Workshop

Workshop on Nutrition and Microbiome in Allogeneic Hematopoietic Stem Cell Transplantation

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University of Regensburg

Regensburg, Germany

Abstracts

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Abstracts of Invited Lectures

Workshop

WORKSHOP ON NUTRITION AND MICROBIOME IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Regensburg, Germany
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Session I

Microbiome in allogeneic hematopoietic stem cell transplantation I

Human microbiome – an introduction

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Humans exist as meta-organisms comprised of both the macroscopic host and its symbiotic commensal microbiota. With approximately 100 trillion cells, bacteria outnumber host cells by at least a factor of 10 and express at least 100-fold more unique genes than their host's genome. The tremendous enzymatic capability of the microbiome results in a plethora of metabolites found in humans which play a fundamental role in nearly all aspects of host physiology and disease development including metabolic, cardiovascular and even neuro-psychatric illnesses.

Since 2000, large-scale 16S rRNA or metagenomic studies have dramatically expanded the knowledge about diversity of the human gut microbiome. Approximately 80% of the bacteria found by molecular tools are uncultured so far, and hence can be characterized only by high throughput sequencing and adequate bioinformatics analysis. Applying our patented NGS-quality control tools we completed four European external quality assessments (EQAS) comparing results from different next generation sequencing (NGS) centers with special emphasis on critical preanalytic steps, nucleic acid preparation and bioinformatic data processing.

Furthermore, our goal is to achieve a functional understanding of bidirectional microbe-host interactions in health and diseases (e.g. graft-versus-host disease and depression), beyond largely descriptive compositional and metagenomic analyses.

Mechanisms of intestinal microbiome damage

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Epithelial barriers are crawling with commensal bacteria and other microorganisms, collectively called the microbiome. Maintaining a healthy microbiome is of utmost importance, as commensal microbiota not only maintain epithelial barriers, and contain outgrowth of pathobionts, but also regulate local and systemic immune responses. Moreover, commensal microbiota protect us against a wide range of inflammatory and non-inflammatory conditions, and even modulate responses to cancer therapy, including toxic side effects.

The microbiome is established early in life and remains relatively constant after that through a synergistic interplay with dietary products, the epithelium and the innate and adaptive immune system of the host. The importance of polymeric IgA, produced by intestinal plasma cells, in shaping the bacterial repertoire has been long appreciated. Other immune cells, such as innate lymphoid cells, contribute indirectly to a healthy microbiome, via maintenance of the epithelial barrier and thereby securing epithelial excretion of antimicrobial products such as defensins and AMP that are needed to prevent outgrowth of pathobionts. The microbiome keeps itself in shape by its fermentation of nutritional products and excretion of microbial products such as free short chain fatty acids (butyrate) and aryl hydrocarbon receptor (Ahr) ligands that serve to feed intestinal immune cells and epithelial cells. Thus, by taking good care of its supportive network, the microbiome plays an important part in keeping its own health.

This health can be challenged in a number of ways. Antibiotics are the most direct threat and can damage the microbiome severely, in particular in case of repeated or prolonged use. Other factors that directly or indirectly may affect the microbiome are diet and malnutrition, immune deficiency, chemotherapy and radiotherapy. In patients with hematologic malignancies, the microbiome typically endures multiple of these assaults, often at the same time. In particular allogeneic hematopoietic cell recipients are characterized by having an injured microbiome, with the extent of damage being associated with outcome. A thorough understanding of mechanisms that damage the intestinal microbiome is important as this forms a basis to develop novel approaches to prevent and repair that damage and to improve patients' outcomes.

Microbiome and GvHD

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Although allogeneic stem cell transplantation (ASCT) is a potentially curative treatment option for various hematological diseases, acute graft-versus-host disease (GvHD) is a major cause of morbidity and mortality, and its management is clinically very important. In recent years the development of new biological techniques like 16S RNA sequencing provided deeper insights into the complex composition of intestinal microbiota and has improved our understanding of the interactions between intestinal mucosa and enteric microbiota including the setting of ASCT.

Serial analyses of fecal specimens taken from recipients of an ASCT showed a loss of intestinal microbiome diversity and a shift to an enteropathogenic flora with a predominance of Gram-negative *Enterobacteriales (E. coli, Klebsiella, Enterobacter spec.)* and Gram-positive *Lactobacillales (Lactobacillus, Enterococcus* and *Streptococcus spec.)* during the course of transplantation. Intensive microbiota disruptions with a loss of protective commensal bacteria like *Clostridiales* and their protective metabolites e.g. indoles and short-chain fatty acids (SCFA) particularly around the time of engraftment seem to be associated with a significantly worse clinical outcome mainly due to acute gastrointestinal (GI) GvHD. Both, indoles and SCFAs have been shown to stabilize epithelial integrity and to modulate immunoregulatory cells towards a tolerogeneic phenotype.

