Transplantation and Cellular Therapy 27 (2021) 180.e1–180.e8

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Supportive Care

Enteral versus Parenteral Nutrition as Nutritional Support after Allogeneic Hematopoietic Stem Cell Transplantation: a Systematic Review and Meta-Analysis

Daniele Zama[1], Davide Gori[2], Edoardo Muratore[1,*], Davide Leardini[1], Flavia Rallo[2], Silvia Turroni[3], Arcangelo Prete[1], Patrizia Brigidi[4], Andrea Pession[1], Riccardo Masetti[1]

[1] *Pediatric Oncology and Hematology Unit "Lalla Seràgnoli", Department of Pediatrics, University of Bologna, Sant'Orsola Malpighi Hospital, Bologna, Italy*
[2] *Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy*
[3] *Unit of Microbial Ecology of Health, Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy*
[4] *Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy*

Article history:
Received 5 October 2020
Accepted 15 November 2020

Key Words:
Hematopoietic stem cell transplantation
Enteral Nutrition
Parenteral Nutrition
Nutritional Support
Gut microbiota
Acute graft versus host disease

A B S T R A C T

Nutritional support for patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been widely debated. Enteral nutrition (EN) is recommended as first-line nutritional support by the main international guidelines. However, these recommendations are based on weak evidence, and there is wide variability in the types of nutritional support among transplantation centers, with the majority providing parenteral nutrition (PN) instead of EN. Here we provide an up-to-date systematic review and meta-analysis of studies comparing EN and PN for nutritional support during the neutropenic period after allo-HSCT. The literature search strategy identified 13 papers, of which 10 compared clinical transplantation outcomes, 2 compared gut microbiota (GM) compositions, and 1 compared systemic metabolic profiles. For the meta-analysis, among the 10 clinical studies, 8 studies in which 2 groups were compared were selected: in 1 group, EN was provided as primary nutritional support in the neutropenic phase after allo-HSCT with or without the addition of PN (EN group), whereas in the other group, only PN was provided as nutritional support. The incidence rates of acute graft-versus-host disease (aGVHD) (relative risk [RR], 0.69; 95% confidence interval [CI], 0.56 to 0.86; $P = .0007$), aGVHD grade III-IV (RR, 0.44; 95% CI, 0.30 to 0.64; $P < .0001$), and gut aGVHD (RR, 0.44; 95% CI, 0.30 to 0.66; $P < .0001$) were lower in the EN group than in the PN group. No differences were found between the 2 groups with regard to the incidence of severe oral mucositis (RR, 0.95; 95% CI, 0.83 to 1.09; $P = .46$) or overall survival at day +100 (RR, 1.07; 95% CI, 0.95 to 1.21; $P = .29$). Other variables were too heterogeneous to perform quantitative analyses. The results of the meta-analysis showed that EN reduced the incidence of aGVHD, specifically grade III-IV and gut aGVHD. This result should prompt improved efforts to implement EN as first-line nutritional support in patients undergoing allo-HSCT. Considering the emerging evidence regarding the association between GM dysbiosis and aGVHD onset, we speculate that this protective effect could be attributed to the improved gut eubiosis observed in enterally fed patients. Further studies are warranted to better address the relationship between the GM composition, aGVHD, and the nutritional administration route during HSCT.

© 2020 The American Society for Transplantation and Cellular Therapy. Published by Elsevier Inc. All rights reserved.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the primary treatment for many oncologic, hematologic, metabolic, and immunologic diseases [1,2]. There is growing interest in supportive care for allo-HSCT recipients, with nutritional support increasingly being considered a key feature [3]. The side effects of the conditioning regimen, mainly vomiting, anorexia, diarrhea and mucositis, impair oral intake in the early post-transplantation period. Gastrointestinal acute graft-versus-host-disease (aGvHD), infections and associated treatments, and other medications, such as opioids, also have been correlated with decreased oral feeding [4]. The consequent reduction in caloric intake combined with the catabolic effect of therapies and transplantation-related complications [5] results in a rapid deterioration of nutritional status [3,4], which is associated with increased morbidity and decreased overall survival

Financial disclosure: See Acknowledgments on page 180.e7.

*Correspondence and reprint requests: Edoardo Muratore, MD, Pediatric Oncology and Hematology Unit "Lalla Seràgnoli", Department of Paediatrics, University of Bologna, Sant'Orsola Malpighi Hospital, Bologna, Italy.

E-mail addresses: edoardo.muratore@studio.unibo.it, edoardo.muratore@gmail.com (E. Muratore).

https://doi.org/10.1016/j.jtct.2020.11.006
2666-6367/© 2020 The American Society for Transplantation and Cellular Therapy. Published by Elsevier Inc. All rights reserved.

[6–9]. Thus, nutritional support during the early post-transplantation period becomes an essential and challenging issue for allo-HSCT recipients.

Artificial nutrition is usually indicated if oral caloric intake falls below 60% to 70% of basic requirements for 3 consecutive days [10,11]. Historically, parenteral nutrition (PN) was considered the method of choice for nutritional support in patients undergoing allo-HSCT [12]. However, in light of PN-related complications, including sepsis, metabolic complications (eg, hyperglycemia, hypertriglyceridemia, and electrolytic imbalance), hepatic disorders (ie, fatty liver disease, intrahepatic cholestasis, and cholelithiasis), and gut mucosal atrophy [13], some concerns have been raised regarding its use [14–16]. In addition to these clinical considerations, PN also has been associated with high direct and indirect economic costs [17]. The other feeding option is enteral nutrition (EN), defined as the type of artificial nutrition in which a nonvolitional application of nutrients via enteral tubes, mainly a nasogastric tube, is provided [11]. It has already been shown to be feasible and effective in other clinical settings [18–20], particularly in critically ill patients [21]. Currently, the international guidelines provided by European Bone Marrow Transplantation, European Society for Clinical Nutrition and Metabolism, and American Society for Parenteral and Enteral Nutrition recommend EN as first-line nutritional support for patients undergoing allo-HSCT [5,10,11,22]. Nevertheless, these recommendations are based on weak evidence [3,11]. A recent survey showed that the majority of European transplantation centers still use PN rather than EN, mainly due to constant central venous access [23]. Another possible explanation is caregivers' preference for PN because of the perceived invasiveness of EN [24]. In a survey of Australian adult allo-HSCT units, Andersen et al. [25] found wide variability in the types and timing of nutritional support, with the most frequent barriers to the use of EN being the perception of poor EN tolerance, the medical team's preference for PN, the presence of gastrointestinal symptoms, and the development of thrombocytopenia.

