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Original article

Oral nutritional support to adult patients with acute intestinal Graft Versus Host Disease (GVHD): A proposal for dietary intervention as a model to clinical trials

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SUMMARY

Background: Acute Graft Versus Host Disease (GVHD) affects about 20%–80% of the patients after the hematopoietic stem cell transplant (HSCT) and it is amongst the main causes of morbidity and mortality both in children and adults. The intestine is one of the most affected organs by GVHD causing important alterations in the nutritional status and quality of life, considering that the dysfunctional intestine could decrease food intake as well as an inappropriate dietary plan could worsen the clinical condition. In addition to GVHD, chemotherapy conditioning regimen suppresses the immune system, promotes mucositis and increases the risk of infectious complications. Taking the above into consideration, when per oral diet is possible; the food choices should be carefully planned and monitored to promote nutritional support and avoid worsening the intestinal function and clinical condition.
Objective: This work was aimed to present a practice guideline proposal, to be validated, based on literature review, regarding to oral dietary recommendations for acute intestinal GVHD after HTSC.
Methods: Two research phases were defined: Phase one: evidence-based literature review; Phase 2: Practice Guideline Proposal.
1: Evidence based literature review
Search methods: A literature review (1997–2019) was performed including PubMed, in English, and Lilacs, in Portuguese electronic database to address the subject of dietary intervention for intestinal GVHD related to the HSCT, with children and adults, whose receiving oral or tube feeding nutrition therapy.
Selection criteria: The study selection was based on the PRISMA method. Controlled clinical trials were searched. Randomization was not possible considering the rare condition.
Data collection and analysis: Two independent authors assessed the abstracts of the selected studies to determine the articles feasible to compose the review as the base to elaborate the practice guideline proposal protocol, object of the present study. To determine the level of evidence of the selected article, GRADE criteria were used.
Main results: One controlled clinical trial study was included. The study was developed in Japan with a total of 35 patients. The dietary plan was characterized by gradual increasing food consistency/density. They found better nutritional parameters in the treated group, however, following GRADE criteria, we rated the quality of evidence as very low.
Authors' conclusions: We could not demonstrate confidence in the effect estimate based on the selected study. However, considering the lack of literature information and the relevance of the topic, we decided to proceed and propose a practice guideline for an oral diet protocol for acute intestinal GVHD as a reference to be a starting point to validate protocols in future clinical trials.
2: Practice Guideline Proposal
The criteria to elaborate the protocol were based on the RIGHT Statement. In addition to the literate information about diet and intestinal health, recommendations already adopted in the Service of Bone

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Marrow Transplant in the Complex Hospital of Clinics of Curitiba, in the state of Paraná, Brazil, were also considered.

1. Introduction

One of the most serious condition related to mortality after hematopoietic stem cell transplant (HSCT), in addition to disease relapse, is the acute Graft Versus Host Disease (GVHD) [1,2]. The intestine is one of the most affected organs by GVHD, leading to a severe diarrhea, which may exceed the volume of 2 liters a day and may also be accompanied by bleeding and severe abdominal pain. Consequently, there is a reduction in the absorption of nutrients, zinc deficiency, reduction in the dietary intake, metabolic disorders and malnutrition [3–5].

Nutrition has a fundamental role in the treatment of intestinal GVHD and may contribute to the preservation of the nutritional status and to promoting quality of life. However, the diet must be cautiously introduced not to worsen the symptoms and to provide a step manner introduction of selective nutrient sources, however, to our knowledge, there is no guidelines or consensus indicating the best approach to manage this dietary intervention.

This work was aimed to organize practice recommendations in order to indicate adjustments on the oral diet for acute intestinal GVHD as a model for future controlled clinical trials. The focus is to manage the gastrointestinal symptoms that affect food intake and nutrients absorption that affect nutritional status to decrease mortality risk amongst patients with acute intestinal GVHD after bone marrow transplantation.