Multiple risk factors contribute to a significant disruption of the intestinal microbiome including administration of conditioning therapy, alterations in nutrition and of course the previous and peri-ASCT use of systemic broad-spectrum antibiotics for prevention and therapy of neutropenic infections. Here not only the type of antibiotic therapy but also the beginning of systemic antibiotics significantly influenced the acute GI GvHD-associated transplant related mortality.

These clinical results are also supported by experimental data and therefore led to the hypothesis that correction of intestinal dysbiosis may be a promising treatment strategy for acute GI GvHD. First convincing results were reported by a Japanese and Austrian group who successfully treated patients with steroid-refractory GI GvHD with fecal microbiota transplantation (FMT). A further group in Boston treated patients with third-party FMT capsules within 4 weeks after neutrophil engraftment and was able to document a restoration of intestinal microbiome diversity after ASCT. These results may indicate that FMT appears to be a feasible and safe possibility to treat and to prevent acute GvHD of the GI tract and controlled clinical trials are on the way.

Furthermore, intervention in the gut microbiota with a nutritional approach including prebiotics or postbiotics, and antibiotics selection may also be promising options for prophylaxis or treatment of acute GvHD.

The role of the intestinal microbiome in allogeneic hematopoietic cell transplantation

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Relationships between microbiota composition and clinical outcomes of patients following allogeneic hematopoietic cell transplantation (allo-HCT) have been described in single-center studies. Geographic variations in the composition of human microbial communities and differences in clinical practices across institutions raise the question of whether these associations are generalizable.

Therefore, we studied 8767 fecal samples from 1362 allo-HCT patients at four centers on three continents by 16S ribosomal sequencing. In an observational study, we examined associations between microbiota diversity and overall survival during two years of follow-up after allo-HCT with proportional-hazards analysis. We observed reproducible patterns of microbiota disruption characterized by loss of diversity and domination by single taxa. Low diversity in the peri-neutrophil engraftment period was reproducibly associated with increased risk of death (multivariate-adjusted HR = 0.48, 95% CI: 0.30–0.77; p = 0.002 in the largest cohort). Subset analysis suggested that these reductions in overall survival were in part due to an increased risk of transplant-related mortality and graft-versus-host disease (GvHD). Baseline pre-HCT samples already bore evidence of microbiome disruption, and low diversity prior to transplantation was associated with poor survival.

In addition, we found that Enterococcus faecium dominates the intestinal microbiota of up to 65% allo-HCT patients early after transplant at all four transplant centers. Enterococcus domination was associated with an increased incidence of acute GvHD, increased GvHD-related mortality, and reduced overall survival. Post-transplant expansion of Enterococci was also observed in mouse models of GvHD in the absence of antibiotic treatment. Spiking a minimal flora with Enterococci in gnotobiotic mice exacerbated lethal GvHD. Metagenomic sequencing of human and murine Enterococcus-dominated fecal samples revealed an enrichment of lactose and galactose degradation genes, a pathway necessary for Enterococcus growth in vitro. A lactose-free chow attenuated the intestinal outgrowth of Enterococcus and reduced the severity of lethal GvHD in mice. In patients, a lactose-non-absorber genotype was associated with an increased Enterococcus abundance after cessation of antibiotic treatment after allo-HCT.

In conclusion, the concordance of microbiota disruption patterns and their associations with clinical outcomes suggests that approaches to manipulate the intestinal microbiota with the aim of improving allo-HCT clinical outcomes may be generalizable.