A systematic review published in 2017 addressed the topic of nutritional support for allo-HSCT patients, including 2 prospective studies with a focus on the comparison between EN and PN [4]. The feasibility and safety of EN, as well as the potential beneficial effect on transplantation-related outcomes, were highlighted. Only 1 systematic review performed in 2019 specifically compared EN versus PN in terms of clinical and nutritional outcomes in pediatric patients [26]. That review reported favorable benefits regarding aGvHD and platelet engraftment, although it comprised few, widely heterogeneous studies.

Considering the increasing knowledge of the role of gut microbiota (GM) dysbiosis in the development of many complications after HSCT [27], there may potentially be a significant link between the route of nutritional administration and the maintenance of gut eubiosis and epithelium integrity after HSCT [28].

Here we provide an up-to-date systematic review and meta-analysis of studies comparing EN and PN for nutritional support during the neutropenic period after allo-HSCT. Their relationship with clinical outcomes as well as the impacts of the different types of nutritional support on the metabolic profile and GM composition are addressed.

METHODS

Literature Search

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. Electronic databases, including PubMed, Trip, and CINAHL, were searched to identify relevant studies published up to May 2020. The string used to perform the search is provided in the Supplementary Material.

The search was restricted to English-language studies involving human subjects undergoing allo-HSCT, including both pediatric and adult patients, that assessed EN and PN as first-line nutritional support during the neutropenic period. Two reviewers (E.M. and D.L.) independently identified potentially eligible studies by screening titles and abstracts. The same authors assessed the full texts of potentially relevant studies for inclusion and consulted the references of previously published primary and secondary papers to manually search for additional relevant papers. Any disagreement regarding eligibility and inclusion in the systematic review was resolved through discussion and consensus between the 2 readers. If consensus was not reached, the opinion of a third author (R.M.) who acted as a "blind" final arbiter was requested. Investigators and corresponding authors were contacted to obtain additional information about studies with incomplete data.

Data Extraction and Meta-Analysis

We used the same methodology for data extraction, performed independently by the same 2 reviewers (E.M. and D.L.) under the supervision of a third author (R.M.). Data were summed and analyzed using Microsoft Office Excel 2013 (Microsoft, Redmond, WA) and Stata 13 (StataCorp, College Station, TX). Subsequently, we performed a meta-analysis considering the different outcomes that were analyzed in the included studies: the incidence of aGvHD, incidence of aGvHD grade III-IV, incidence of gut aGvHD, incidence of mucositis grade III-IV, and overall survival (OS) at day +100. We analyzed statistical heterogeneity to determine the feasibility of summing the results of the different studies considered eligible for the meta-analysis. We assessed heterogeneity by graphic funnel plots and by calculating the I^2 statistic, which represents the percentage of the variance in effect estimates that is caused by heterogeneity rather than by sampling bias (chance). An I^2 statistic $>50\%$ was considered significantly heterogeneous. When the number of studies was <5 or studies were substantially heterogeneous, we used a random-effects model in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [30]. We followed the method of DerSimonian and Laird [31] to compute the random-effects estimates for the corresponding statistics. We chose to use forest plots to graphically show effect estimates with 95% confidence intervals (CIs) for individual trials and pooled results. We carried out the meta-analysis using RevMan version 5.3 (https://revman.cochrane.org).

Quality Assessment

We used the Cochrane Tool for Quality Assessment and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess the study quality of the experimental and observational original studies included in this systematic review. The Cochrane tool allows for the analysis of 7 types of bias: sequence generation and allocation concealment (both within the domain of selection bias or allocation bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and an auxiliary domain, "other bias" [32]. For each type of bias, it was possible to assign a value of "high," "low" or "unclear" risk of bias when it was not specified whether a specific type of bias was present. Each bias judgment aids in assigning a global assessment to every RCT (good, fair, or poor) according to the Agency for Healthcare Research and Quality standards [33].

The STROBE statement is a 22-item tool specifically designed to evaluate the quality of observational studies [34]. Items are associated with different sections of an article, such as title and abstract (item 1), introduction (items 2 and 3), methods (items 4-12), results (items 13-17), discussion (items 18-21), and other information (item 22 for funding). Eighteen items are identical for 3 different study designs, whereas 4 items (items 6, 12, 14, and 15) are differentially intended for a specific study type (ie, cohort or case-control study). The STROBE statement does not provide scoring stratification. As a general rule, the higher the score, the higher the quality of the study. Thus, we created 3 score thresholds corresponding to 3 levels of quality: 0 to 14 was considered poor quality; 15 to 25, intermediate quality; 26 to 33, good quality.

RESULTS

Literature Search

The literature search strategy identified a total of 1490 references (695 in PubMed, 553 in Trip, and 242 in CINAHL).

As shown in Figure 1, the number of potentially relevant papers identified by full titles was 35. Among these 35 studies, 20 were excluded from the systematic review because they were reviews or did not compare EN and PN. Of the 15 studies assessed, 12 compared clinical and nutritional outcomes [35–46], 2 focused on the characterization of the GM composition in children [47] and adults [48], and 1 examined the plasma metabolic profile [49]. Of the 12 clinical studies, 2

