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Reviews

Nutritional and Post-Transplantation Outcomes of Enteral versus Parenteral Nutrition in Pediatric Hematopoietic Stem Cell Transplantation: A Systematic Review of Randomized and Nonrandomized Studies

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A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) involves the administration of chemotherapy followed by the infusion of donor stem cells. After treatment, children can consequently experience nausea, vomiting, diarrhea, anorexia, and mucositis, which negatively impact oral intake, leading to rapid deterioration in nutritional status and risk of malnutrition. Nutrition support therefore becomes necessary to circumvent these adverse effects. This has traditionally been provided via parenteral nutrition (PN), but pediatric evidence is increasingly advocating enteral nutrition (EN) as a preferential alternative. The objective of this review is to determine the efficacy of any forms of EN versus PN provided during admission to children aged ≤ 18 years undergoing HSCT. Primary outcomes considered efficacy in relation to various nutritional parameters, and secondary outcomes included a range of post-transplantation parameters. Data sources included English and non-English articles from the start date of MEDLINE, EMBASE, AMED, CINAHL and Cochrane Controlled Trials register, up to July 2018. Key journals were also hand searched, reference lists scanned, clinical experts contacted, and gray literature searched using EThOS and Open Grey. Randomized and observational studies comparing any forms of EN versus PN in children aged ≤ 18 years undergoing HSCT investigating nutritional or post-transplantation outcomes were eligible. Data were extracted from included studies using a custom extraction form that had previously been piloted. Because included studies were observational, risk of bias was assessed using Risk of Bias in Non-randomised Studies of Interventions. Because only a small number of heterogenous studies reporting a wide range of differently defined outcomes were included, meta-analyses were not performed and data were presented in narrative form. Conflicting results in favor of either method of nutrition support or no difference between methods were seen for duration of interventions, nutritional intakes, biochemical and anthropometric changes, mortality, infections, length of admission, and neutrophil engraftment. EN may provide favorable benefits over PN regarding acute graft-versus-host-disease (aGVHD) and platelet engraftment. A paucity of studies was found investigating the question posed by this review. Included studies were clinically heterogenous regarding populations, interventions, and outcomes, at moderate to serious risk of bias due to the absence of randomization, confounding parameters, statistical control, retrospective designs, and participant selection. Some studies were more than 15 years old. Despite the limited number and poor quality of identified studies, results support the growing body of pediatric evidence that EN is feasible during HSCT. Similar differences regarding many nutritional and post-transplantation outcomes were seen in both forms of nutrition support, but EN could provide benefits above PN including reduced incidence of aGVHD and faster platelet engraftment.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has become a well-recognized treatment for malignant and nonmalignant diseases in children [1]. On commencement of treatment patients experience rapid deterioration in nutritional status, putting them at risk of malnutrition [2]. This may be caused by the toxic effects of intensive conditioning regimens causing side effects, including vomiting, diarrhea, anorexia, and mucositis [3], which negatively impact on dietary intakes [4]. Potential secondary complications, including infections and acute graft-versus-host-disease (aGVHD) after

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the receipt of donor cells, also contribute to decreased oral intake and poor nutritional status [5]. Negative associations have been found between malnutrition and therapy tolerance [6] and infections [7] in pediatric cancer and between overall survival (OS), transplant-related mortality, and relapse risk in adult HSCT [8]. Nutrition support therefore becomes essential during HSCT to circumvent these adverse outcomes.

Traditionally, parenteral nutrition (PN) has been the method of choice during HSCT [9]. However, American and European adult guidelines [10,11] have recommended first-line enteral nutrition (EN) because of higher risks associated with PN, including infections [12], metabolic disorders [13], gut mucosal atrophy [14], and increased costs [15]. PN is only recommended in severe mucositis, intractable vomiting, severe malabsorption, protracted diarrhea, or gut aGVHD [11]. However, these recommendations are based on weak evidence [8]. Consequently, clinical practices deviate widely [16,17], with centers lacking nutrition support protocols [18] and continuing to use first-line PN [19].