2. Methods

2.1. Literature review

The literature review was based on the research question: The restriction of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs), dietary and functional fibers, fat, caffeine and other intestinal excitants is able to minimize symptoms amongst patients with acute intestinal GVHD after hematopoietic stem cell transplant (HSCT)?

To answer this question, clinical trials were used and the outcomes selected were: Nutritional status, adverse effects, and intestinal symptoms.

2.1.1. Search strategy

The electronic database search included PubMed, in English, and Lilacs, in Portuguese, with the following descriptors: nutritional support (suporte nutricional), diet (dieta), graft versus host disease (doença do enxerto contra o hospedeiro), intestines (intestine), and nutritional support (suporte nutricional). Articles which address the subject of dietary intervention for intestinal GVHD related to the HSCT, with children and adults, whose receiving oral or tube feeding nutrition therapy, published between 1997 and 2019 were included. Review articles and use of probiotics were excluded. The study selection to elaborate de guideline was based on the PRISMA method [6]. The type of studies searched were controlled clinical trials and the participants were children or adults with intestinal GVHD.

2.2. Practice guideline proposal

The Practice guideline proposal was based on the RIGHT Statement [7]. In addition to the literature information about diet and intestinal health, recommendations already adopted in the Service of Bone Marrow Transplant in the Complex Hospital of Clinics of Curitiba, in the state of Paraná, were also considered.

The main goal of the proposal was to define inclusion and exclusion criteria to prescribe oral diet for acute intestinal GVHD, during the transition from parenteral nutrition to oral nutrition, as well as to indicate food choices to preserve intestinal health and nutritional status in a step-up manner.

3. Results

3.1. Evidence based literature review

A total of 448 abstracts were identified via the electronic search strategy. Of these, 203 were duplicated, and 181 were found to be ineligible for inclusion due to inappropriate topic or non-data based papers (e.g. reviews, topic discussions). From the remaining 58 papers, 11 were considered not eligible after the summary reading. After complete reading of the articles, one remaining study met inclusion criteria [8].

PRISMA diagram (Fig. 1) was utilized to select the eligible articles according to the research question and design as follow.

3.1.1. General features of included study

The search in the databases resulted in 1 article [8], published in 2006, referring to the proposed subject. The work developed in Japan consisted of a longitudinal clinical trial study aiming to test the feasibility and nutritional benefits of a gradual progression of an oral diet for patients with intestinal GVHD as compared to patients receiving total parenteral nutrition.

3.1.2. Study groups and treatment

Seventy seven patients were selected and, after exclusion criteria were applied such as intestinal bleeding, intestinal obstruction, severe pancreatitis or cytomegalovirus enterocolitis, a total of 35 patients, with ages between 22 and 69 years old, were enrolled in the study. They had GVHD diagnosed with biopsied specimens and clinically diagnosed as stage I to III gut GVHD. The symptoms occurred within 100 days after SCT 17 patients (48%) who developed GVHD before July 2002 were treated with Total Parenteral Nutrition (TPN) and nothing per oral (NPO), while the 18 patients (52%) who developed GHVD after July 2002 were treated with oral diet, gradually introduced in 6 steps (programmed GVHD dietary intervention).

3.1.3. Intervention characteristics

The dietary plan was characterized by gradual increasing food consistency/density (from liquid to solid) and the assessment of the acceptability considering intestinal digestion was performed. In a step-up manner, foods were made more solid and dense and, to