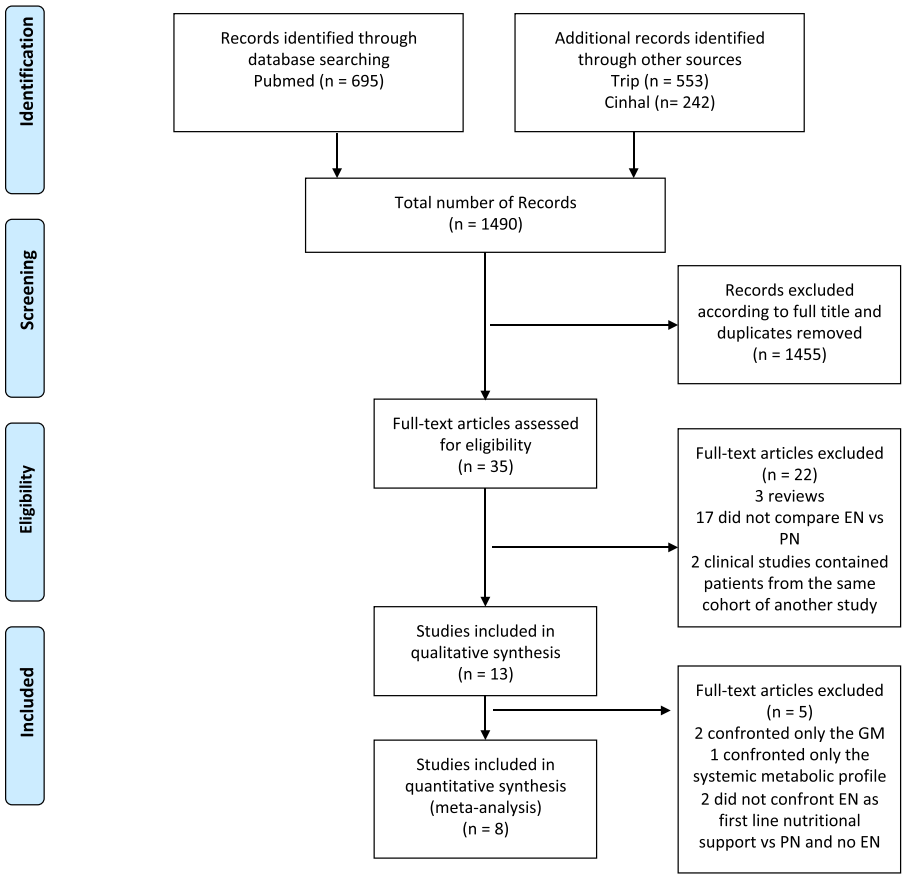


Figure 1. PRISMA flow diagram of the search strategy and included studies. The relevant number of papers at each point is given.

included patients from the same cohort of another study [43,45] and thus were excluded from the qualitative and quantitative syntheses. Of the remaining 10 papers, 3 were randomized studies in adults [39–41], 3 were prospective studies in adults [29,31,37], 2 were prospective studies in children [37,46], 1 was a prospective study with a historical comparison cohort in children [35] and 1 was a multicentric pediatric study in which EN patients from a single center were matched with PN controls from other centers [42] (Table 1). The quality of the included clinical studies was assessed as described in Methods. The 3 randomized controlled studies were rated as poor quality [39–41]. Of the 7 cohort studies, 3 were rated as good quality [36,42,44], 2 as intermediate quality [35,38], and 2 as low quality [37,46] (Table 1).

To perform the meta-analysis, studies in which 2 groups were compared were selected. In 1 group, EN was provided as primary nutritional support in the neutropenic phase after transplantation, with or without the addition of PN (EN group); in the other group, PN was provided as first-line nutritional support, and EN was not administered (PN group). Thus, of the 10 clinical studies, we excluded 2 that did not meet our inclusion criteria. One study compared EN for >7 days with EN for <7 days plus PN [35], and the other study compared patients who maintained adequate oral nutritional intake and received 4 or more days of EN versus adequate PN with or without EN with patients who received inadequate nutrition with or without PN and EN [36].

In the 8 studies in which quantitative analyses were performed, the only outcomes reported consistently enough to allow for a meta-analysis and that were clinically relevant were the following: incidence of aGvHD grade I-IV, incidence of aGvHD grade III-IV, incidence of gut aGvHD, incidence of mucositis grade III-IV, and OS at day +100.

aGvHD

Seven of the 8 studies included in the meta-analysis reported the incidence of aGvHD [37–40,42,44,46], with a total of 495 patients. The incidence of aGvHD was significantly lower in the EN group than in the PN group (97 of 276 versus 106 of 219), with a relative risk (RR) of 0.69 (95% confidence interval [CI], 0.56 to 0.86; $P = .0007$). Heterogeneity among studies was absent (0%) (Figure 2A). The incidence of aGvHD grade III-IV was reported in 5 studies [38,41,42,44,46], with a total of 522 patients. The pooled results showed a reduction in aGvHD grade III-IV in the EN group (34 of 288 versus 64 of 234), with an RR of 0.44 (95% CI, 0.30 to 0.64; $P < .0001$) and no heterogeneity among studies (Figure 2B). A similar result regarding gut aGvHD was observed in the 4 studies that reported the incidence of this complication [37,39,42,44], with a total of 396 patients. Gut aGvHD occurred less frequently in the EN group compared with the PN group (34 of 231 versus 54 of 165), with an RR of 0.44 (95% CI, 0.30 to 0.66; $P< .0001$) and low heterogeneity among studies (6%) (Figure 2C). The results of the 2 papers that did not meet the inclusion criteria for the meta-analysis are in line with the reported results. Zama et al. observed a nonsignificant reduction in the incidence of severe gut aGvHD and steroid-resistant gut aGvHD in children enterally fed for >7 days [35]. Beckerson et al. found increased incidence rates of gastrointestinal GVHD of any stage and aGvHD grade ≥II in patients who received PN compared to adequate EN [36].

Table 1
Summary of Included Clinical Studies.

