina propria phagocytes and, in particular, it could increase the production of pro-IL1β in resident macrophages19 and neutrophils,20 that could be rapidly activated in IL1β in response to pathogens. Microbiota could also influence systemic neutrophil response enhancing their bactericidal activity triggering the NOD1 signaling through peptidoglycan stimulation.

Microbiota and the Adaptive Immune Response. Data from germ-free (GF) animals demonstrated that when the microbiota is absent, there is a shift through a T-helper (Th)2 response, due to a reduced number of Th1 and Th17 cells, which could be reversible in case of colonization of the gut by flora. In particular, in the small intestine Th17 cells could be stimulated mainly by segmented filamentous bacteria (SFB), species belonging to commensal Clostridia-related bacteria,21-24 and Lactobacillus johnsonii.25

Beyond T cells, also B cells and immunoglobulins production are influenced by microbiota. In fact, the intestinal mucosa is essential to the correct development of B cells as well as fetal liver and bone marrow, and microbiota is able to regulate intestine-specific B-cell receptor.26,27 In fact, the presence of commensal microorganisms in the gut stimulates gut-associated lymphoid tissues (GALTs), such as both Peyer’s patches and isolated lymphoid follicles.28,30

The continuous stimulation induces germinal center formation in isolated lymphoid follicles and Peyer’s patches and IgA production, differently from systemic lymphoid organs where germinal center formation does not occur under physiological condition, but only after a specific- i.e. infectious- stimulation.31 In fact, microbial products are required to stimulate the germinal centers in lymphoid follicles and IgA production, in particular through Nucleotide-binding oligomerization domain-containing protein (NOD)1-mediated signaling.18,32,33

Tolerance Education by Microbiota. Colonic FoxP3+ T regulatory (Treg) cells are strongly influenced by the presence of gut microbiota. In fact, they are reduced in colonic lamina propria in the absence of gut microbiota stimulation, whereas the presence of gut microbiota is less relevant for Treg of the small intestine or mesenteric lymph nodes.23,35 In particular, murine data demonstrated that Clostridia and Bacteroides fragilis could be the most powerful inducers of Treg,34,39 probably working through different mechanisms which could be dependent and independent from toll-like
receptors (TLRs) signaling. Among TLRs-independent pathways, short-chain fatty acids (SCFAs) - bacterial metabolites deriving from carbohydrates fermentation, including acetate, propionate, isobutyrate and butyrate - seem to be able to increase the acetylation of the Foxp3 locus, increasing the number of Treg directly or, indirectly, increasing the production of TGFβ in the intestinal epithelium.6,40-42 Furthermore, SCFAs induced the expression of the receptor GPR15, responsible for recruitment of Treg in the large intestine.40-50 Similarly, the folic acid produced by colonic microorganisms could increase the survival of Treg cells.51 Furthermore, gut microbiota could stimulate the production of the anti-inflammatory cytokine IL10 by intestinal macrophages.52

The Allogenic Transplant and the Graft-versus-Host Disease. Every year, more than 3900053 HSCT are performed only in Europe for an ever expanding number of neoplastic and non-neoplastic diseases, in particular for hematological conditions such as leukemias and lymphomas.54 Nevertheless, HSCT is still limited by the development of GVHD, a condition that results from the interaction between the host cells which are targeted by the transplanted donor immune cells, primarily T cells.55

GVHD was historically classified in acute and chronic, respectively, if the onset of symptoms was before or after 100 days. However recent advantages questioned these definitions, and current consensus states that clinical features define GVHD as acute or chronic.5 aGVHD56 occurs mainly in the skin, GI, and liver. GI manifestations of aGVHD include secretory diarrhea, vomiting, abdominal pain and, in severe cases, bleeding. The severity of aGVHD is classified in four grades on the basis of the involvement of the organs mentioned above.57 On the other hand, cGVHD manifestations are typically variable, and many organs can be involved, frequently with autoimmune-like diseases characteristics.58

GVHD Pathogenesis and the Role of Gut Microbiota. The mechanisms leading to GVHD are usually divided into steps: organ damage, priming of the immune response, activation of T cells and destruction of target organs by means of the activated immune cells.2,57,59 (Figure 1). The incidence of GVHD is positively correlated with the degree of human leucocyte antigen (HLA) mismatch as the histocompatibility antigens are the main proteins recognized by donor immune cells.60 The connection between GVHD and microbiota was firstly suggested in pioneering studies in mice.61,62 However, studies in humans are still scant and characterized by small sample sizes. These studies mainly investigated variations in the gastrointestinal microbiota before and after HSCT and the impact of its composition on the transplant outcomes (Table 1).

Taur et al. demonstrated that there is a marked reduction after HSCT in the microbiota diversity which leads to the selection of a limited number or, even, of a single “dominating” bacterial genus. Interestingly, patients who developed intestinal domination showed an increased risk of bacteremia which was frequently caused by the same identified “dominating” bacteria.63 The authors also described the effects of different antibiotics on the development of specific bacterial prevalences: for example, fluoroquinolones reduced the risk of gram-negative bacteremia by decreasing proteobacterial domination.63

Other studies investigated variations of the microbiota in relation to the development of GVHD, the second most common cause of mortality in the context of allogeneic HSCT.64 In particular, the onset of GVHD seems to be associated with a progressive reduction of the microbiota diversity with a relative increase in Lactobacillales and a relative decrease in Clostridiales.65 Noteworthy, these findings are consistent with those in mice, suggesting that animal studies may, at least, guide the research in humans.