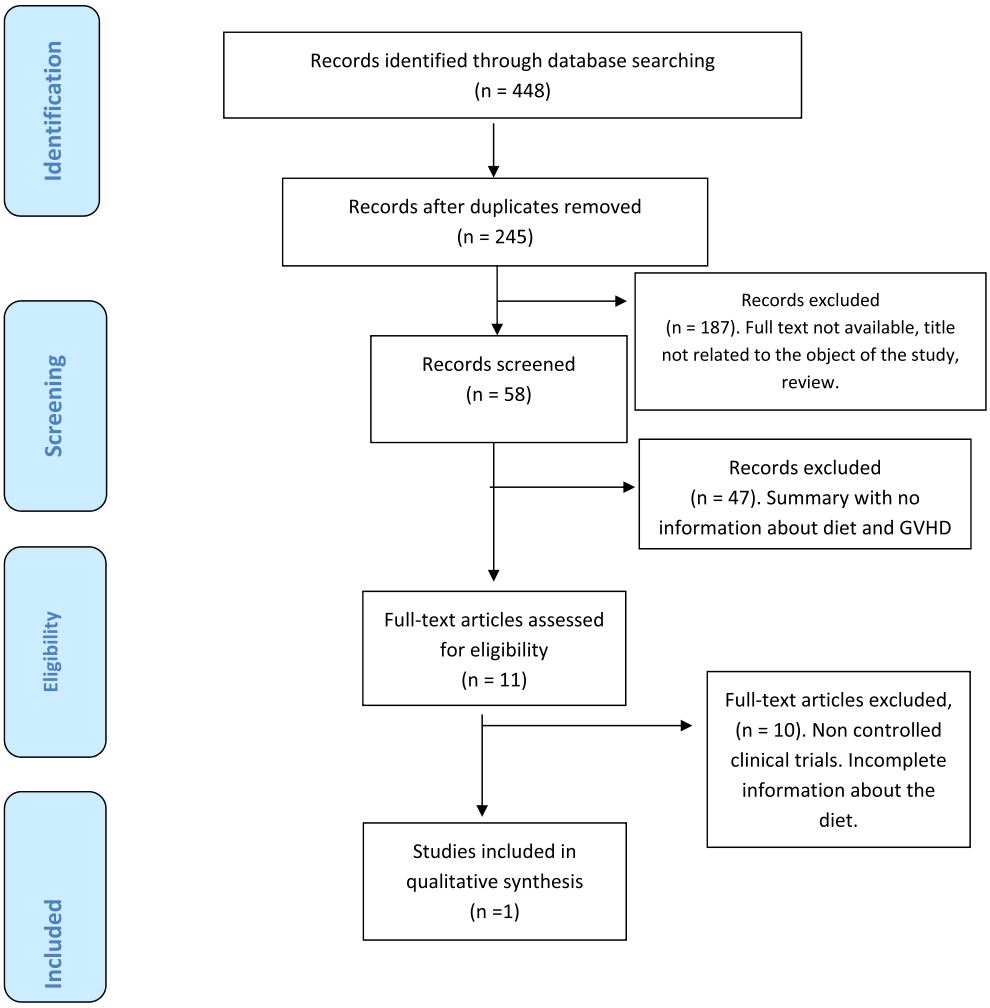

Fig. 1. PRISMA diagram. Used to select publications related to nutritional support and oral diet applied to patients with intestinal GVHD related to the HSCT; published between 1997 and 2019. The electronic database search included PubMed and Lilacs.

pass from one step to the next, the symptoms should be stable for at least 3 days. If the symptoms got worse, the diet went back to the previous step and, in the case of more severe symptoms such as nausea, vomiting and abdominal pain, the diet was interrupted and NPO was applied.

3.1.4. Main outcomes and statistical analysis

The outcomes analyzed along 29 days of follow-up were: mean volume of diarrhea, mean frequency of diarrhea, change of body mass index, and change in serum albumin level. The net values were considered and ANOVA was applied to verify de mean differences between groups along the follow-up time. In addition, time to complete dietary recovery was analyzed with a time-event cumulative curve, and the log-rank test was used to compare groups considering the time period up to 80 days and the percentage of diet recovery considering 100% a total recovery. $P \leq 0.05$ was considered as the type I error.