First Author	Year	Study Design	Population	Total Patients, n	EN intervention group, n	PN intervention group, n	EN intervention	PN intervention	Quality Assessment
Zama [35]	2020	Prospective with an historic cohort	Children	42	14	28	EN > 7 days	EN < 7 days, PN	Intermediate*
Andersen [39]	2020	Randomized	Adults	44	22	22	EN and EN+PN	PN or no intervention	Poor†
Beckerson [36]	2019	Prospective	Adults	484	245	148 + 91	Patients who maintained an adequate nutritional intake either orally or those that also required 4 or more days of EN.	Patients that achieved adequate nutritional intakes during the period that included 4 or more days of PN + Inadequate nutrition	Good*
Skaarud [41]	2018	Randomized	Adults	119	59	60	Daily energy intake measured and controlled, EN and EN +PN	Daily energy intake not measured, PN	Poor†
Gonzales [42]	2017	Multicentric, patients from a single center matched with PN controls from other centers	Children	194	97	97	EN and EN+PN	PN	Good*
Andersen [40]	2015	Randomized	Adults	9	5	4	EN and EN+PN	PN	Poor†
Guieze [38]	2013	Prospective	Adults	56	28	28	Accepted initial EN (EN and EN + PN)	Refused initial EN and started PN	Intermediate*
Seguy [44]	2012	Prospective	Adulst	121	94	27	EN and EN + PN	PN or no intervention	Good*
Hopman [46]	2003	Prospective	Children	39	12	22	EN and EN + PN	PN	Low*
Papadopoulou [37]	1998	Prospective	Children	39	20	19	EN and EN + PN	PN	Low*

Abbreviations: EN= Enteral Nutrition; PN= Parenteral Nutrition
* Quality assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for prospective cohorts.
† Quality assessed using the Cochrane Tool for Quality Assessment for randomized controlled trial.

Oral Mucositis

Five of the 8 studies included in the meta-analysis reported the incidence of mucositis grade III-IV [38,39,41,42,44], with a total of 530 participants. There was no statistically significant difference in the incidence between the 2 groups (178 of 296 versus 152 of 234), with an RR of 0.95 (95% CI, 0.83 to 1.09; *P*= .46) and no heterogeneity among studies (Figure 3). Of the 2 papers that did not meet the inclusion criteria for the meta-analysis and that did not contain patients from the same cohort of another study, only 1 reported the incidence of mucositis grade III-IV, with no significant difference [35].

Survival

OS at day +100 was reported in 5 studies [38,39,41,42,44], with a total of 530 participants, and no statistically significant difference was found, with a RR of 1.07 (95% CI, 0.95 to 1.21; *P*= .29) and medium-high heterogeneity (69%) (Figure 4). Of the 2 papers with exclusive cohorts that did not meet the inclusion criteria for the meta-analysis, 1 reported OS at day +100, with no significant difference [35]. The other study showed an association between adequate EN during the early transplantation course and reduced nonrelapse mortality [36].

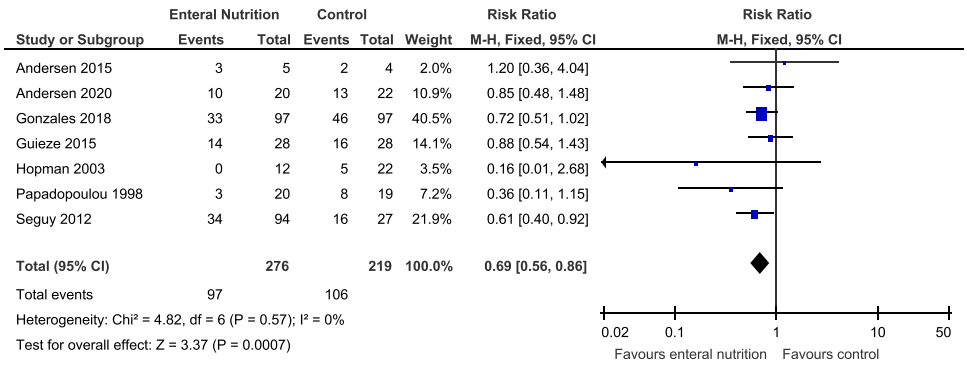
Infections

Data regarding infectious complications of allo-HSCT were too heterogeneous to allow for a meta-analysis. Zama et al. observed a reduced incidence of bloodstream infections in the EN group. The type of nutritional support was also the only variable independently associated with bloodstream infections in the multivariate analysis [35]. Andersen et al. found no difference in the incidence of grade 3-4 catheter-related infections [39]. Skaarud et al. reported no significant differences in infectious complications, namely, bloodstream infections, fungal and viral infections, and non-agent-specific pneumonia [41]. Gonzales et al. found no differences in the incidence of septicemia and viral infections [42]. Guieze et al. observed a lower median duration of fever, less need for empirical antifungal therapy, and a lower rate of central venous catheter replacement in the EN group compared with the PN group, whereas there were no differences in documented bacteremia, viral reactivation, or duration of antibiotic therapy [38]. Seguy et al. found a higher percentage of patients with ≥2 episodes of infection in the PN group and a lower incidence of fungal infections in the EN group, but no between-group differences in the rates of bacterial and viral infections [44]. Hopman et al. found no between-group difference in the incidence of sepsis [46], and Papadopoulou et al. documented fewer and shorter febrile episodes in the EN group compared with the PN group [37].

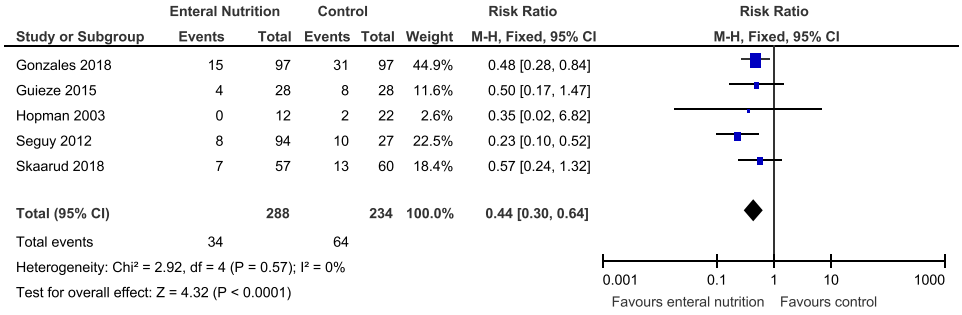
Hematologic Recovery

Platelet recovery was addressed in 6 studies, but the reported data were too heterogeneous to allow for a meta-analysis. Zama et al. found that platelet engraftment was shorter in the PN group than in the EN group when considering a threshold of $>20 \times 10^9$/L, but this correlation was not confirmed when considering a threshold of $>50 \times 10^9$/L [35]. Other studies found no difference between the 2 groups in the percentage of patients who achieved platelet engraftment by day +100 [39] or in the number of days to reach platelet engraftment with a threshold of either $>20 \times 10^9$/L [41] or $>50 \times 10^9$/L [38]. Gonzales et al. observed that the percentage of patients who achieved platelet engraftment by day +100 was higher in the EN group than in the PN group for thresholds of $>20 \times 10^9$/L and $>50 \times 10^9$/L, and a decreased time to platelet engraftment in the EN group in patients receiving only EN [42]. Seguy et al. observed a shorter time to platelet engraftment in the EN group than in the PN group considering a threshold of $>20 \times 10^9$/L, but the data were not confirmed in a multivariate analysis; rather, they found a correlation between the administration of