Given these data and considering the already mentioned dramatic impact of GVHD on survival, it is not surprising that microbiota diversity was also found to be an independent risk factor for mortality in patients undergoing HSCT.66

Consequent studies focused on the analysis of bacterial composition, researching if specific genera or species could be more implicated than others in the development of GVHD. For example, analysis of bacterial genera found that the abundance of a specific genus, namely Blautia (which belong to the Clostridia class), is associated with GVHD-related mortality.67 Although it was not possible to demonstrate causality in this study, these data may represent a starting point for the development of a GVHD mortality biomarker in the near future.

Similarly, other authors reported that there is an increase after HSCT in the relative abundance of enterococci that was persistent and more pronounced in adults patients with active GVHD.68 Similar results have been obtained in children by Biagi et al., who analyzed fecal samples collected from 10 children before HSCT and three times in the following 100 days. After HSCT, a profound alteration of the gut ecosystem occurred in all children, with the loss of about 30% in average of alpha diversity - a measure of diversity within a population in terms of number and distribution- compared to pre-HSCT samples. However, the last samples collected showed a minor degree of difference compared to pre-HSCT specimens, suggesting a natural trend to recover after the disturbance caused by the HSCT. The fecal amount of short-chain fatty acids (SCFA) followed the
Table 1: Summary of human studies assessing gastrointestinal microbiota in Graft versus Host Disease.

| Author and Year | Transplant | Most common indication | Specimens type | Specimens analysis | Population | Aim | Groups | Patients | Results |
|-----------------|------------|------------------------|----------------|-------------------|------------|-----|--------|----------|---------|
| Jeng, 2012      | allo HSCT  | Leukemia               | fecal          | 16s rRNA gene sequencing | Adults     | microbiota variation | GVHD (8 pts) vs No GVHD (10 pts) | 18       | GVHD is associated with reduced flora diversity (increases in Lactobacillales and decreases in Clostridiales). [65] |
| Vossen, 2014    | allo HSCT  | Leukemia               | -              | -                 | Children   | occurrence of GVHD   | GID (57 pts) vs No GID (55 pts) | 112      | Successful total GID resulted in significantly less acute GVHD ($p = 0.013$; log-rank test). [78] |
| Holler, 2014    | allo HSCT  | Leukemia               | fecal          | 16s rRNA gene sequencing | Adults     | microbiota variation | pre and post transplant comparison | 31       | Increase in Enterococci and decrease in other Firmicutes and phyla after allo HSCT. Shift most pronounced in active GVHD. [68] |
| Jeng, 2015      | allo HSCT  | Leukemia               | fecal          | 16s rRNA gene sequencing | Adults     | microbiota variation and outcome | pre and post transplant comparison | 115      | Intestinal flora diversity and Blautia abundance is associated with reduced GVHD lethality. [67] |
| Taur, 2014      | allo HSCT  | Leukemia               | fecal          | 16s rRNA gene sequencing | Adults     | microbiota variation and outcome | pre and post transplant comparison | 80       | Intestinal microbiota diversity is an independent predictor of mortality. [66] |
| Taur, 2012      | allo HSCT  | Leukemia               | fecal          | 16s rRNA gene sequencing | Adults     | microbiota variation and outcome | pre and post transplant comparison | 94       | Bacterial “domination” is associated with increased risk of bacteremia. [63] |
| Chiusolo, 2015  | allo/auto HSCT | Leukemia         | fecal          | 16s rRNA gene sequencing | Adults     | Microbiota variation and outcome | pre and post transplant comparison | 8        | Increase of Proteobacteria and reduction of Bacteroidetes after auto HSCT. Increase of Bacteroidetes and reduction of Firmicutes after allo HSCT. GVHD associated with more Firmicutes and Proteobacteria and less Bacteroidetes. [69] |

Abbreviations: allo HSCT, allogenic hematopoietic stem cell transplantation; auto HSCT, autologous hematopoietic stem cell transplantation; GVHD, graft versus host disease; GID, gastrointestinal decontamination.

variations of microbiota: it decreased by 76% after HSCT, being propionate the most reduced (mean loss 86%), and trend to recover distancing the HSCT. Although these differences are common in patients with and without aGVHD, the 5 children who developed aGVHD also showed an overgrowth of Enterococcus and Clostridiales and a corresponding decrease of Faecalibacterium and Ruminococcus. At phylum level, patients with aGVHD showed a drop in Firmicutes abundance after HSCT but, distancing the HSCT, they showed higher abundance than the initial one, whereas they demonstrated a lower abundance of Bacteroidetes compared to non-aGVHD patients. Even if alterations of gut microbiota induced by conditioning regimen and HSCT seem to be crucial to the pathogenesis of GVHD, the pre-HSCT characteristics of gut microbiota could also play a major role. In fact, children who developed aGVHD showed lower diversity and richness before HSCT compared to the other patients and, in particular, they demonstrated a lower abundance of Bacteroides and Parabacteroides, whose abundance positively correlated with the concentration of propionate and SCFA.  

Our group identified that the conditioning regimen, starting from the same baseline microbiota composition, promotes changes in the microbiome, which are different between Autologous (auto-) and Allogeneic Stem Cell Transplantation (allo-SCT). After auto-SCT we documented an increase of Proteobacteria (Klebsiella, Proteus, Acinetobacter, Haemophilus, Pseudomonas, Enterobacteriaceae) and a reduction of Bacteroidetes (Bacteroides, Sapropirae, Prevotella). After allo-SCT, instead, there was an increase of Bacteroidetes and a reduction of Firmicutes (Bacilli, Lactobacilli, Clostridium, Enterococi, Streptococi). Moreover, patients who developed GVHD harbored more Firmicutes and Proteobacteria and fewer Bacteroidetes than patients without this complication. In patients with gut GVHD, Proteobacteria were more represented than in patients with liver or skin involvement.  