Session II

Microbiome in allogeneic hematopoietic stem cell transplantation II

The microbiome and GvHD of the respiratory tract

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Changes in the lung microbiome have been observed in several respiratory tract diseases and resident microbes play a beneficial role in maintaining human health. However, the exact underlying interactions are not understood. Longitudinal analyses of the lung microbiome after allograft transplantation revealed significant differences in transplanted lungs form healthy lungs, and microbiome phenotypes could be associated with increased versus decreased risks of acute allograft rejection and bronchiolitis obliterans syndrome (BOS).
While the intestinal microbiome has been focus of significant research in the field of graft versus host disease (GvHD), the lung microbiome has not been studied in this patient population. Pulmonary complications cause significant morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and it is not well understood, why some patients do develop these detrimental complications like idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage (DAH) or BOS. Studying the lung microbiome is hindered due to its more complex accessibility, and surrogate microbiome profiles are being studied. One possibility seems the microbiome to be studied on samples obtained after oral/throat rinse. At the University of Kentucky we currently undertake a prospective microbiome study, in which changes of the microbiome of throat rinse are compared with microbiome changes in the intestinal tract, and both are correlated with HSCT outcomes. Primary endpoint is the identification of microbiome pattern changes in the throat rinse microbiome and their association with acute and chronic lung injury after HSCT. Specimens are being collected 1) at baseline prior to the start of conditioning, 2) at the end of conditioning e.g. T0+1, 3) day +7 (time of mucositis), 4) 3rd day of engraftment (defined as third day in a row with ANC > 0.5/ml. Additional samples are being obtained in the absence of GvHD on day +30, +100 and +180, or at day of onset of GvHD. The protocol is currently being submitted for extension until day 730 (day 365, day 540, day 730 or onset of non-infectious lung injury). Genomic DNA was amplified for V4 hypervariable region of the 16S rRNA gene and subjected to Illumina sequencing at University of Kentucky genomics core. Preliminary data shows that the microbiome changed in the mouth and throat rinse specimens after allo-transplant; however the changes remained non-significant at phylum level. Principal component analysis revealed no significant differences in microbiota among different time points after allo-HSCT. The Genera Neisseria, Granulicatella, Corynebacterium, Solobacterium, Veillonella remained significantly abundant at day +180. Staphylococcus, Gemmiger, Dorea, Alistipes were significantly abundant at engraftment stage. While the number of patients with lung complications at this point is too small for detailed association studies, we observed significantly increased abundance of Leptotrichia in patients with GvHD patients. *Leptotrichia* spp. is a constituent of normal oral flora and acts as opportunistic pathogens, and has been shown to involve in a variety of diseases. Mucositis, oral lesions, wounds, and abscesses may predispose to *Leptotrichia* septicemia and *Leptotrichia* preponderance may be associated with pulmonary disease. We will review our preliminary data and will provide insights into the role of the microbiome in other pulmonary disease and its potential utility for allo-HSCT recipients.

High-resolution mycobiota analysis reveals dynamic intestinal translocation prior to invasive candidiasis in allogeneic hematopoietic cell transplant recipients

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The intestinal microbiota is a complex community of bacteria, archaea, viruses, protists and fungi. While the composition of bacterial constituents has been linked to immune homeostasis and to infectious susceptibility, the role of non-bacterial constituents and of cross-kingdom microbial interactions in these processes is poorly understood. Fungi represent a major cause of infectious morbidity and mortality in immune-compromised individuals, though the relationship of intestinal fungi (i.e., the mycobiota) with fungal bloodstream infections (BSI) remains undefined. We integrated an optimized bioinformatics pipeline with high-resolution mycobiota sequencing and comparative genomic analyses of fecal and blood specimens from recipients of allogeneic hematopoietic cell transplant (allo-HCT). Patients with *Candida* BSI experienced a prior marked expansion of pathogenic *Candida* species; this expansion consisted of a complex dynamic between multiple species and subspecies with a stochastic translocation pattern into the bloodstream. The intestinal expansion of pathogenic *Candida* species was associated with a significant loss in bacterial burden and diversity, particularly in the anaerobic flora. Thus, simultaneous analysis of intestinal fungi and bacteria identifies dysbiosis states across kingdoms that promote fungal translocation and facilitate invasive disease. These findings support microbiota-driven approaches to identify patients at risk for fungal BSI for pre-emptive therapeutic intervention.

Modulation of adaptive immunity by the gut microbiota

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The adult gut is typically colonized by a diverse collection of eubacteria but also archaea, viruses, phages and eukaryotic microorganisms. As a whole, this collection of microorganisms is referred to as intestinal microbiota. Animal and human studies have documented critical roles of the microbiota in metabolism, development, immune function and pathogenesis. However, how intestinal microbial communities determine the selection and accumulation of intestinal T cells and B cell populations is poorly understood.

Here we show that microbiota-dependent antigens are a major determinant for the expansion of pathogenic CD4 T cells. We modified the adoptive transfer model of colitis to the transfer of highly similar collections of T cell clones into recipients with different microbiota composition. T cell receptor (TCR) sequencing revealed, first, the expansion of shared clonotypes in recipients with identical but not with different microbiota, second, an inverse correlation of disease severity and clonal diversity, and third, a congruent expansion of clonotypes in the effector CD4 T cell population. Our results suggest that individual members of the intestinal microbiota critically contribute to select the intestinal T cell repertoire and emphasize the role of few dominating species in the gut microbiota to focus the antigen specificity of gut T cells.