A: aGvHD



B: aGvHD III-IV



C: gut aGvHD

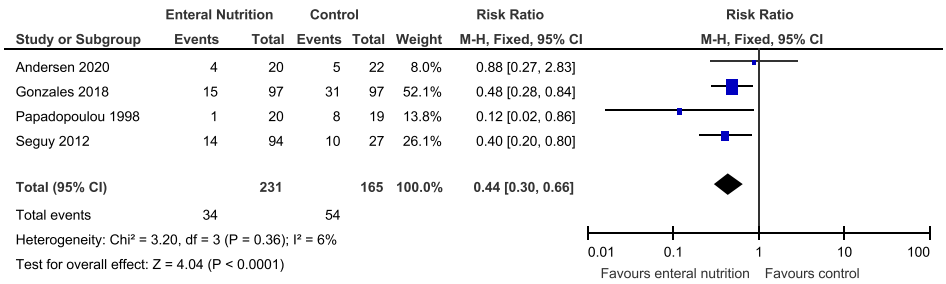


Figure 2. Forest plot showing the association between the use of EN as first-line nutritional support after allo-HSCT and the reduced incidence rates of aGvHD (A), aGvHD grade III-IV (B), and gut aGvHD (C).

Mucositis grade III-IV

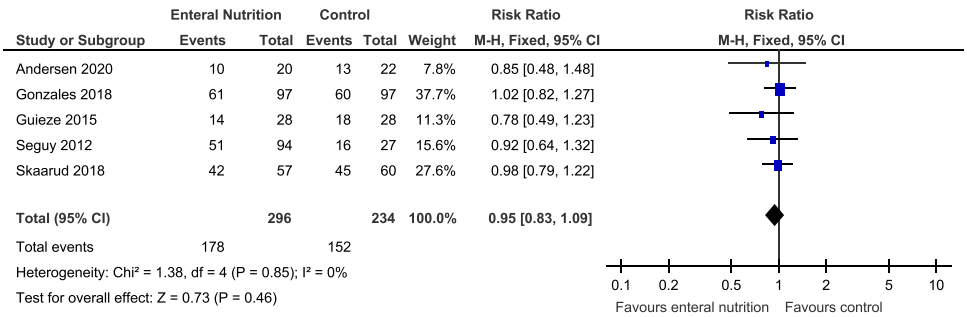


Figure 3. Forest plot showing no association between the use of EN as first-line nutritional support after allo-HSCT and the incidence of severe mucositis.

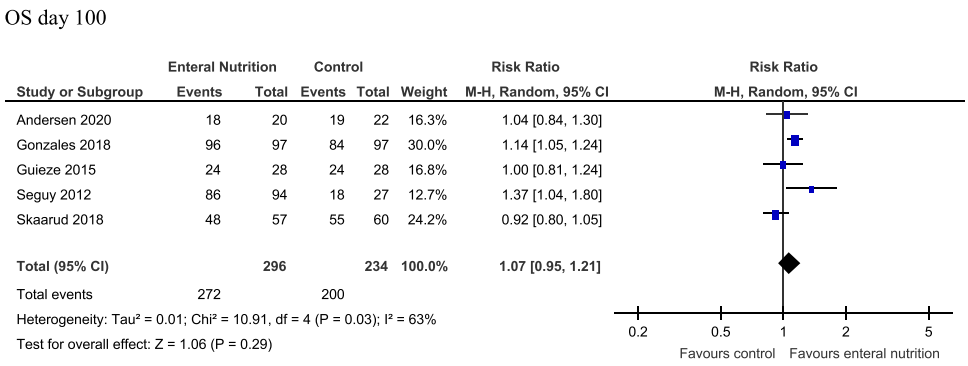


Figure 4. Forest plot showing no association between the use of EN as first-line nutritional support after allo-HSCT and overall survival at day +100.

PN and delayed platelet engraftment [44]. Only Seguy et al. reported a difference in the time to neutrophil engraftment, which was shorter in the EN group than in the PN group in the univariate and multivariate analyses [44]. The other studies found no difference.

Length of Hospital Stay and Transfer to the Intensive Care Unit

Clinical outcomes in terms of length of hospital stay and transfer to intensive care were reported in the studies included in the qualitative synthesis as follows: 7 studies did not find a between-group difference between the length of hospital stay [35,37-41,44], whereas Gonzales et al. observed a shorter length of stay in the EN group compared with the PN group [42]. Guieze et al. reported a lower rate of transfer to the intensive care unit in the EN group [38], whereas the other 2 studies did not find any between-group difference [35,44].

Systemic Metabolic Profile

Tvedt et al. [49] compared pretransplantation and post-transplantation (3 weeks from HSCT) plasma metabolomic profiles in 10 patients receiving mainly EN and 10 patients receiving mainly PN from the cohort of Skaarud et al. [41]. They observed increased concentrations of medium- and long-chain carnitines and decreased levels of fatty acids and mitochondrial activation markers in the PN group after HSCT, suggesting that these patients had altered oxidative metabolism due to insufficient energy intake. Significant increases in heme and porphyrin metabolites were also found in the PN group. Increased levels of sulfated dopamine metabolites were observed in patients receiving mainly EN, perhaps due to greater oral intake and reduced mucosal toxicity. Nevertheless, the differences between pretransplantation and post-transplantation samples in the 2 groups were larger than the differences observed at the same time points, suggesting that the plasma metabolomic profile is determined mainly by HSCT toxicity and not by nutritional support [49].