Collectively, these studies showed that the intestinal microbiota is heavily affected by HSCT, being the principal finding, reported in all studies, the reduction in the overall bacterial diversity. At the same time, some studies reported specific alterations which are
interestingly correlated with the development of the major complications of HSCT, such as bacteremia and GVHD. While a causative role of the microbiota in these conditions is yet to be demonstrated, these and future studies may give a better comprehension of the complex mechanisms underlying HSCT and GVHD, ultimately allowing better outcomes.

**New Perspectives: the Role of Paneth Cells and Genetic Modifiers of Gut Microbiota.** Recently, researchers focused on Paneth cells in an attempt to find a mechanistic relation between microbiota and GVHD. Paneth cells secrete antimicrobial peptides such as alpha-defensins which contribute to the regulation of the GI microbiota. During GVHD, Paneth cells appear to be damaged with a consequent reduction in alpha-defensins production. Noteworthy, alpha-defensins activity is directed mostly toward non-commensal bacteria, thus decreased levels of these peptides lead to a reduction of commensal bacteria and, intuitively, to an impairment in their beneficial effects.

A subsequent study investigated if Paneth cells number may correlate with the severity, response to treatment and survival of GVHD. Authors found that Paneth cells number was inversely correlated with the clinical severity stage with a strong correlation between the two parameters. Response to treatment at 4 weeks was also found to be positively correlated with Paneth cells number, being highest in patients with a complete response and lowest in patients who did not respond. Finally, a threshold of 4 Paneth cells per high power field (HPF) was found to discriminate between high and low-risk patients regarding non-relapse mortality (NRM), with also a significant difference in the overall survival.

Similarly, Ferrara et al. demonstrated that a specific lectin secreted by Paneth cells, namely regenerating islet-derived 3-alpha (REG3alpha), has diagnostic value in acute GI GVHD permitting to differentiate between GVHD-related diarrhea and other causes of diarrhea. The authors also demonstrated a prognostic value of REG3alpha in GVHD, in particular, a positive correlation between plasma levels and NRM was found. This result may appear in contrast with the previous data, in particular with the evidence supporting a protective role of Paneth cells. However, the authors hypothesized that the GI mucosal barrier disruption which occurs in GVHD permits to the nearby Paneth cells secretions to enter the bloodstream.

Similarly, there is an increasing interest in the role of the Fucosyltransferase 2 (FUT2) gene, a genetic modifier of the GI microbiota which seems to be associated with different GI diseases. Various antigens are expressed in the intestinal mucin layer, for example, ABH antigens are oligosaccharides that constitute a site of attachment and a carbon source for intestinal bacteria. Their expression is regulated by an enzyme which in humans is encoded by the FUT2 gene. Polymorphisms in the FUT2 gene are correlated with alteration of the GI microbiota both in the compositional and functional level. Recently, homozygosity for the loss-of-function alleles (non-secretors, A/A genotype) was demonstrated to be associated with increased susceptibility to Crohn’s disease. Rayes et al. also showed that FUT2 polymorphisms influence the risk of GVHD and bacteremia in the context of HSCT. Specifically, the Authors found that there was a reduced risk of acute GVHD with A/A genotype (non-secretors) and an increased risk with the G/G genotype (secretors) while an increased risk for bacteremia was found with A/A and A/G (secretors) genotypes.

**Gut Microbiota Modulation as a Preventive Strategy Against GVHD.** Considering the major role of gut microbiota in the pathogenesis of GVHD, its modulation with probiotic, probiotic and antibiotic could be a strategy to reduce the incidence of GVHD.

Some studies reported reduced numbers and less severe GVHD after the use of broad-spectrum antibiotics to “decontaminate” the gastrointestinal tract. However, GI decontamination fell into disuse in the 1990s mostly because of heterogeneous successful decontamination rates, high costs and lack of corroborating data of its utility. The reasons behind the failure of total gut decontamination in the clinical setting are still unknown. However, many Authors hypothesized that an explanation may be that this practice affects the microbiota as a whole, without distinction between “good” bacteria and pathogens. In fact, as discussed above, there is evidence that bacteria diversity is the cornerstone of the “healthy” microbiota while a decreased diversity is often found in many GI and extra gastrointestinal diseases.

Probiotics drew growing interest in the world of gut microbiota modulation and suggested in murine models that they could be effective in decreasing the aGVHD severity. However, the use of probiotics in immunosuppressed patients is limited by possible safety issues. Ladas et al. evaluated the safety of the administration of *Lactobacillus plantarum* during the conditioning regimen and the post-HSCT neutropenic period in 30 children and adolescents. The majority of patients (70%) did not develop GVHD. Three patients died within 100 days from the HSCT, but the causes of death are judged unrelated to probiotics. Furthermore, no episodes of *Lactobacillus plantarum* bacteremia were observed. Even if these results are preliminary, they laid the foundation for larger clinical trials to evaluate the efficacy and the safety of probiotics in prevention and treatment of GVHD.
Prebiotics are defined as nondigestible food components that are able to modulate the intestinal microbiota with a possible beneficial effect on the human body. In particular, oligosaccharides represent an important fraction of human milk and are known to exert a prebiotic effect. Modulation of the microbiota is also achieved indirectly, as oligosaccharides can prevent adhesion of enteropathogens acting as soluble decoys. Both these mechanisms indirectly reduce inflammation, even if recent evidence suggest that oligosaccharides also have a direct inhibitory effect on inflammation.