In the study described here, the oral diet was introduced gradually and, in general terms, the features of the evaluated diet consisted of low amount of fats, lactose, fibers, acids and gastrointestinal irritants, with protein restriction at the first moment. The diet used as well as the results of the study is detailed in Table 1.

3.1.5. Oral progressive diet as intervention for patients with GVHD related to the HSCT

To explore the quality of evidence we based our analysis on GRADE criteria [9].The research question was clearly present in the study and was formulated according PICO model. The researchers identified the patients, the intervention describing treatment and control group, as well as the outcomes. Although the selected outcomes were considered surrogate outcomes, we considered them to be important since the gastrointestinal symptoms of GVHD result in undernourishment and increase risk of mortality.

Based on the decrease in BMI and better maintenance of serum albumin in the treated group (EN) as compared to de TPN group, we considered that EN diet showed some evidence of preserving nutritional status of intestinal GVHD patients. However, we rated the quality of evidence as very low due to the following:

1 There is no indication that the study sample was randomized, increasing the risk of bias. Although there were no essential differences between groups in the baseline, as stated by the authors, there is no indication of any statistical analysis demonstrating that the groups were homogeneous.
2 There is no indication of the criteria used to determine the sample size; the power of the analysis was not presented as well as effect size.

Table 1
Description and main findings of a dietary protocol tested by Imataki et al. [8] to introduce oral intake amongst patients experiencing GVHD after HSCT.

Author/year	Intervention step by step	Results
Itamaki et al. (2006)	1st step: only liquids, such as percolated juices and electrolyte solutions 2nd step: water and starch porridge, clear soups and misso 3rd step: start the introduction of solids like potato, vegetables, canned fruit, vegetable juices, pasta, tofu and white fish 4th step: rice porridge, eggs, bread, banana and apple 5th step: cooked rice, other types of fish, oil (3 g/day) 6th step: rice prepared with oil, chicken, yogurt, oil (8 g/day)	- Better nutritional parameters. The decrease in body weight and serum albumin was lower in the exclusive oral diet group during the treatment ($p < 0.001$); - There was no difference between groups in relation to diarrhea volume; frequency and - There was no difference between groups at time to complete dietary recovery.

3 The follow-up time started in different periods for each study group as stated by the author as a limitation
4 The statistical analysis to compare means (control group vs treated groups) did not consider adjustments for potential confounders related to the nutrient input such as fasting time and dietary energy intake.
5 Imprecision was present considering a wide variation between patients regarding to volume and frequency of diarrhea and body weight as informed by the authors. The confidence intervals or standard deviations from the mean were not informed in the paper.

3.1.6. Conclusion

More studies, especially randomized controlled clinical trials are needed to give support to introduce a step-by step oral diet in the case of transplanted patients affected by acute intestinal GVHD.

3.2. Practice guideline proposal

In spite of the lack of studies in the literature, the findings in the analyzed work at the literature review phase showed that the oral diet for patients with acute intestinal GVHD might be feasible and do not worsen the clinical and nutritional status. Thus, considering the relevance of suggesting safe approaches to offer per oral nutritional support to patients at risk of mortality due to acute GVHD intestinal symptoms, we decided to elaborate a guideline reference as a starting point to validate protocols in future clinical trials.

The recommendations are focused on hospitalized patients undergone bone marrow transplantation and affected by acute intestinal GVHD at specialized units and followed by a multiprofessional team. It is important to mention that all the recommendation is based on the transition from parenteral to oral nutrition.

The intended guideline audience are nutritionists and physicians responsible for the acute intestinal GVHD dietary transition treatment from parenteral to oral feeding after bone marrow transplantation, whose prescribe the diet and follow the clinical evolution of the patients in a daily basis. The protocol should be considered a "to validate" proposal as a reference for a step-by-step dietary intervention research protocol in order to avoid long periods of fasting and increased risk of undernourishment due to the nutrient and water intense loss, characteristic of intestinal GVHD diarrhea. Should be applied as part of tertiary health care.