GM Composition

Two studies compared the GM of patients receiving EN and patients receiving PN. Andersen et al. [48] examined 23 adult patients from the cohort of Andersen et al. [39], of whom 13 received predominantly EN and 10 received predominantly PN, and collected fecal samples 30 days after allo-HSCT, and found no difference in microbial diversity but a greater relative abundance of *Faecalibacterium* and *Ruminococcus bromii* in patients who received predominantly EN [48]. These taxa are commonly associated with increased production of short-chain fatty acids (SCFAs), microbial metabolites with a multifaceted role in human physiology [50], considered keystone components of a "healthy-like" ecosystem [51,52]. D'Amico et al. [47] longitudinally analyzed the recovery trajectory of the compositional and functional profile of GM in 20 pediatric patients undergoing HSCT, of whom 10 received EN and 10 received total PN. They observed prompt recovery of a eubiotic, diverse GM composition and SCFA layout after allo-HSCT-induced disruption in EN patients only. Interestingly, among the genera that were restored in the EN group during post-HSCT recovery, they identified *Faecalibacterium, Dorea, Blautia, Bacteroides, Parabacteroides*, and *Oscillospira*, all of which are well-known health-associated GM components capable of producing SCFAs [47].

DISCUSSION

The present study is, to the best of our knowledge, the first comprehensive meta-analysis comparing clinical outcomes between patients receiving EN and those receiving PN as nutritional support during the neutropenic period after allo-HSCT.

The quantitative analysis showed reduced incidence rates of aGvHD, aGvHD grade III-IV, and gut aGvHD in patients receiving EN, with an overall good quality of evidence. The studies not included in the meta-analysis also showed a protective effect of EN against aGvHD [35,36]. This effect could be attributed to the role of EN in maintaining gut ecosystem homeostasis after upsetting events, such as allo-HSCT. Several factors may contribute to the alteration of the intestinal environment, and PN and reduced intestinal transit have been associated with GM dysbiosis and gut mucosal atrophy [28,53]. Moreover, some authors have suggested a trophic effect provided by EN on the gut epithelium, either directly due to a greater presence of nutrients *in loco* or indirectly via the production of SCFAs by GM [54,55].

The improvement in gut barrier function combined with the influence of a eubiotic GM on the underlying inflammatory process and intestinal immune system may explain the protective role of EN against gut aGvHD. The potential role of EN in reducing the translocation of microbial molecules and microbes while increasing the production of SCFAs also could lead to systemic anti-inflammatory and immunomodulatory effects, contributing to a reduction in the overall incidence of aGvHD, especially severe forms. These hypotheses seem to be supported by the 2 studies comparing the GM of patients receiving EN and PN [47,48], but larger prospective cohort studies are needed to confirm these findings. Furthermore, metagenomic and metabolomic analyses could shed light on the complex interplay between nutrition and GM after allo-HSCT in the future.

The quantitative analysis showed no correlation between the type of nutritional support and the incidence of severe forms of oral mucositis. This may be explained by predominant roles of the type of conditioning regimen and the oral microbiota in the pathogenesis of oral mucositis [56].

This meta-analysis failed to observe a statistically significant improvement in OS at day +100 in the EN group. This can be explained by the wide heterogeneity (69%) observed among the studies. Moreover, one of the studies that was not included in the quantitative analysis showed a reduction in nonrelapse mortality in patients receiving adequate EN [36]. These data must be confirmed in future studies to better address the impact of EN and PN on survival after HSCT. The protective effect of EN against aGvHD, combined with the promotion and maintenance of a eubiotic GM composition, which was demonstrated to be an independent predictor of mortality per se [27], could lead to speculation about the improved survival in patients fed enterally. This idea may be reinforced by the finding of improved survival in children admitted to the intensive care unit and fed with EN, although this is a totally different scenario [18].

The data on infectious complications are conflicting and very heterogeneous. Thus, it is not possible to draw any meaningful conclusion regarding the role of nutritional support in preventing infections after allo-HSCT. In other settings, EN was reported to reduce the rate of infectious complications [17]. Interestingly, it has been suggested that the reduction in bacterial infections, which has not been observed in other studies, could be due to the use of antibiotic prophylaxis and gut decontamination, potentially overlapping the protective role of EN [35]. The supposed role of EN in preventing bacterial infections is supported by potential improvements in intestinal permeability and GM homeostasis, a consequent reduction in the risk of bacterial translocation [57], and a lower frequency of central venous catheter handling due to the reduced use of PN [13]. This topic must be a focus of future research to better understand the relationship between nutritional support and bacterial infections.

A deleterious effect of PN on platelet engraftment was reported in only 2 studies [42,44]. The authors attributed this finding to the hyperactivation of the monocyte-macrophage system consecutive to lipid infusion, which causes medullar hemophagocytosis [58] and to the increased incidence of aGvHD that may lead to medullar insufficiency by blocking hematopoietic stem cells [59]. However, other groups failed to replicate this result.

The present meta-analysis has some limitations that should be taken into account. First, there was wide heterogeneity in the intervention group (EN group). The time of positioning of the nasogastric tube and start of EN, the extent of nutritional assessment and counseling, and the dose, duration, and types of formulas varied greatly across the different experiences. Considering the quantitative and qualitative differences observed in the studies regarding caloric intake, we opted to not include the evaluation of nutritional status in this systematic review and meta-analysis. This may be relevant due to the possible correlation between malnutrition and clinical outcomes after allo-HSCT [6-8,60]. We believe that these considerations do not affect the findings presented in this study, because the role of EN in preventing aGvHD could be independent of nutritional status and potentially mediated by improved intestinal homeostasis, as stated above. Nevertheless, future studies must better address nutritional outcomes by evaluating the type of nutrition using metabolic parameters and anthropometric measures to assess nutritional status and investigating their relationship with clinical outcomes associated with allo-HSCT. Furthermore, the included studies were published between 1998 and 2020, and over this time span transplantation procedures and diagnostic capabilities changed significantly. The absent to low heterogeneity regarding aGvHD and mucositis observed in the meta-analysis, and the fact that no gross difference was found in the data reported by year, may support the validity of the present results. Finally, we decided to include both randomized controlled studies and prospective nonrandomized cohorts in the quantitative analysis, to obtain a significant number of patients. The choice to not perform a meta-analysis of only the randomized studies was supported by the poor quality of the studies included and by the sensitivity analysis results showing that the result of the meta-analysis for each variable did not change when the randomized studies were excluded (Supplementary Figures S1 to S5).