In parallel experiments, we profiled the antigen specificity of intestinal B cell populations. Screening a comprehensive panel of monoclonal antibodies derived from human gut plasma cells, we observed several monoclonal antibodies that show extensive cross-species reactivity. In most cases microbiota binding capacity of human IgA was lost upon germ-line reversion and did not correlate with polyspecificity. We postulate that in adult humans a system of affinity matured IgA dominates SIgA-microbiota interactions.

Session III

Nutrition after allogeneic hematopoietic stem cell transplantation I

Microbiome & nutrition – potential impact of intervention

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The intestinal microbiome is suggested to play an essential role in the regulation of human health and disease susceptibility. Human cohort studies demonstrated changes in gut microbiota composition and function in a variety of different pathologies including metabolic and inflammatory disorders, however, evidence for disease-related causality in microbiome changes is limited due to large variations as well as environmental confounders (e.g. diet, medication). Diet has profound effects on microbiota composition and function, but the role of diet-induced microbiome changes in therapeutic applications remain undefined. To extract functionally and clinically relevant information from microbiome changes in human populations, the combined information of prospective cohort and intervention studies in patients needs to be integrated. KORA is a regionally confined and prospectively followed population study with a focus on diet-related metabolic disorders. Permutational multivariate analysis identified 46 subject-related variables that significantly explained nine percent of the variations in gut microbiota profiles including diet and life style, metabolic parameters, medication and diseases. Predictive modelling identified microbial risk profiles associated with disease-related changes reaching a maximal accuracy of 78% for type-2 diabetes. Interestingly and in contrast to metabolic diseases, patient cohorts with Crohn's disease discretely clustered in the phylogenetic make-up of KORA. Fecal transfer from Crohn's disease into germ-free mouse models reproduced causality of microbe-host interactions in the pathogenesis of intestinal inflammation and identified bacterial risk profiles associated with sulfur metabolism. Considering diet as a modulator of microbiome changes, exclusive enteral nutrition drives therapeutic improvement in Crohn's disease patients, providing ample evidence for a protective role of nutritional intervention in inflammatory disorders of the intestine. Similar to the protective role of diet in metabolic disorders, the causal role of microbiome changes in mediating these beneficial effects remains to be elucidated. In conclusion, the stratification of diet-microbiome interactions in modulating health and disease requires integrated human and experimental studies to generate a better mechanistic understanding.

Principles of nutrition after allo-HCT

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Most patients present themselves in a relatively healthy nutritional status for allogeneic stem cell transplantation (HCT). Yet, patients may experience rapid deterioration of nutritional status upon treatment. Impaired nutritional status before and during transplantation is associated with lower overall survival as well as higher complication rates during treatment. In contrast to most disease-specific factors influencing outcome of allo-HCT, nutritional status is potentially modifiable through nutritional support. However, nutritional interventions compared to hydration only, did not demonstrate a benefit on clinical outcome, so far.

Current clinical research does not focus on closing this gap, but focuses on subtopics of nutritional support, e.g. energy requirements in HCT, composition of macro- and micronutrients, dosage of nutrients, route of administration or benefits of so called immunonutrients. Most studies performed, unfortunately, had small patient numbers or a retrospective design. Therefore, practice guidelines are missing the solid foundation needed. Naturally, acceptance and implementation of these guidelines in clinical practice is limited and variability of nutritional support, therefore, is broad.

In general, routine screening for risk of malnutrition is recommended to improve awareness of the team in charge and prompt nutritional support if indicated. Nutritional support then should be guided by a standardized algorithm to reduce variability the clinical approach within one center. Ideally, strategic algorithms should be consented by several centers or even internationally. Internationally accepted strategies improve comparability of results and ease future clinical research. The algorithm recommended by the EBMT will be demonstrated in the lecture “Nutrition during early transplant inpatient period”.

Although not scientifically proven, there is broad consensus on the importance of nutritional support among transplanting centers. Parenteral nutrition is used primarily to cover caloric deficits. Criteria to start or stop parenteral nutrition, however, vary among centers. Compared to chemo- and radiotherapy, nutritional interventions have less side-effects, yet might cause harm and influence clinical outcome negatively. Based on observations in critically ill patients inappropriate feeding in acute illness, in particular in inflammation, might cause metabolic stress and lead to impaired patient outcome. It is therefore crucial to deepen our understanding of metabolic processes in acute inflammatory states by further research to improve nutritional support in general and move towards a more personalized approach of support.