Fecal microbiota transplantation (FMT), the infusion of feces from a healthy donor into the gut of a recipient patient, was recently proven to be safe and effective in Clostridium difficile infection after HSCT when conventional therapy failed. In fact, patients undergoing HSCT are exposed, due to antibiotic prophylaxis and to the procedure itself, to colonization by multi-drug resistant bacteria with a negative impact on the main transplant outcomes, such as overall survival and non-relapse mortality, but also on the development of clinically relevant aGVHD.

Interestingly the same authors found, in a preliminary study, that FMT was able to eradicate resistant bacteria harbored in the gut of an immunocompromised patient affected by multiple myeloma.

While further studies are awaited, these data suggested that FMT may represent, in the near future, a novel strategy to modulate the gut microbiota with a possible impact on GVHD.

**Conclusions.** Gut microbiota and its continuous stimulation of immune system is essential for the development and the “maintenance” of a healthy gut. HSCT-related procedures could alter this balance laying the foundation for the development of GVHD. The possibility of modulation of gut microbiota as a preventive or curative strategy for GVHD is intriguing and should be developed in the future, to reduce the morbidity and mortality of this condition.

**References:**

1. Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfield GM, Hold G, Quraishi MN, Kinross J, Smidt H, Tuohy KM, Thomas LV, Zoetendal EG, Hart A. The gut microbiota and host health: a new clinical frontier. Gut 2016; 65: 330-339. http://dx.doi.org/10.1136/gutjnl-2015-309990
2. Pasquini MC. Impact of graft-versus-host disease on survival. Best practice & research Clinical haematology 2008; 21: 193-204. http://dx.doi.org/10.1016/j.beha.2008.02.011
3. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. Nature reviews Immunology 2012; 12: 443-458. http://dx.doi.org/10.1038/nri3212
4. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Prepiorka D, Couriel D, Cowen EW, Dunndorf P, Farrell A, Hartzman R, Hanselle-Downey J, Jacobsohn D, McDonald G, Mittleman B, Rizzo JD, Robinson M, Schubert M, Schultz R, Shulman H, Turner M, Vogelsang G, Flowers ME. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2005; 11: 945-956. http://dx.doi.org/10.1016/j.bbmt.2005.09.004
5. Rajilic-Stojanovic M, de Vos WM. The first 1000 cultured species of the human gastrointestinal microbiota. FEMS microbiology reviews 2014; 38: 996-1047. http://dx.doi.org/10.1111/1574-6976.12075
6. Shreiner AB, Kao JY, Young VB. The gut microbe in health and in disease. Current opinion in gastroenterology 2015; 31: 69-75. http://dx.doi.org/10.1097/MOG.0000000000000139
7. Lozupone CA, Rhodes ME, Neff CP, Fontenot AP, Campbell TB, Palmer BE. HIV-induced alteration in gut microbiota: driving factors, consequences, and effects of antiretroviral therapy. Gut microbes 2014; 5: 562-570. http://dx.doi.org/10.4161/gmic.32132
8. Salas JT, Chang TL. Microbiome in human immunodeficiency virus infection. Clinics in laboratory medicine 2014; 34: 733-745. http://dx.doi.org/10.1016/j.cll.2014.08.005
9. Jain N, Walker WA. Diet and host-microbial crosstalk in postnatal intestinal immune homeostasis. Nature reviews Gastroenterology & hepatology 2015; 12: 14-25. http://dx.doi.org/10.1038/nrgastro.2014.153
10. Tomkovich S, Jobin C. Microbiota and host immune responses: a love-hate relationship. Immunology 2016; 147: 1-10. http://dx.doi.org/10.1111/imn.12538
11. Johansson ME, Phillipson M, Petersson J, Velgich A, Holm L, Hansson GC. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. Proceedings of the National Academy of Sciences of the United States of America 2008; 105: 15064-15069. http://dx.doi.org/10.1073/pnas.0803124105
12. Bergstrom KS, Kissoon-Singh V, Gibson DL, Ma C, Montero M, Sham HF, Ryz N, Huang T, Velchik A, Finlay BB, Chadee K, Vallance BA. Muc2 protects against lethal infectious colitis by disassociating pathogenic and commensal bacteria from the colonic mucosa. PLoS pathogens 2010; 6: e1000902. http://dx.doi.org/10.1371/journal.ppat.1000902
13. Vaishnava S, Behrendt CL, Ismael AS, Eckmann L, Hooper LV. Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. Proceedings of the National Academy of Sciences of the United States of America 2008; 105: 20858-20863. http://dx.doi.org/10.1073/pnas.0808723105
14. Sonnenberg GP, Monteleoni LA, Amling T, Fung TC, Hutnick NA, Kunisawa J, Shibata N, Grunberg S, Sinha R, Zahn AM, Tardif MR, Sathiyalaywa T, Kubota M, Farber DL, Collman RG, Chaked A, Fouser LA, Weiner DB, Tessier PA, Friedman JR, Kiyono H, Bushman FD, Chang KM, Artis D. Innate lymphoid cells promote anatomical containment of lymphoid-resident commensal bacteria. Science 2012; 336: 1321-1325. http://dx.doi.org/10.1126/science.1227551
15. Strugnell RA, Wijburg OL. The role of secretory antibodies in infection immunity. Nature reviews Microbiology 2010; 8: 656-667. http://dx.doi.org/10.1038/nrmicro2384
16. Fagarasan S, Muramatsu M, Suzuki K, Nagaoa H, Hibi H, Honjo T. Critical roles of activation-induced cytidine deaminase in the homeostasis of gut flora. Science 2002; 298: 1424-1427. http://dx.doi.org/10.1126/science.1077336
17. Wei M, Shinkura R, Doi Y, Maruya M, Fagarasan S, Honjo T. B cell activation in the gut in Aicda-deficient mice. Science 2008; 319: 1325-1328. http://dx.doi.org/10.1126/science.1150691
18. Kamada N, Nunez G. Regulation of the immune system by the resident intestinal bacteria. Gastroenterology 2014; 146: 1477-1488. http://dx.doi.org/10.1053/j.gastro.2014.01.060
19. Franchi L, Kamada N, Nakamura Y, Burberry A, Kuffa P, Suzuki S, Shaw MH, Kim YG, Nunez G. NLRC4-driven production of IL-1beta discriminates between pathogenic and commensal bacteria and promotes host intestinal defense. Nature immunology 2012; 13: 449-456. http://dx.doi.org/10.1038/nm.2263
20. Hasegawa M, Kamada N, Jiao Y, Liu MZ, Nunez G, Inohara N. Protective role of commensals against Clostridium difficile
infection via an IL-1β-mediated positive-feedback loop. Journal of
immunology 2012; 189: 3085-3091. http://dx.doi.org/10.4049/jimmunol.1200821