CONCLUSIONS

According to the results of the present meta-analysis, the use of EN as nutritional support during the neutropenic period after allo-HSCT was associated with reduced incidence rates of aGvHD, aGvHD grade III-IV, and gut aGvHD. No effect on the onset of severe mucositis was observed, and no statistically significant association between OS at day +100 after transplantation and type of nutrition was found. These findings corroborate the recommendation of the current international guidelines [5,10,11,22] and should prompt increased efforts to implement EN as first-line nutritional support in patients undergoing allo-HSCT. Nevertheless, additional studies involving a larger cohort of patients are needed to confirm the present results and better understand the critical issues raised by this systematic review, such as the correlation between the type of nutritional support and OS and the incidence of infections. A more in-depth analysis of the nutritional outcomes of EN and PN also could help shed light on the complex interplay between nutritional status and clinical outcomes. Moreover, we are only starting to scratch the surface on the potential implications of the route of nutritional administration on the GM, and further studies are warranted to address this compelling topic. In particular, how the composition of the formula affects the GM and the potential clinical outcomes are key questions that await some answers in future research.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported by the Italian Ministero della Salute (Bando Ricerca Finalizzata 2013, Giovani Ricercatori section, code GR-2013-02357136, to R.M.).

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: R.M., D.Z., E.M. and D.L. conceptualized the study design; D.G. contributed to developing the review protocol; E.M. and D.L. performed the literature search and data collection; D.G. and F.R. performed the meta-analysis; S.T., P.B., A. Prete, and A. Pession contributed to data interpretation; E.M. and D.L. wrote the first draft of the manuscript; E.M., D.G. and F.R. produced the tables and figures; all authors contributed to reviewing and editing the final version; and E.M. had responsibility for final submission of the manuscript.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2020.11.006.

REFERENCES

1. Jenq RR, van den Brink MRM. Allogeneic haematopoietic stem cell transplantation: individualized stem cell and immune therapy of cancer. *Nat Rev Cancer*. 2010;10:213–221.
2. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354:1813–1826.
3. Baumgartner A, Hoskin K, Schuetz P. Optimization of nutrition during allogeneic hematologic stem cell transplantation. *Curr Opin Clin Nutr Metab Care*. 2018;21:152–158.
4. Baumgartner A, Bargetzi A, Zueger N, et al. Revisiting nutritional support for allogeneic hematologic stem cell transplantation–a systematic review. *Bone Marrow Transplant*. 2017;52:506–513.
5. Nava T, Ansari M, Dalle JH, et al. Supportive care during pediatric hematopoietic stem cell transplantation: beyond infectious diseases. A report