Current practice in nutrition after allo-HSCT

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Malnutrition is associated with an adverse prognosis after allogeneic stem cell transplantation (allo-HSCT). Therefore, nutrition is one of the major challenges in the post-transplant period. Only a few studies addressed the question of the optimal nutritional support in these patients. Even though there is a general agreement that the body weight and nutritional intake can be used to guide nutritional support and that enteral nutrition should be preferred. To document the current clinical approach in nutritional support, we designed a questionnaire concerning the current practice in nutrition after allo-HSCT and distributed it to centers performing allo-HSCT in Germany, Austria and Switzerland.

The survey was conducted from November 2018 to October 2019. Our questionnaire consisted of 24 questions. For evaluation and statistic purposes the majority of them were provided with predefined options. The first part was about nutrition during conditioning and the first month after allo-HSCT with regard to restrictions concerning oral nutrition of patients especially during the neutropenic phase. Furthermore, we evaluated the use of parenteral nutrition including the application mode and the initial trigger. The second part dealt with nutrition in intestinal graft-versus-host disease (GvHD) including the use of special diets (gluten or lactose-free) and/or food supplements. Finally, we addressed questions towards special laboratory testing and the experience with food-associated infections. Hereafter, we summarize some of the results.

The majority of centers offer special nutrition during the phase of neutropenia but permit patients to have food prepared by their relatives at home applying special hygienic guidelines. Also the trigger for parenteral nutrition directly after allo-HSCT seems to be consistent; parenteral nutrition is usually started if the oral nutritional intake or the bodyweight falls below a certain limit. However, the daily practice concerning the combination of parenteral and oral nutrition, as well as the actual provided food in detail (i.e. fresh salad and tea) differs significantly. In the setting of GvHD the current practice appears to be more heterogenous. Only half of the centers follow a special diet, adding food stepwise modulated by GvHD symptoms. Additionally, the use of special food supplements and application of gastric tubes to permit enteral nutrition differs considerably between the centers. In contrast, the majority of centers apply a lactose-free diet in patients with gastrointestinal GvHD during the phase of food-reintroduction. Only half of the centers are measuring vitamin levels on a routine basis and if so measure vitamin B_{12}, 25-hydroxyvitamin D (25[OH]D), and folic acid together. Finally none of participating centers has ever seen a food associated infection during hospitalization, whereas some food associated infections have been seen in the out-patient clinic. The detailed results of the survey will be presented to provide participants with insight into current practice in nutrition after allo-HSCT in Germany, Austria and Switzerland. Furthermore, the survey will add to the development of nutritional guidelines for patients after allo-HSCT.

Session IV

Nutrition after allogeneic hematopoietic stem cell transplantation II

Nutrition after allo HSCT – hygiene aspects

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In 2010, the German Commission for Hospital Hygiene and Infection Prevention (KRINKO) published recommendations concerning infection control and prevention (ICP) efforts during clinical management of immunocompromised patients. These recommendation focused on cancer patients with neutropenia and defined 3 risk groups. The KRINKO recommendations have recently been reevaluated by a KRINKO working group comprising clinical experts for pediatric and adult hematology and oncology (including stem cell transplantation), ICP and infectious diseases. Taking the current published evidence into consideration, the working group strongly argued against any kind of “neutropenic diet” due to the missing clinical benefit and to the inconvenience for patients and their families. In contrast, the new recommendations emphasize the outstanding role of education and training in immunocompromised in- and outpatients, promoting basic elements of food hygiene. Concerning case reports and case series with bloodstream infections caused by the same species, the safety of probiotics, which might alleviate symptoms and accelerate clinical convalescence in patients with chemotherapy- or radiotherapy-induced mucositis and diarrhea, remains still an unresolved question.

Nutrition during early transplant inpatient period

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Patients undergoing hematopoietic stem cell transplantation (HCT), particularly allogeneic transplantation are at risk for malnutrition. Most patients are well-nourished or even overweight upon admission to HCT, but experience rapid deterioration of nutritional status during treatment. Weight loss results from a complex interplay of toxic, inflammatory und immunological mechanisms leading to caloric deficits by anorexia as well as a catabolism of the metabolism. Nutritional support is meant to reduce caloric deficit and reduce the risks for negative metabolic effects. This hypothesized benefit, however, has not been proven so far. Due to a lack of large-scale, randomized controlled trials (RCTs) international recommendations e.g. by the European Society of Parenteral and Enteral Nutrition (ESPEN) are primarily based upon physiological considerations and result from observational and small interventional trials.