21. Luzzo F, Parrello T, Monteleone G, Sebkova L, Romano M, 
Zarrilli R, Imeneo M, Pallone F. Up-regulation of IL-17 is 
associated with bioactive IL-8 expression in Helicobacter pylori-
infected human gastric mucosa. Journal of immunology 2000; 165:
5332-5337. http://dx.doi.org/10.4049/jimmunol.165.9.5332

22. Ivanov, II, Frutos Rde L, Manel N, Yoshinaga K, Ritkin DB, 
Sartor RB, Finlay BB, Littman DR. Specific microbiota direct the 
differentiation of IL-17-producing T-helper cells in the mucosa of 
the small intestine. Cell host & microbe 2008; 4: 377-388. 
http://dx.doi.org/10.1016/j.chom.2008.06.009

23. Gabonau-Routhua V, Rakotobe S, Lecuyer E, Mulder I, An, 
Bridonneau C, Rochet V, Pisi A, De Paeppe M, Brandi G, Eberl G, 
Snel J, Kelly D, Cerf-Bensussan N. The key role of segmented 
filamentous bacteria in the coordinated maturation of gut helper T 
cell responses. Immunity 2009; 31: 677-689.

24. Ivanov, II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, 
Wei D, Goldfarb KC, Santee CA, Lynch SV, Taneou T, Imaoka A, 
Itoh K, Takeda K, Umesaki Y, Honda K, Littman DR. Induction of 
testinal Th17 cells by segmented filamentous bacteria. Cell 2009; 
139: 485-498. http://dx.doi.org/10.1016/j.cell.2009.09.033

25. Lau K, Benitez P, Ardisone S, Wilson TD, Collins EL, Lorca G, 
Li N, Sankar D, Wasserfall C, Neu J, Atkinson MA, Shatz D, 
Triplet EW, Larkin J, 3rd. Inhibition of type 1 diabetes correlated 
to a Lactobacillus johnsonii N6.2 free mice: life 
limiting humoral mucosal immune response while 
28. 243-273. http://dx.doi.org/10.1146/annurev.immunol.030409.101314

30. Aratashi K, Tanoue T, Shinami T, Imaoka A, Kuwahara T, Momose 
Y, Cheng G, Yamazaki S, Saito T, Obha Y, Taniguchi T, Takeda 
K, Hori S, Ivanov, II, Umesaki Y, Itoh K, Honda K. Induction of 
colonic regulatory T cells by indigenous Clostridium species. 
Science 2011; 331: 337-341. 
http://dx.doi.org/10.1126/science.1198469

31. Aratashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa 
H, Fukuda S, Saito T, Narushima S, Hase K, Kim S, Fritz JV, 
Wilmes P, Ueha S, Matsushima K, Ohno H, Olie B, Sakaguchi S, 
Taniguchi T, Morita H, Atarashi K, Honda K. Treg induction by a 
rationally selected mixture of Clostridia strains from the human 
microbiota. Nature 2013; 500: 232-236. 
http://dx.doi.org/10.1038/nature12331

32. Dewhurst FE, Chien CC, Paster BJ, Erickson RL, Orent RP, 
Schauer DB, Fox JG. Phylogeny of the defined murine microbiota: 
altered Schaudinn and environmental microbiology 1999; 65: 3287-3292. 
PManf:10427008 PMCats:PMCID:PMC1943

33. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell 
development by a communal bacterium of the intestinal microbiota. 
Proceedings of the National Academy of Sciences of the United States 
of America 2010; 107: 12204-12209. 
http://dx.doi.org/10.1073/pnas.0919221107

34. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian 
SK. The Toll-like receptor 2 pathway establishes commensalism by a 
commensal of the human microbiota. Science 2011; 334: 974-977. 
http://dx.doi.org/10.1126/science.1206095

35. Smith PM, Howitt MR, Panikov N, Michaud G, Galli CA, 
Bohlooly YM, Glickman JN, Garrett WS. The microbial 
metabolites, short-chain fatty acids, regulate colonic Treg cell 
homeostasis. Science 2013; 341: 569-573. 
http://dx.doi.org/10.1126/science.1231465