The group involved in the development process of this guideline was composed by: two nutritionists responsible by the nutritional assistance and one physician responsible for the clinical assistance at then Bone Marrow Transplant Service of the Complex Hospital of Clinics UFPR, Curitiba, PR, Brazil – Denise Johnsson Campos (MSc); Geovana Carla Chiconato (BS) and Vaneuza Araújo Moreira Funke (MD), respectively; two professors at the Department of Nutrition of the Federal University of Paraná (UFPR), Curitiba, PR, Brazil – Ana Cláudia Thomaz (MSc) and Regina Maria Vilela (PhD).

Suggested title to the practice guideline proposal: Dietary practice recommendation proposal: After HCST oral diet for acute intestinal GVHD (odai-GVHD).

The dietary practice recommendations proposal (Table 2) to minimize symptoms amongst patients with acute intestinal GVHD after hematopoietic stem cell transplant (HSCT) were elaborated taking into consideration that oral food intake could preserve nutritional status as long as gluten, low fermentable carbohydrates such as oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP), dietary and functional fibers, fat, caffeine and other intestinal excitants were restricted [10–12].

Considering that patients undergone bone marrow transplantation have their immune response suppressed by the treatment, food should be prepared in special facilities with sanitary conditions to decrease bacterial activity. The food choices presented were based on the dietary usually present in Brazilian hospitals, which are similar to the basic choices in American and European hospitals. The costs involved providing the food supplies and machinery to process them would have, if so, very low impact on the hospital budget. Specific staff training would be necessary; however, considering that the need of parenteral nutritional could decrease by the increase of oral intake, the costs involved in the training would be minor. Considering that, we understand that cost-effectiveness would be suitable.

Some basic and fundamental aspects should be emphasized when choosing the food options along the treatment: 1- the suggested oral diet does not replace parenteral nutrition, especially when there is undernourishment 2- the patients are under low immune competency and the intestines are debilitated due to the disease and its symptoms; 3- The diet should not have foods with high fiber content, mainly insoluble fibers; the food should be treated to decrease the bacterial load at the maximum, giving especial attention to the fresh ones; the FODMAP content and other causes of abdominal pain or discomfort due to bacterial fermentation or other food characteristics should be avoided; risk of bacteria intestinal translocation should be addressed by the multiprofessional team.

It is suggested that the steps are progressed in accordance to symptoms stability (as part of the physician care) for, at least, 3 days and the serving sizes should be controlled according to diet individual tolerance at each meal (checked as part of the nursing care). Body weight should be daily recorded. Additionally, the nutritionist should assess daily total energy and protein intake and proceed with periodical complete nutritional assessment. Moreover, the criteria to start oral intake, interrupt or end the process should be careful observed as following:

1 Inclusion criteria. The odai-GVHD should be introduced, in addition to parenteral nutrition, when patients develop stage II to IV gut GVHD, and only after careful clinical and nutritional condition assessment.

Table 2
Dietary practice recommendation proposal: introduction of oral diet following parenteral nutrition for acute intestinal GVHD after bone marrow transplant.