from workshops on supportive care of the Pediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2020;55:1126–1136.
6. Kerby EH, Li Y, Getz KD, et al. Nutritional risk factors predict severe acute graft-versus-host disease and early mortality in pediatric allogeneic hematopoietic stem cell transplantation. *Pediatr Blood Cancer*. 2018;65:e26853.
7. Liu P, Wang B, Yan X, Cai J, Wang Y. Comprehensive evaluation of nutritional status before and after hematopoietic stem cell transplantation in 170 patients with hematological diseases. *Chin J Cancer Res*. 2016;28:626–633.
8. Fuji S, Mori T, Khattry N, et al. Severe weight loss in 3 months after allogeneic hematopoietic SCT was associated with an increased risk of subsequent non-relapse mortality. *Bone Marrow Transplant*. 2015;50:100–105.
9. Fuji S, Einsele H, Savani BN, Kapp M. Systematic nutritional support in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant*. 2015;21:1707–1713.
10. Carreras E, Dufour C, Mohty M, Kröger N, eds. *The EBMT Handbook : Hematopoietic Stem Cell Transplantation and Cellular Therapies*. Chan, Switzerland: Springer International; 2019.
11. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36:11–48.
12. Arends J, Bodoky G, Bozzetti F, et al. ESPEN guidelines on enteral nutrition: non-surgical oncology. *Clin Nutr*. 2006;25:245–259.
13. Hartl WH, Jauch KW, Parhofer K, Rittler P. Complications and monitoring—guidelines on parenteral nutrition, Chapter 11. *Ger Med Sci*. 2009;7:Doc17.
14. Papadopoulou A, MacDonald A, Williams MD, Darbyshire PJ, Booth IW. Enteral nutrition after bone marrow transplantation. *Arch Dis Child*. 1997;77:131–136.
15. Langdana A, Tully N, Molloy E, Bourke B, O'Meara A. Intensive enteral nutrition support in paediatric bone marrow transplantation. *Bone Marrow Transplant*. 2001;27:741–746.
16. Murray SM, Pindoria S. Nutrition support for bone marrow transplant patients. *Cochrane Database Syst Rev*. 2009;4: CD002920.
17. Cangelosi MJ, Auerbach HR, Cohen JT. A clinical and economic evaluation of enteral nutrition. *Curr Med Res Opin*. 2011;27:413–422.
18. Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children—an international multicenter cohort study. *Crit Care Med*. 2012;40:2204–2211.
19. Gong D, Yu X, Wang L, Kong L, Gong X, Dong Q. Exclusive enteral nutrition induces remission in pediatric Crohn's disease via modulation of the gut microbiota. *Biomed Res Int*. 2017;2017: 8102589.
20. Kudsk KA. Gut mucosal nutritional support—enteral nutrition as primary therapy after multiple system trauma. *Gut*. 1994;35(1 suppl):S52–S54.
21. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38:48–79.
22. August DA, Huhmann MB, American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *JPEN J Parenter Enter Nutr*. 2009;33:472–500.
23. Peric Z, Botti S, Stringer J, et al. Variability of nutritional practices in peritransplant period after allogeneic hematopoietic stem cell transplantation: a survey by the Complications and Quality of Life Working Party of the EBMT. *Bone Marrow Transplant*. 2018;53:1030–1037.
24. Williams-Hooker R, Adams M, Havrilla DA, Leung W, Roach RR, Mosby TT. Caregiver and health care provider preferences of nutritional support in a hematopoietic stem cell transplant unit. *Pediatr Blood Cancer*. 2015;62:1473–1476.
25. Andersen S, Banks M, Brown T, Weber N, Kennedy G, Bauer J. Nutrition support during allogeneic stem cell transplantation: evidence versus practice. *Support Care Cancer*. 2020;28:5441–5447.
26. Evans JC, Hirani SP, Needle JJ. Nutritional and post-transplantation outcomes of enteral versus parenteral nutrition in pediatric hematopoietic stem cell transplantation: a systematic review of randomized and non-randomized studies. *Biol Blood Marrow Transplant*. 2019;25:e252–e259.
27. Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2020;382:822–834.
28. Jenq RR, Taur Y, Devlin SM, et al. Intestinal blautia is associated with reduced death from graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21:1373–1383.
29. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
30. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
31. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
32. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
33. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011. Available at; www.cochrane-handbook.org. Accessed 5 April 2020.
34. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499.
35. Zama D, Muratore E, Biagi E, et al. Enteral nutrition protects children undergoing allogeneic hematopoietic stem cell transplantation from blood stream infections. *Nutr J*. 2020;19:29.
36. Beckerson J, Szydlo RM, Hickson M, et al. Impact of route and adequacy of nutritional intake on outcomes of allogeneic haematopoietic cell transplantation for haematologic malignancies. *Clin Nutr*. 2019;38:738–744.
37. Papadopoulou A, Williams MD, Darbyshire PJ, Booth IW. Nutritional support in children undergoing bone marrow transplantation. *Clin Nutr*. 1998;17:57–63.
38. Guièze R, Lemal R, Cabrespine A, et al. Enteral versus parenteral nutritional support in allogeneic haematopoietic stem-cell transplantation. *Clin Nutr*. 2014;33:533–538.
39. Andersen S, Weber N, Kennedy G, Brown T, Banks M, Bauer J. Tolerability of proactive enteral nutrition post allogeneic haematopoietic progenitor cell transplant: a randomised comparison to standard care. *Clin Nutr*. 2020;39:1364–1370.
40. Andersen S, Kennedy G, Banks M. A randomised controlled comparison of enteral versus parenteral nutritional support post allogeneic haematopoietic cell transplantation. *Clin Nutr ESPEN*. 2015;10:e102–e106.
41. Skaarud KJ, Hjermstad MJ, Bye A, et al. Effects of individualized nutrition after allogeneic hematopoietic stem cell transplantation following myeloablative conditioning; a randomized controlled trial. *Clin Nutr ESPEN*. 2018;28:59–66.
42. Gonzales F, Bruno B, Alarcón Fuentes M, et al. Better early outcome with enteral rather than parenteral nutrition in children undergoing MAC allo-SCT. *Clin Nutr*. 2018;37(6 Pt A):2113–2121.
43. Azarnoush S, Bruno B, Beghin L, et al. Enteral nutrition: a first option for nutritional support of children following allo-SCT? *Bone Marrow Transplant*. 2012;47:1191–1195.
44. Seguy D, Duhamel A, Ben Rejeb M, et al. Better outcome of patients undergoing enteral tube feeding after myeloablative conditioning for allogeneic stem cell transplantation. *Transplantation*. 2012;94:287–294.
45. Seguy D, Berthon C, Micol JB, et al. Enteral feeding and early outcomes of patients undergoing allogeneic stem cell transplantation following myeloablative conditioning. *Transplantation*. 2006;82:835–839.
46. Hopman GD, Peña EG, Le Cessie S, Van Weel MH, Vossen JMJJ, Mearin ML. Tube feeding and bone marrow transplantation. *Med Pediatr Oncol*. 2003;40. 375-359.
47. D'Amico F, Biagi E, Rampelli S, et al., et al. Enteral nutrition in pediatric patients undergoing hematopoietic SCT promotes the recovery of gut microbiome homeostasis. *Nutrients*. 2019;11:2958.
48. Andersen S, Staudacher H, Weber N, et al. Pilot study investigating the effect of enteral and parenteral nutrition on the gastrointestinal microbiome post-allogeneic transplantation. *Br J Haematol*. 2020;188:570–581.
49. Tvedt THA, Skaarud KJ, Tjønnfjord GE, Gedde-Dahl T, Iversen PO, Bruserud Ø. The systemic metabolic profile early after allogeneic stem cell transplantation: effects of adequate energy support administered through enteral feeding tube. *Biol Blood Marrow Transplant*. 2020;26:380–391.
50. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell*. 2016;165:1332–1345.
51. Ze X, Duncan SH, Louis P, Flint HJ. *Ruminococcus bromii* is a keystone species for the degradation of resistant starch in the human colon. *ISME J*. 2012;6:1535–1543.
52. Martín R, Bermúdez-Humarán LG, Langella P. Searching for the bacterial effector: the example of the multi-skilled commensal bacterium *Faecalibacterium prausnitzii*. *Front Microbiol*. 2018;9:346.
53. Buchman AL, Moukarzel AA, Bhuta S, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. *JPEN J Parenter Enteral Nutr*. 1995;19:453–460.
54. Shen TY, Qin HL, Gao ZG, Fan XB, Hang XM, Jiang YQ. Influences of enteral nutrition combined with probiotics on gut microflora and barrier function of rats with abdominal infection. *World J Gastroenterol*. 2006;12:4352–4358.
55. Ríos-Covián D, Ruas-Madiedo P, Margolles A, Gueimonde M, de Los Reyes-Gavilán CG, Salazar N. Intestinal short chain fatty acids and their link with diet and human health. *Front Microbiol*. 2016;7:185.
56. Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer*. 2004;4:277–284.
57. Taur Y, Xavier JB, Lipuma L, et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis*. 2012;55:905–914.
58. Goulet O, Girot R, Maier-Redelsperger M, Bougle D, Virelizier JL, Ricour C. Hematologic disorders following prolonged use of intravenous fat emulsions in children. *JPEN J Parenter Enter Nutr*. 1986;10:284–288.
59. Lin Y, Hu X, Cheng H, et al. Graft-versus-host disease causes broad suppression of hematopoietic primitive cells and blocks megakaryocyte differentiation in a murine model. *Biol Blood Marrow Transplant*. 2014;20:1290–1300.
60. Yang J, Xue SL, Zhang X, et al. Effect of body mass index on overall survival of patients with allogeneic hematopoietic stem cell transplantation. *Eur J Clin Nutr*. 2017;71:750–754.