36. Furusawa Y, Obata Y, Fukuda S, Endo TA. Nakato K, Takahashi 
D, Nakanishi Y, Uetake C, Kato K, Takeda T, Takahashi M, Fukuda 
NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, 
Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M., Hori S, 
Oksa H, Kikuchi J, Honda K, Hase K, Ohno H. Commensal microbial-derived butyrate induces the 
differentiation of colonic regulatory T cells. Nature 2013; 504: 
446-450. http://dx.doi.org/10.1038/nature12721

37. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos 
P, Liu H, Cross JR, Pleffer K, Colfer PJ, Rudensky AY. 
Metabolites produced by commensal bacteria promote peripheral 
regulatory T-cell generation. Nature 2013; 504: 451-455. 
http://dx.doi.org/10.1038/nature12726

38. Le Poul E, Loison C, Struyf S, Springael JY, Lannoy V, Decoene 
ME, Brezillon S, Duprez V, Vassart G, Van Damme J, Parmentier 
M, Detheux M. Characterization of human receptors for 
short chain fatty acids and their role in polymorphonuclear 
cell activation. The Journal of biological chemistry 2003; 278: 25481-
25489. http://dx.doi.org/10.1074/jbc.M301403200

39. Vinolo MA, Rodrigues HG, Nachbar RT, Curi R. Regulation of 
inflammation by short chain fatty acids. Nutrients 2011; 3: 858-
876.10.3390/nu3100858 http://dx.doi.org/10.3390/nu3100858

40. Coombs JL, Siddiqui KR, Arancibia-Carcamo CV, Hall J, Sun 
CM, Belkaid Y, Powrie F. A functionally specialized population of 
mucostral CD103+ DCs induces Foxp3+ regulatory T cells via a 
TGF-beta and retinoic acid-dependent mechanism. The Journal of 
experimental medicine 2007; 204: 1757-1764. 
http://dx.doi.org/10.1084/jem.20070590

41. Sun CM, Hall JA, Blank RB, Bouladoux N, Oukka M, Mora JR, 
Belkaid Y. Small intestine lamina propria dendritic cells promote de 
ovo generation of Foxp3+ Treg cells via retinoic acid. The Journal 
of experimental medicine 2007; 204: 1775-1785. 
http://dx.doi.org/10.1084/jem.20070602

42. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, 
Cheroutre H. Reciprocal TH17 and regulatory T cell differentiation 
mediated by retinoic acid. Science 2007; 317: 256-260. 
http://dx.doi.org/10.1126/science.1145697

43. Welty NE, Staley C, Ghilardi N, Sadowsky MJ, Igarto BZ, 
Kaplan DH. Intestinal lamina propria dendritic cells maintain T 
cell homeostasis but do not affect commensalism. The Journal of 
experimental medicine 2013; 210: 2011-2024. 
http://dx.doi.org/10.1084/jem.20110727

44. Singh N, Gurav A, Sivaprasakas S, Brady E, Padia R, Shi H, 
Tangaraju M, Prasad PD, Maniassamy S, Munn DH, Lee JR, 
Offermans S, Ganapathy V. Activation of Gpr109a, receptor for 
niacin and the commensal metabolite butyrate, suppresses colonic 
inflammation and carcinogenesis. Immunity 2014; 40: 128-139. 
http://dx.doi.org/10.1016/j.immuni.2013.12.007

45. Kim SV, Xiang WV, Kwak C, Yang Y, Lin XW, Ota M, Sarpel U, 
Rifkin DB, Xu R, Littman DR. GPR15-mediated homing controls 
intestinal homeostasis in the large intestine mucosa. Science 2013; 
340: 1450-1459. http://dx.doi.org/10.1126/science.1237013

46. Rossi M, Amaretti A, Raimondi S. Folate production by probiotic 
bacteria. Nutrients 2011; 3: 118-134. 
http://dx.doi.org/10.3390/nu3010118

www.mjhd.org Medit J Hematol Infect Dis 2016; 8: e2016025
52. Rivollier A, He J, Kole A, Valatas V, Keshav BL. Inflammation switches the differentiation program of Ly6Chi monocytes from anti-inflammatory macrophages to inflammatory dendritic cells in the colon. The Journal of experimental medicine 2012; 209: 139-155. http://dx.doi.org/10.1084/jem.20101387

53. Storb R, Prentice RL, Buckner CD, Clift RA, Appelbaum F, Deeg J, Doney K, Hansen JA, Mason M, Sanders JE, Singer J, Sullivan KM, Witherspoon RP, Thomas ED. Graft-versus-host disease and survival in patients with aplastic anemia treated by marrow grafts from HLA-identical siblings. Beneficial effect of a protective environment. The New England journal of medicine 1983; 308: 302-307. http://dx.doi.org/10.1056/NEJM198303243081106

54. Passweg JR, Bibollet-H, Basler P, Bonum C, Cesario S, Dreger P, Duarte RF, Dufour C, Falkenburg JH, Farge-Bancel D, Gennery A, Kroger N, Lanza F, Nagler A, Sureda A, Mohty M. European Society for B, Marrow T. Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haplidentical donors but fewer cord blood transplants. Bone marrow transplantation 2015; 50: 476-482. http://dx.doi.org/10.1038/bmt.2014.312

55. Socie G, Blazar BR. Acute graft-versus-host disease: from the bench to the bedside. Blood 2009; 114: 4327-4336.10.1182/blood-2009-06-204669 http://dx.doi.org/10.1182/blood-2009-06-204669