To homogenize clinical management, nutritional support according to a standardized algorithm is recommended. Screening for malnutrition at admission to transplantation as well as repetitive reevaluation of nutritional status during hospitalization is key to improve awareness of patients at higher risk and facilitate early adaptation of nutritional support. According to the ESPEN guidelines nutritional interventions should be started if oral caloric intake falls below 60–70% of basic requirements for three days consecutively. Nutritional support should preserve normal gastrointestinal paths as long as possible. Therefore, fortification of oral foods and oral nutritional supplements should be implemented first. In case of persistent insufficient caloric intake, enteral and parenteral nutrition should be evaluated. Enteral nutritional support has been evaluated in small prospective trials and might have beneficial effect on overall survival, acute graft-versus-host disease and neutrophil engraftment, yet results have to been proven by larger RCTs. Safety and feasibility in children and adults seem to be solid enough in order to recommend enteral instead of parenteral nutritional support as second step of the algorithm.

Immunonutrients started to gain attention as supplements to ordinary macro- and micronutrients. So far, they are understudies in RCTs or did not show a protective effect on overall survival.

The concept of a low-bacterial diet has been proposed by theoretical reasons. Yet, current data from large observational studies did not show a benefit in comparison to a save food handling concept. To broaden the food palette of transplanted patients without risking food-borne infections is an important tool to reduce anorexia in this patient population.

As most of the current recommendations rely on small or retrospective trials, further research is needed in order to improve patient outcome. We need better understanding of pathophysiological mechanisms during acute states of illness and inflammation and concomitantly, have to work towards a more personalized approach in nutritional support.

Nutrition and intestinal GvHD

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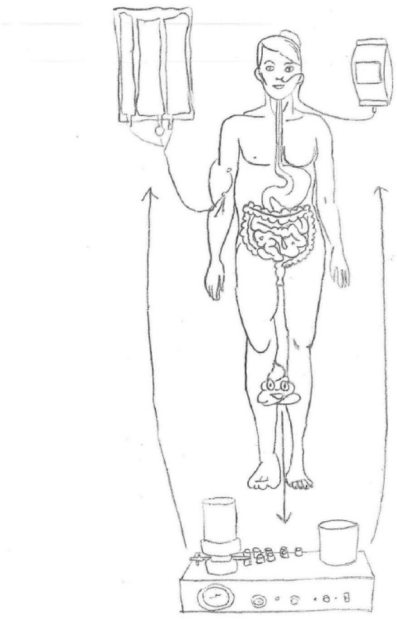
Severe graft-versus-host disease (GvHD) is an important complication after allogeneic stem cell transplantation (allo-SCT). Intestinal GvHD occurs in approximately 30% of the patients [1]. Inflammation and other intestinal GvHD-related complaints as dysphagia, abdominal pain, anorexia and intolerance of oral and/or enteral nutrition can reduce the nutritional status, due to insufficient intake of energy and macronutrients [2]. Malnutrition is also encouraged by loss of nutrients due to excessive vomiting or severe diarrhea, and is an independent risk factor of poor prognosis, such as increased length of hospital stay and transplant-related mortality, decreased overall survival [1, 3]. Diarrhea can rise to 5–6 liters per day [4] and may, among other things, result in dehydration, loss of electrolytes and proteins, malabsorption of protein and fat [2]. Management of intestinal GvHD includes therefore nutritional support and maintenance of fluid and electrolyte balance.

The general rule is: ‘If the gut works: use it!’. But does the gut work in intestinal GvHD? Various diagnostic markers may be useful in objectifying and quantify malabsorption and determine nutritional policy. The dietician can, as part of a multidisciplinary team, play an important role in the treatment of this complex patient group.

In this lecture, Inge Dekker, MSc, clinical dietician in Amsterdam UMC, the Netherlands will give an overview of nutrition and intestinal GvHD and the role of the dietician.



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Nutrition of immuno-compromised outpatients

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Immuno-compromised patients are more susceptible to food-associated infections and food hygiene becomes highly relevant. This includes the conditions and measures necessary to ensure the safety of food from production to consumption. Criteria to define this patient group vary but frequently include a granulocyte count of less than 0.5 or less than 1.0 G/l. The risk of bacterial and fungal infections is raised significantly with neutrophils below 0.5 G/l and increases with the duration of neutropenia; a higher limit of 1.0 G/l granulocytes is used frequently to recommend specific dietary restrictions but is not based on reliable epidemiologic or clinical data. Unfortunately, there are no uniformly adopted international nor national guidelines on nutrition in immuno-compromised patients. Thus, recommendations may still vary among centers.