Despite no international pediatric guidelines for nutrition support in HSCT, 2 Cochrane reviews examining the efficacy of EN and PN through randomized controlled trials (RCTs) have been published. One focused on HSCT but included adult and pediatric studies [20], whereas the second focused on pediatrics but included those with cancer who had and had not received HSCT [21]. Across both reviews only 3 studies were conducted specifically in pediatric HSCT and investigated oral glutamine in the prevention of mucositis [22] or compared PN solutions [23,24]. Therefore, no RCTs have been found investigating EN versus PN in pediatric HSCT up to the review conducted in 2014 [21]. Furthermore, a recent systematic review focused on adult HSCT [8], and the most recent (nonsystematic) review including observational studies in adult and pediatric HSCT is now over 10 years old [25].

This highlights the absence of a review including randomized and nonrandomized studies in pediatric HSCT. Children differ metabolically from adults, with continued growth and development desired throughout therapy that often spans many years [21]. It is therefore important to assess the most up to date evidence of efficacy comparing the 2 main modalities for providing nutrition support to this population. This review aims to support clinical guideline development, guide the decision-making of clinicians, and address uncertainty and variation in clinical practices. A scoping search of PROSPERO and PubMed Health in December 2017 identified no similar systematic reviews recently published or underway in this area.

The objective of this review was to determine, through randomized and observational studies, the efficacy of any forms of EN versus PN provided during admission to children (aged ≤ 18 years) undergoing HSCT. The primary outcomes considered efficacy in relation to nutritional parameters, including nutritional intakes, nutritional status, and use of nutritional interventions. Secondary outcomes included various post-transplantation parameters, such as mortality, infections, and GVHD.

METHODS

Protocol

The protocol was written according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [26] but was not registered. This systematic review adheres to the PRISMA guidelines [27].

Study Designs

We included RCTs, controlled (nonrandomized) clinical trials, quasi-RCTs, prospective and retrospective cohort studies, cross-sectional studies, case-control studies, and case series. Gray literature was included, if appropriate. Qualitative and animal studies, reviews, and commentaries were excluded. No restrictions were imposed regarding date, language, country, or setting of studies. Non-English studies were translated using the translate function within EPPI-Reviewer (Social Sciences Research Unit, Institute of Education, University of London) or Google translate (translate.google.com), but only included if they could be fully translated.

Participants

Participants included children aged ≤ 18 years undergoing autologous or allogenic HSCT from any donor or cell source, for any diagnosis, receiving any type of chemotherapy. If a study included a mixed population of adults and children or children who did and did not receive HSCT, it was included if data were reported separately for children or those who had HSCT.

Interventions

Nutrition support was defined as the administration of nutrients alongside or in place of normal eating. It excluded micronutrient or glutamine supplementation because the aim of these interventions differ from general nutrition support. Interventions included any form of EN, defined as the delivery of any substance of nutritional value that passes any part of the gastrointestinal tract, typically delivered via a tube. Comparators included any form of PN, defined as the intravenous administration of nutrients, containing a minimum of glucose and amino acids, and therefore bypassing the gastrointestinal tract. During HSCT it is common for patients to receive various sequences of EN and/or PN, and studies were therefore likely to compare EN and PN in various ways. No nutrition support included usual food intake or fluid therapy. Studies were excluded if they used no nutrition support as a control and did not compare EN versus PN.

Outcomes

In the absence of standardized outcomes, and consequently a diverse range of endpoints reported across the literature [28], outcomes from Cochrane reviews [20,21] were investigated.

Primary outcomes included nutritional parameters: intakes of calories, protein, or fluid; percentage of nutritional requirements achieved via the intervention; days to resume oral intake; changes in nutritional status including anthropometric measurements or albumin; use of interventions including proportions requiring EN and/or PN; duration, time of initiation and cessation; and changes in biochemical micronutrients such as zinc (μmol/L).

Secondary outcomes included post-transplantation parameters: OS at day 100; admission length; time to neutrophil and platelet engraftment [29]; incidence of GVHD [30]; veno-occlusive disease [31]; diarrhea and vomiting (as defined by study authors); infections including positive blood cultures; oral mucositis (measured by National Cancer Institute Common Terminology Criteria [32]); functional or perceived health status, such as Lansky Performance Status [33]; and changes in liver function tests, such as γ-glutamyltransferase.