56. Biagi E, Zama D, Nastasi C, Consolandi C, Fiori J, Rampelli S, Turroni S, Centannii M, Severgnini M, Peano C, de Bellis G, Littmann ER, Morjaria S, Ling L,anni M, Severgnini M, Peano C, de Bellis G, Lazar BR. Acute graft-versus-host disease and Cytokine production in gastrointestinal graft-versus-host disease. Blood 2014; 124: 1174-1182. http://dx.doi.org/10.1182/blood-2014-02-554725

57. Jenq RR, Taur Y, Devlin SM, Ponce DM, Goldberg JD, Ahr KF, Littmann ER, Ling L, Gobourne AC, Miller LC, Docampo MD, peled JU, Arapaia N, Cross JR, Peets TK, Lumish MA, Shono Y, Dudakov JA, Poreck H, Hanash AM, Barker JN, Perales MA, Giralt SA, Pamer EG, van den Brink MR. Immunogenic Bladder Is Associated with Reduced Death from Graft-versus-Host Disease. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2015; 21: 1373-1383. http://dx.doi.org/10.1016/j.bbmt.2015.04.016

68. Holler E, Brutthammer P, Schmalz K, Hamanncker C, Koester J, Peter K, Zhu Y, Dzio K, Hinrichs S, Heintz T, Kreutz M, Holler B, Wolff D, Edinger M, Andreessen R, Levine JE, Ferrara J, Gessner A, Spang R, Ofenf PJ. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. Biology of blood and marrow transplantation ; journal of the American Society for Blood and Marrow Transplantation 2014; 20: 640-645.10.1016/j.bbmt.2014.01.030 http://dx.doi.org/10.1016/j.bbmt.2014.01.030

69. Chiussolo P, Metatfni E, Paroni Sterbini F, Giannamario S, Masucci L, Levine G, Sica S. Gut Microbiome Changes after Stem Cell Transplantation. Blood 2015; 126: 1953-1965

70. Ergiuchi Y, Takashima S, Oka H, Shimoji S, Nakamura K, Ury H, Shiomada S, Iwasaki H, Shiono N, Ayabe T, Akashi K, Teshima T. Graft-versus-host disease disrupts intestinal microbial ecology by inhibiting Paneth cell production of alpha-defensins. Blood 2012; 120: 223-231. http://dx.doi.org/10.1182/blood-2011-12-401166

71. Levine JE, Huber E, Hampton ST, Harris AC, GreenJKN, Braun TM, Ferrara JL, Holter E. Low Paneth cell numbers at onset of gastrointestinal graft-versus-host disease in patients with high risk for nonrelapse mortality. Blood 2013; 122: 1505-1509. http://dx.doi.org/10.1182/blood-2013-02-458513

72. Ferrara JL, Harris AC, GreenJKN, Braun TM, Holter E, Teshima T, Levine JE, Choi SW, Huber E, Landreid K, Akashi K, Vander Lugt M, Reddy P, Chin A, Zhang Q, Hanash S, Pacezny S. Regenerating selet-derived 3-alpha is a biomarker of gastrointestinal graft-versus-host disease. Blood 2011; 118: 6702-6708. http://dx.doi.org/10.1182/blood-2011-08-375006

73. Rayes A, Morrow AL, Payton LR, Lake KE, Lane A, Davies SM. A Genetic Modifier of the Gut Microbiome Influences the Risk of Graft-versus-Host Disease. Frontiers in immunology 2014; 5: 337. http://dx.doi.org/10.3389/fimmu.2014.00337

74. Welniak LA, Blazar BR, Murphy WJ. Immunobiology of allogeneic hematopoietic stem cell transplantation. Annual review of immunology 2007; 25: 139-170. http://dx.doi.org/10.1146/annurev.immunol.25.020106.141606

75. Jones JM, Watson R, Bealmea PM. Mortality and gross pathology of secondary disease in germfree mouse radiation chimeras. Radiation research 1971; 45: 577-588. http://dx.doi.org/10.2307/3573066 PMid:4986814

76. van Bekkum DW, Rooodenburg J, Heidt P, van der Waaia D, Mitagation of secondary disease of allogeneic mouse radiation chimeras by modification of the intestinal microflora. Journal of the National Cancer Institute 1974; 52: 401-404 PMid:4150164

77. Taur Y, Xavier JB, Lipuma L, Ubeda C, Goldberg J, Gobourne A, Lee handled, DUjin KA, Socci ND, Viale A, Perales MA, Jenq RR, van Den Brink MR, Pamer EG. Intestinal dominance and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012; 55: 905-914. http://dx.doi.org/10.1093/cid/css580

78. McDonald-Hyman C, Turka LA, Blazar BR. Advances and challenges in immunotherapy for solid organ and hematopoietic stem cell transplantation. Science translational medicine 2015; 7: 280rv282. http://dx.doi.org/10.1126/scitranslmed.aaa6853

79. Jenq RR, Ubeda C, Taur Y, Menezes CC, Khanrin R, Dudakov JA, Liu C, West M, Singer NV, Equinda AC, Gobourne A, Lipuma L, Young LF, Xu X, O'M, Ghosh A, Yu A, Ayasoma K, Blazar BR, Pamer EG, van den Brink MR. Regulation of intestinal inflammation by microbiota following allogeneic marrow transplantation. The Journal of experimental medicine 2012; 209: 903-911. http://dx.doi.org/10.1084/jem.20124208

80. Taur Y, Gobourne AC, Littmann ER, Ling L, No D, Gobourne A, Viale A, Dahl PB, Ponce DM, Barker JN, Giralt S, van den Brink M, Pamer EG. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood 2014; 124: 1174-1182. http://dx.doi.org/10.1182/blood-2014-02-554725