Specific “neutropenic” or “low-bacterial” diets prohibiting all fresh fruits and vegetables have been prescribed regularly by most centers for many years since the initiation and establishment of hematopoietic cell transplantation. This policy, however, has been challenged repeatedly during the last 10 years and more liberal rules for food selection have been adopted by many centers. The reason for this has been the persistent failure to demonstrate a clear benefit and a lower incidence of infections for strict avoidance-based diets if strict rules of food hygiene were followed. In fact, in some trials, neutropenic diets were associated with an increased rate in diarrhea and infections.

Measures to ensure food hygiene are described and explained by national health agencies and are based on reliable hand-washing (> 20 sec) and cleaning of foods (wash under running water for > 30 sec), completely separating raw and cleaned/prepared foods, adequately chilling stored foods before preparation (short-term < 4 °C, long-term < -18 °C) and adequately cooking foods (> 70 °C, keeping warm at > 60 °C). Following these rules, patients may consume all animal products if completely cooked or pasteurized, raw fruits and vegetables washed thoroughly if smooth-skinned or washed and peeled.

In addition to strict food hygiene, in patients with severe neutropenia < 0.5 G/l, most centers still recommend avoiding foods with a very high risk of carrying potential pathogens, e.g. raw meat, fish, eggs or similar products, unpasteurized milk, soft non-pasteurized or blue old cheese, raw sprouts and to avoid public salad bars. After granulocyte recovery and in the outpatient setting these restrictions may be loosened while standard measures for food hygiene need to best be adopted life-long. Always, patients should be counselled to consume adequate amounts of energy, vital nutrients and water.

Session V

Nutrition and microbiome after allogeneic hematopoietic stem cell transplantation – Conclusions

Aspects of nutrition, the microbiome and intestinal GvHD (iGvHD) in PEDs & AYAs

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The correlation of HSCT-patient characteristics, nutritional assessment, dietary exposures and the gut microbiota with transplant-related complications has attracted increasing scientific interest. In contrast to the efforts to understand the genetic and microbial background of iGvHD there is less data on pediatric/adolescent patients in this context. The aim of this presentation is to provide an overview on specific aspects regarding nutrition, gut microbiota and iGvHD- or comparable clinical conditions.

Nutrition: Various guidelines regarding the evaluation of malnutrition and nutritional support have been published but there is a lack of randomized controlled studies and and broad variability in current clinical practice, which has been recently addressed by an expert workshop on behalf of the EBMT-PD-WP. Evidence shows that pediatric – similar to adult – iGvHD is associated with malnutrition and loss of lean body mass correlating with dismal clinical outcome. Critically ill children are more vulnerable because of their intrinsic lack of endogenous stores and greater baseline requirements. Adequate nutritional support, preferably attempting enteral nutrition over parenteral nutrition first, is a supportive measure most recommendations agree upon. In this context the unicentric experience of two nutritional treatment modalities, which are in use at our transplant unit will be provided: exclusive enteral nutrition and Moro's carrot soup. Adherence of microorganisms to the intestinal mucosa is mediated by carbohydrate structures and can be blocked by carbohydrate receptor analogues. Moro's carrot soup contains acidic oligosaccharides, which are able to block adherence of various enteropathogenic microorganisms to HEp-2 cells and human intestinal mucosa in vitro.

Microbiome: Although the knowledge about the composition of the microbiome is progressing rapidly, gaps exist about the functional capacity in correlation with age and diseases. The intestinal microbiota modulates within the first 2–3 years of life (being exposed to more infectious diseases) and thereafter remains more stable in an adult-like abundance. Significant differences between AYA and adult microbiota have been less well described. Importantly, environmental and disease related factors determine the microbiota composition. Increasing data suggest an association between severe and/or chronic diseases with pediatric age-related gut microbial dybiosis. In what way the specialty of PED/AYA-HSCT with numerous non-malignant diseases (e.g. severe combined immunodeficiencies) impacts dysbiosis with or without iGvHD remains unclear; recent data suggest an association between antibiotic-related depletion of anti-inflammatory clostridia and pediatric iGvHD.

The interplay of these thematic domains in the context of non-malignant versus malignant HSCT in PEDs/AYAs is likely to be useful for future research questions.