Information Sources

Databases searched via OVID were MEDLINE (1946 onward), EMBASE (1974 onward), Cochrane Central Register of Controlled Trials, AMED (1985 onward), and CINAHL (via EBSCO). Gray literature searched included EThOS (ethos.bl.uk), Open Grey (www.opengrey.eu), bestevidence.info, metaRegister (http://www.controlled-trials.com/mrct/), and ClinicalTrials.gov.

The last search was run on July 3, 2018. To ensure literature saturation the table of contents of key journals *Biology of Blood and Marrow Transplantation* and *Bone Marrow Transplantation* both from Issue 1, January 2008, and *Clinical Nutrition* from February 2008 were hand searched (dates since the most recent [nonsystematic] review including observational studies [25]), reference lists scanned, and clinical experts contacted in May 2018. One author searched all sources and developed the search strategy, which was peer reviewed by the other authors. The final MEDLINE (OVID) search strategy (July 2018) (see Supplementary Appendix) was adapted for use with the other databases.

Study Selection

Studies were managed using EPPI-Reviewer 4 [34] and references using Mendeley [35]. Search results were imported into EPPI-Reviewer and duplicates removed and then checked manually to remove missed duplicates and multiple study reporting. All references were independently double screened. Records were screened against the eligibility criteria, and disagreements were resolved by consensus. The full text of eligible and potentially eligible studies was retrieved as required.

Data items and extraction

Data extracted were general information (author, title, country, aims, funding sources, conflicts of interest), population (inclusion/exclusion criteria, patient demographics, sample size, between-group differences), confounders and co-interventions (transplantation modalities and procedures including conditioning), outcomes (outcome measurements, results of dichotomous, continuous and time-to-event data), and conclusions and limitations. A data extraction form was developed and piloted on 2 included studies. Extracted data were checked by a second reviewer.

Risk of Bias Assessment

The search identified only observational studies and 1 quasi-randomized trial. Therefore, the Risk of Bias In Non-randomised Studies of Interventions [36] was used. Risk of bias was assessed by 1 author on domains of confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Bias in each domain was classified as "low," "moderate," "serious," "critical," or "no information." Each study was given an overall risk of bias equivalent to the most severe level in any domain.

Data Synthesis

Included studies were clinically heterogenous regarding designs, populations, interventions, and outcomes. Therefore, quantitative meta-analyses were not performed, and results are presented qualitatively in narrative form.

RESULTS

Included Studies

Database searches yielded 4412 studies. No additional studies were identified. After removing duplicates, 3379 remained. After reviewing abstracts, 3312 were discarded for not meeting the eligibility criteria. Full text of the 65 remaining studies was examined, of which 61 did not meet the inclusion criteria. Four studies were finally included. A flow diagram showing the study selection process is displayed in Figure 1 with a summary of included studies in Table 1.

Settings and Designs

All studies were in English. Two studies were 15 to 20 years old [37,38], and studies ranged from 1 year [38] to 11 years [19] in duration. All were single-center studies conducted in Europe, except 1 multicenter study [19].

Designs were mostly cohort studies conducted prospectively [37,39], or retrospectively [19], with the latter matching children on relevant covariates. One study attempted an RCT, but because of nasogastric tube refusals, participants who did and did not consent to randomization were combined, thus resulting in a quasi-randomized study [38].

Participants

Most children received allogenic transplants, except 3 who received autologous transplant [37]. Children had malignant and nonmalignant diseases and received various conditioning regimens, except in 2 studies that focused on those receiving myeloablative conditioning [19,39]. No studies reported sample size calculations, and samples were generally small, from 34 [38] to 194 [19], with 332 participants included in this review.

Interventions

Studies typically compared those who received EN versus PN. However, within each study patients received a mixture of interventions, as expected, with none including a control group. EN was provided similarly across studies. Although 1 study only mentioned "tube feeding" without stating the tube type [38], most used nasogastric tubes. However, differences existed in timing of EN initiation, which was either started systematically the day after HSCT [19,39], when oral intake provided $\leq$75% requirements on 3 consecutive days [38], or when a child lost $>$ 5% of admission weight and/or $\geq$10% decrease in mid-upper arm circumference (MUAC) [37].

PN was initiated systematically the day after HSCT [19]. In other studies children initially received EN and went on to receive PN in cases of poor tolerance, nasogastric tube refusal, gut aGVHD [38,39], or oral mucositis [37].