81. Jenq RR, Taur Y, Devlin SM, Ponce DM, Goldberg JD, Ahr KF, Littmann ER, Ling L, Gobourne AC, Miller LC, Docampo MD, peled JU, Arapaia N, Cross JR, Peets TK, Lumish MA, Shono Y, Dudakov JA, Poreck H, Hanash AM, Barker JN, Perales MA, Giralt SA, Pamer EG, van den Brink MR. Immunogenic Bladder Is Associated with Reduced Death from Graft-versus-Host Disease. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2015; 21: 1373-1383. http://dx.doi.org/10.1016/j.bbmt.2015.04.016

82. Vossen JM, Guot HF, Lankester AC, Vossen AC, Bredius RG, Wolterbeek R, Bakker HD, Heidt P. Complete suppression of the gut microbiome prevents acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. PloS one 2014; 9: e105706. http://dx.doi.org/10.1371/journal.pone.0105706

83. Docampo MD, Aulella J, Jenq RR. Emerging Influence of the Intestinal Microbiota during Allogeneic Hematopoietic Cell
Transplantation: Control the Gut and the Body Will Follow. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2015; 21: 1360-1366. http://dx.doi.org/10.1016/j.bbmt.2015.02.016

80. Murphy S, Nguyen VH. Role of gut microbiota in graft-versus-host disease. Leukemia & lymphoma 2011; 52: 1844-1856. http://dx.doi.org/10.3109/10428194.2011.580476

81. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature 2012; 489: 220-230. http://dx.doi.org/10.1038/nature11550

82. Gerbitz A, Schultz M, Wilke A, Linde HJ, Scholmerich J, Andreessen R, Holler E. Probiotic effects on experimental graft-versus-host disease: let them eat yogurt. Blood 2004; 103: 4365-4367. http://dx.doi.org/10.1182/blood-2003-11-3769

83. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics—approaching a definition. The American journal of clinical nutrition 2001; 73: 361S-364S PMid:11157342

84. Hennet T, Weiss A, Borsig L. Decoding breast milk oligosaccharides. Swiss medical weekly 2014; 144: w13927. http://dx.doi.org/10.4414/smw.2014.13927

85. Yu ZT, Chen C, Newburg DS. Utilization of major fucosylated and sialylated human milk oligosaccharides by isolated human gut microbes. Glycobiology 2013; 23: 1281-1292. http://dx.doi.org/10.1093/glycob/cwt065

86. Newburg DS, He Y. Neonatal Gut Microbiota and Human Milk Glycans Cooperate to Attenuate Infection and Inflammation. Clinical obstetrics and gynecology 2015; 58: 814-826. http://dx.doi.org/10.1093/cin/gmv048

87. He Y, Liu S, Kling DE, Leone S, Lawlor NT, Huang Y, Feinberg SB, Hill DR, Newburg DS. The human milk oligosaccharide 2′-fucosyllactose modulates CD14 expression in human enterocytes, thereby attenuating LPS-induced inflammation. Gut 2016; 65: 33-46. http://dx.doi.org/10.1136/gutjnl-2014-307544

88. Newburg DS, Ko JS, Leone S, Nauthakumar NN. Human Milk Oligosaccharides and Synthetic Galactosyloligosaccharides Contain 3′-, 4′-, and 6′-Galactosylactose and Attenuate Inflammation in Human TH4, NCM-460, and H4 Cells and Intestinal Tissue Ex Vivo. The Journal of nutrition 2016; 146: 358-367. http://dx.doi.org/10.3945/jn.115.220749

89. Ortega-Gonzalez M, Ocon B, Romero-Calvo I, Anzola A, Guadix E, Zarruzel A, Suarez MD, Sanchez de Medina F, Martinez-Augustin O. Nondigestible oligosaccharides exert nonprobiotic effects on intestinal epithelial cells enhancing the immune response via activation of TLR4-NF-kappaB. Molecular nutrition & food research 2014; 58: 384-393. http://dx.doi.org/10.1002/mnfr.201302926

90. Neemann K, Eischele DD, Smith PW, Bociak R, Akhtari M, Freifeld A. Fecal microbiota transplantation for fulminating Clostridium difficile infection in an allogeneic stem cell transplant patient. Transplant infectious disease : an official journal of the Transplantation Society 2012; 14: E161-165. http://dx.doi.org/10.1111/tid.12017

91. de Castro CG, Jr., Ganc AF, Ganc RL, Petrolli MS, Hamerschlag N. Fecal microbiota transplant after hematopoietic SCT: report of a successful case. Bone marrow transplantation 2015; 50: 145. http://dx.doi.org/10.1038/bmt.2014.212

92. Bilinski J, Robak K, Peric Z, Marchel H, Karakulski-Prystupiuk E, Halaburda K, Rusicka P, Swoboda-Kopiec E, Wroblewska M, Witktor-Jedrzejczak W, Basak GW. Impact of Gut Colonization by Antibiotic-Resistant Bacteria on the Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation: A Retrospective, Single-Center Study. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2016. DOI: 10.1016/j.bbmt.2016.02.009.10.1016/j.bbmt.2016.02.009

93. Bilinski J, Grzesiowski P, Muszynski J, Wroblewska M, Madry K, Robak K, Dzieciatkowski T, Witktor-Jedrzejczak W, Basak GW. Fecal Microbiota Transplantation Inhibits Multidrug-Resistant Gut Pathogens: Preliminary Report Performed in an Immunocompromised Host. Archivum immunologiae e et therapiae experimentalis 2016. http://dx.doi.org/10.1007/s00005-016-0387-9