Oral diet for acute intestinal GVHD feed transition (odai-GVHD).			
Step	Features	Food	Do not use
Step I: Stage II to IV acute intestinal GVHD and only after clinical assessment. When diarrhea volume is 1000–2000 mL)	Only liquids Animal-protein and vegetable oil free	Boiled natural percolated peeled fruit juices 50% diluted with water (melon, pineapple, passion fruit, low acidity orange-lime, raspberry and blueberry) Percolated water Coconut water Clear teas (chamomile tea) Isotonic drinks for oral rehydration (sugar free)	Honey, sucrose and alcoholic sweeteners (polyols such as sorbitol and xylitol) Additive and conservative added industrialized juices Carbonated beverages Coffee and alcoholic beverages Milk, cheese, eggs, meat or processed animal proteins Coconut oil or milk Nuts milk
Step II: After 3 days of symptoms stability, and diarrhea volume <1000 mL or 20 mL/kg/body weight	The same options of Step I and gradual introduction of cooked meals very low in dietary fibers such as peeled and well-cooked vegetables served in small pieces and/or creamy consistency after smashing or grinding them. Gluten free meals and poor in FODMAPS vegetables. Animal-protein free and low vegetable oil Salt addition is allowed.	Allowed (always prepared with percolated water): Well-cooked rice, noodle rice, quinoa pasta, corn flour (water should be added to achieve a very soft consistency). Bread and simple gluten free biscuits. Sugar free Corn flakes and rice crisps. They should be offered with the liquids mentioned in step I Rice milk. Well-cooked or baked peeled with no seeds vegetables. Allowed: zucchini, carrot, chayote, eggplant, tomato, pumpkin, soft potato with low fiber (English potato). Peeled, with no seeds, fresh fruit: not very ripe banana. Additives: Sucrose (5 g/meal a day)	Honey and alcoholic sweeteners (polyols such as sorbitol and xylitol) Additive and conservative added industrialized juices Carbonated beverages Coffee and alcoholic beverages Coconut oil or milk Milk, cheese, eggs, meat or processed animal proteins Spices and fatty sauces Fried foods
Step III: After 3 days of symptoms stability, and diarrhea volume <500 or 10 mL/kg/body weight	The same options of Step II and gradual introduction of: Solids with low fat, easily digested proteins Vegetable oil (olive oil, soybean oil, sunflower oil) as part of the cooking process (1 soup spoon/day or 8 mL)	Allowed (always prepared with percolated water): Cooked or baked skinless fish; cooked or grilled skinless chicken and turkey, boiled/scrambled eggs; lactose-free cow's milk; Lactose-free supplements. Well cooked vegetables allowed: spinach and celery, green beans, bamboo shoots, bean sprouts, beets, sweet potato, lentils (fresh or canned), green spring onion Lactose-free butter (1 teaspoon/day). Peeled fresh fruit: apricot, pineapple, melon, banana (thin peel should be avoided due to the risk of bacterial contaminants)	Honey and alcoholic sweeteners (polyols such as sorbitol and xylitol) Additive and conservative added industrialized juices Carbonated beverages Coffee and alcoholic beverages Spice and fat sauces Regular milk and cheese Processed animal proteins High fat animal proteins Fried foods
Step IV: After 3 days of symptoms stability and no intestinal symptoms Step that should achieve 70% of dietary daily needs (energy and protein)	The same options of Step III and gradual introduction of: Solids with red meat. Tofu and lentil	Well-cooked ground beef and mutton. The options mentioned in step I to III can be gradually cooked to a firmer consistency.	Honey and alcoholic sweeteners (polyols such as sorbitol and xylitol) Additive and conservative added industrialized juices Carbonated beverages Coffee and alcoholic beverages Spice and fat sauces Processed animal proteins High fat animal proteins Fried foods

2 Criteria to step-down the diet evolution: abdominal pain and/or increased diarrhea volume (approximately 20%). Persistent nauseas or vomiting.
3 Criteria to interrupt oral diet: severe abdominal pain, intestinal bleeding, fistulae, severe impairment of gastric and colonic function (paralytic ileus).
4 Other clinical criteria should be considered as a result of the physicin assessment.

Important: the following protocol should be tested only as part of randomized clinical trials after the team responsible for the patients care carefully and critically analyze its characteristics and the feasibility of applying the recommendations according to the population assisted and hospital resources in order to guarantee its safety as stated by Ethics Committees. As mentioned before, we do not find evidence-based research on this matter to be strong enough to recommend its use as part of the treatment of hospitalized patients so far.

Oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP); excitants, insoluble fibers and hyperosmolar restricted diet to apply to hospitalized patients experiencing the transition between parenteral nutrition to oral feeding during acute intestinal GVHD after HSCT. The food consistency and choices should be offered in a step-by-step manner according to individual tolerance to be checked at each meal as part of nursing care. Oral industrialized supplements should be an option as long as lactose free and with low osmotic activity. The supplements could be present in all stages mentioned, especially in the first stage and should be offered

according to the decision of the physician and nutritionist based on previous protocols. Total energy and protein intake should be daily registered by the nutritionist. This proposal is a model to be validated.

4. Discussion

In spite of the importance of the subject, few studies have tested the effects of the oral diet in the acute intestinal GVHD. The literature suggests that the TPN should be used exclusively in patients with acute intestinal GVHD until the stool volume reduces to 8–10 mL/kg/day and severe abdominal pains decrease [13–15]. However, studies show that the stimulus of enteral nutrition is important to preserve gastrointestinal mucosa and immune response, in addition to keep gastrointestinal motility [16].

As the evidence of effective dietary protocols for acute intestinal GVHD is scarce, dietary recommendations to other clinical conditions which lead to severe diarrhea could be one strategy to be based on when assisting HSCT patients. Patients with active inflammatory bowel disease would rather consume easily absorbed carbohydrates, besides the reduction of organic acids, omega 6 fatty acids, saturated fats, animal protein and food additives which can increase irritation of the intestinal mucosa [17]. The low-content FODMAP diet has also been used as a therapeutic option for patients with Irritable Intestine Syndrome (IIS) as it can reduce gastrointestinal symptoms and diarrhea, as observed by Halmos et al. [18] in a randomized study with 30 patients with IIS who adhered to a diet poor in FODMAP during 3 weeks of intervention.

Recently, Neuman et al. [19] suggested that a gluten free diet should be tested as prophylactic intervention in patients submitted to HSCT, justifying as hypothesis the relation between the intake of gluten found in cereals and grains with the GI toxicity increase in GHVD. Some nutrient supplementation has been suggested to improve intestinal health and preserve the nutritional status such as Zinc, vitamin A, vitamin D, glutamine and proteins [20–22]; however, we focused on presenting oral food options to be offered to patients, considering the lack of information in the current literature. It is important to mention that the intention is to promote a more organized food transition from parenteral to oral nutrition to give more comfort to the patients, with the intention to preserve intestinal integrity and nutritional status. This plan should be accompanied by industrialized oral supplements and vitamins and minerals supplements, in accordance with the health team expertise and the literature.

Taking the discussed above and considering that scientific evidence was not sufficient to provide the efficacy and safety of oral feeding during acute intestinal GVHD in the present review, the guideline development group has decided to present a dietary practice recommendation protocol as a proposal to be validated. It was a unanimous decision based on the lack of randomized clinical trials focused on oral nutrition for this very peculiar condition. Our purpose was publicizing this concept of a step-by-step protocol as first suggested by Imataki [8]; however, providing more detailed information about the diet prescription and the evolution in a stepwise manner, starting with a more structured methodology to build a guideline. We decided to present a proposal focused on the evolution of food offering during the transition period from parenteral to oral nutrition considering the GVHD stage, intestinal symptoms as well as energy intake goals during each stage. Ultimately, we intended to give information to bone marrow transplant teams in order to support future randomized controlled clinical trials and make the process of validation more effective.

Conclusion

The suggested, to validate, diet protocol has the following main features: low oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP), fibers, organic acids and intestinal irritants and gluten free with progression in 4 steps according to symptoms stability, acute intestinal GVHD stage, that could contribute to new clinical trials aiming to investigate the impact of oral diet during the transition from parenteral to oral nutrition and, in the future, give more information to support recommendation of oral diet to treat symptoms of acute intestinal GVHD and preserve nutritional status of patients whose underwent HSCT.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Declaration of competing interest

The authors declare no conflicts of interest and no funding was used to prepare this manuscript.

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