Outcomes

Studies reported a range of outcomes with wide variations in measurement and reporting. Nutritional parameters included duration of EN and PN, which was reported across most studies. Intakes were widely reported but in varying ways, for example, the kcals/kg/day provided once EN and PN were stabilized [19] or intakes from oral $\pm$ EN $\pm$ PN [38]. Changes in nutritional status were also reported in varying ways, from changes in body mass index [19,39], MUAC [37], and triceps skinfold thickness [38]. Albumin was reported as numbers having hypoalbuminemia [39] or change from start to end of nutrition support [37].

Post-transplantation outcomes included OS at day 100 [19,39], discharge [38], length of admission [19,37,39], aGVHD [19,38,39], veno-occlusive disease [39], positive blood cultures [37], time to neutrophil and platelet engraftment [19,39], oral mucositis measured using the National Cancer Institute Common Terminology Criteria [19] but not defined [37], vomiting and diarrhea (varying definitions) [37,38], days γ-glutamyltransferase was above normal [19], and well-being (Lansky scoring) [37].

Risk of Bias within Studies

A summary of the risk of bias assessment for included studies is shown in Table 2.

Confounding

The most detail regarding transplant modalities were provided by 2 studies [19,39], with 1 study matching participants on 5 modalities [19]. This detail, including statistical control, was largely absent in other trials. Therefore, 1 study was considered moderate risk of confounding [19], compared with serious in other studies.

Participant Selection

One study included all eligible participants and started EN or PN day 1 post-graft and was therefore considered low risk of bias [19]. Two studies demonstrated selection bias [37,39]. In 1 study all patients initially started EN but received PN when they developed oral mucositis [37]. In the other study patients received EN and PN because of poor tolerance or gut aGVHD [39]. These groups were subsequently compared with those who did not develop these conditions. Both were therefore considered serious risk of bias.

Classification of Interventions

The interventions provided to each group were clearly defined in 2 studies and considered low risk of bias [19,39] but not in 1 study, which was therefore considered serious risk of bias [38].

Deviation from Intended Interventions

From groups where EN was provided as first-line therapy, approximately 30% [19,37] to 75% [38] required additional or total PN, mainly due to intolerance issues, nasogastric tube refusal, or gut aGVHD. From groups where PN was provided as first-line therapy, lower percentages required additional EN, 3% [19] and 5% [37]. Consequently, most studies were deemed moderate to serious risk of bias.

Missing Data

Most studies reported largely complete data and were considered low risk of bias.