“How we feed” – based on evidence in nutrition

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Although increasing evidence supports the crucial relevance of the nutritional status of patients with critical conditions including patients with treatment of malignancies with enteral nutrition being the preferred mode, the current routine practice in allogeneic hematopoietic stem cell transplantation (allo-HSCT) falls behind focusing more on avoidance of enteral infections by nutrients and broad application of parenteral nutrition during the early phase of transplantation. While undoubtedly prevention of infections by nutrients is crucial some of the practice pattern applied in the past may have interfered with enteral nutrition. Lack of oral nutrition has been already associated with dysbiosis, higher incidence of infectious complications (as shown by preliminary data in allo-HSCT and demonstrated in detail in other diseases) and potential higher frequency of acute graft-versus-host disease (aGvHD). In consequence, the German Commission for Hospital Hygiene and Infection Prevention (*Kommission für Krankenhaushygiene und Infektionsprävention,* KRINKO) already developed new hygiene standards promoting oral intake in neutropenic patients. Therefore, strategies have to be applied to preserve enteral nutrition and parenteral nutrition is required if hypocaloric oral intake manifests. While the latter practice is in consensus with all transplant centers daily practice varies considerably.

First of all, the quality and quantity of oral nutrition of inpatients has been largely ignored for years resulting often in a relative inflexible standard set of meals not necessarily reflecting the individual needs of transplant recipients with special hygiene requirements further narrowing the menu. The increasing evidence on the crucial role of nutrition in health including the impact on the microbiome further supports a well-balanced oral diet which should also contain natural probiotics and possibly prebiotics and vitamins in addition to provision of calories. Secondly, since the oral intake and calorie need usually varies considerably over the course of allo-HSCT daily monitoring during the inpatient phase and regular nutritional assessment during follow up is required.

An area of interest requiring further research is the oral nutrition of patients with gastrointestinal aGvHD. Traditionally, patients were switched to parenteral nutrition only which is not supported by evidence but may be required in high grades of aGvHD in case of severe pain or cramps. In general, guidelines for nutrition of patients with maldigestion and -resorption and/or inflammatory bowel diseases should be followed and increasing evidence supports the avoidance of lactose containing food since inflammation of the intestinal tract frequently results in lactase-deficiency and experimental data point to a potential negative impact of an excess of lactose on a protective microbiome. Whether gluten free nutrition positively impacts gastrointestinal aGvHD has not been studied yet and may only be required in proven gluten intolerance until further evidence is generated.

In summary, the increasing knowledge of the potential role of nutrition and the microbiome in health including allo-HSCT mismatching with scientific clinical evidence urges the clinical community to perform trials evaluating interventions to improve the outcome of allo-HSCT taking into account that nutritional interventions usually come along with low costs compared to overall costs of allo-HSCT including treatment of GvHD.

“How we treat” – based on the microbiome

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Although evidence for a major role of microbiota dysruption in complications of HSCT is convincing and clinical associations with complications such as GvHD have been confirmed on a functional level in experimental models, clear translation in therapeutic or even prophylactic strategies is still missing and just enters the stage of clinical trials.

Classical ***probiotics*** have been suggested to modulate microbiota and modulated GvHD in experimental models, but randomized clinical trials with ***Lactobacillus GC*** failed to show beneficial effects. This may be explained by absence of true commensal anaerobic bacteria in these preparations or by the timing of probiotic use in these trials. Thus, currently ***FMT*** (fecal microbiota transplantation) of whole donor microbiota is the only broadly available option of direct microbiota transfer. While single center trials suggest efficacy in treatment of steroid-resistant GvHD and safety when applied as a prophylactic approach, propective multicenter trials are needed to confirm these observations, and maximal safety issues have to be considered in heavily immunosuppressed GvHD patients. Transfer of ***specific consortia*** might substitute FMT in the future, but needs more detailed knowledge about the specific functions of individual strains.

Prebiotics such as bacterial metabolites (Indoles/SCFA) show promising results in experimental models, but have not been translated into patients, partially due to the difficulty to deliver metabolites to the required sites.

Currently, more restricted use of prophylactic or therapeutic antibiotics seems to be the most realistic approach to modulate microbiota, but this has to be balanced against the individual risk of infections, and again, randomized trials are missing. Nevertheless, microbiota protection should be an additional goal of ***antibiotic stewardship***. Selective protection of the gastrointestinal microbiota during systemic application of antibiotics is currently developed and includes either strategies of general neutralization or enzymatic destruction of specific groups of antibiotics.

Deeper understanding of mechanisms of dysbiosis associated damage by deeper characterization of bacterial strains and strain specific host-microbiota interactions should help to develop more specific interventions in the future.

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