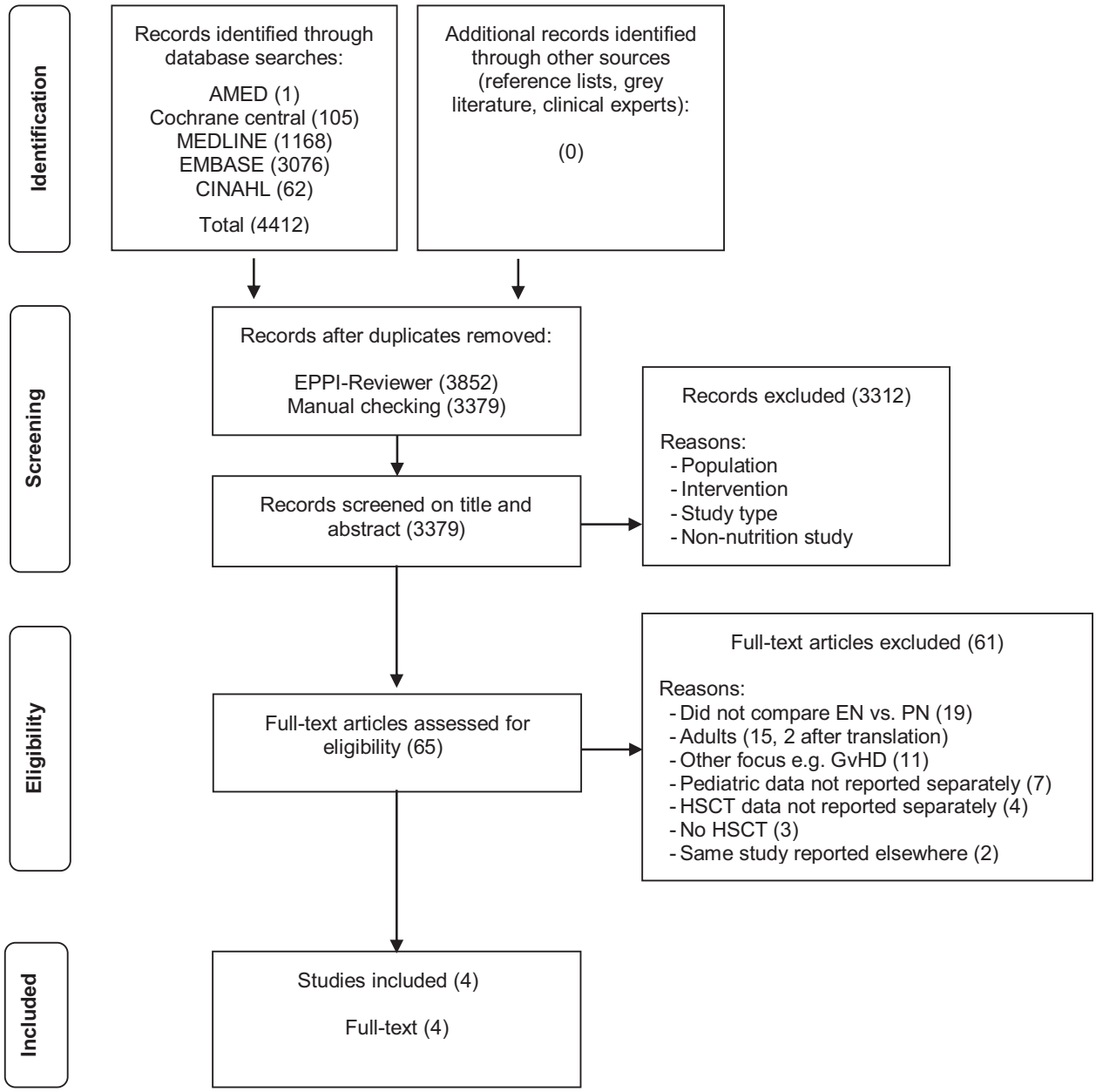

Figure 1. PRISMA flow diagram showing the number of studies included and excluded (with reasons) at each stage of the systematic review.

Outcome Measurement

One study acknowledged that differences in local practices between the EN group managed in 1 center and PN managed across 3 others may have influenced outcomes and was considered moderate risk of bias [19]. Across the remaining studies, certain outcomes required assessor judgement (eg, GVHD), and because studies did not mention assessors being blinded to the intervention, outcomes may have been influenced by this knowledge and were considered moderate risk of bias.

Selective Outcome Reporting

Across all studies, in the absence of any preregistered protocols, there was little evidence of selective reporting, with authors reporting outcomes consistent with the study's aims and outcomes reported in their methods. Risk of bias was therefore moderate for all.

Sources of Bias across Studies

Based on additional information provided by study authors, including funding sources, no significant other risks of bias were identified.

Results of Individual Studies

Summary data reported is shown in Supplementary Tables 1, 2, and 3. Because of the clinical heterogeneity of studies, results frequently omitting confidence intervals, continuous data reported as median [interquartile range] and mean (standard deviation), and some time-to-event data not analyzed using survival analysis with hazard ratios, it was believed to be inappropriate to conduct meta-analyses, and results are reported as a qualitative synthesis.

Primary Outcomes

One study found a longer duration of EN than PN ($P = .001$) [38], whereas another found the opposite ($P < .0001$) [19]. More

Table 1
Summary of Included Studies Investigating the Efficacy of Enteral vs. Parenteral Nutrition in Pediatric HSCT

Author	Groups	Population	Study Design	EN/TF Intervention	PN/EN-PN Intervention	Outcomes
Azarnoush et al. (2012)	EN (n = 50) EN-PN (n = 15)	All received allogenic HSCT after MAC. Malignant and nonmalignant diseases.	Prospective cohort	NGT day 1 postgraft, polymeric feed.	EN supplemented by PN if poor EN tolerance, gut aGVHD.	Various nutritional and post-transplant parameters
Gonzales et al. (2017)	EN (n = 97) PN (n = 97)	All received allogenic HSCT after MAC. Children matched on age, disease, donor, stem cell source, conditioning.	Matched retrospective cohort	NGT day 1 postgraft, polymeric feed until eating >60% requirements.	Initiated day 1 post-graft until discharge.	Various nutritional and post-transplant parameters
Hopman et al. (2003)	TF (n = 12) PN (n = 22)	All received allogenic HSCT. Malignant and nonmalignant diseases. Mixed conditioning regimens.	Quasi-randomized controlled trial	Initiated when intake < 75% requirements. No details of tube, polymeric feed.	Initiated when intake <75% requirements.	Various nutritional and post-transplant parameters
Papadopoulou et al. (1998)	EN (n = 20) PN (n = 19)	Allogenic and autologous. Malignant and nonmalignant diseases. Mixed conditioning regimens.	Prospective cohort	NGT inserted, "before HSCT and oral mucositis developed," when lost ≥5% weight or ≥10% MUAC.	PN given to 19 children who developed oral mucositis.	Various nutritional and post-transplant parameters

TF indicates tube feeding; MAC, myeloablative conditioning; NGT, nasogastric tube.

Table 2
Risk of Bias Summary Using Domains from the Risk of Bias in Non-randomised Studies of Interventions Assessment Tool for Each Included Study

	Gonzales et al. (2017)	Azarnoush et al. (2012)	Papadopoulou et al. (1998)	Hopman et al. (2003)
Confounding	M	S	S	S
Selection of participants	L	S	S	M
Classification of interventions	L	L	M	S
Deviations from intended interventions	M	L	M	S
Missing data	L	L	L	L
Measurement of outcomes	M	M	M	M
Selection of the reported result	M	M	M	M
Overall	M	S	S	S

L indicates low risk of bias: Study is comparable with a well-performed randomized trial; M, moderate risk of bias: study provides sound evidence for a nonrandomized trial but cannot be considered comparable with a well-performed randomized trial; S, serious risk of bias: study has some important problems; C, critical risk of bias: study is too problematic to provide any useful evidence and should not be included in any synthesis. Overall risk of bias: Equal to the most severe level of bias found in any domain.

in the EN versus PN group required EN after discharge (no *P*) [37], yet another study found no difference ($P = .40$) [19].

Higher oral energy, protein, and fluid intakes were reported in the PN group (all $P < .05$), but when combined with EN in the EN group or PN in the PN group, intakes were higher in the EN group (all $P < .05$) [38].

The EN group had lower weight-for-height and MUAC Z-scores than the PN group at admission and day 30 (all $P < .05$) [38]. No differences were found in children losing ≥10% weight ($P > .05$) [39] and change in weight-for-height and MUAC Z-scores from start to end of EN or PN (both $P = .6$) [37]. Triceps skinfold thickness increased from admission to day 30 only in the PN group ($P < .05$) [38]. Body mass index Z-scores from admission to discharge were no different between groups [39], but another study found the EN rather than PN group experienced a significant loss ($P < .0001$) [19]. Correlations were found between duration of EN but not PN and improvements in weight and MUAC ($P < .0001$) [37].

Hypoalbuminemia was more frequent in PN groups ($P = .02$ [39] and $P < .0001$ [19]), as was hypophosphatemia ($P = .02$) [39], although another study found no difference in the latter ($P = .063$) [19]. A lower phosphate during admission was found in the PN versus EN group ($P = .007$) [19]. The lowest albumin during admission was no different between groups ($P = .27$) [19] but was lower in the PN group during nutrition support ($P = .03$) [37]. EN and PN groups experienced a significant albumin reduction from beginning nutrition support to the lowest value but significantly increased in both groups by the end of nutrition support [37]. Significant reductions were found in the PN group but not the EN group in zinc, selenium, and phosphate from pre-HSCT to the lowest level [37].

Secondary Outcomes

Day 100 OS was higher in the EN than PN group (99% versus 86%, $P = .013$) [19], whereas another study found no difference [39]. Day 100 nonrelapse mortality was no different between EN versus PN groups ($P = .066$) [19]. OS during admission was 58% (EN group) versus 68% (PN) and nonrelapse mortality 33% (EN group) versus 23% (PN) [38].

No difference between groups was found for veno-occlusive disease ($P > .05$) [39] or grades I to IV ($P = .07$) [38], skin ($P = .49$), and liver aGVHD ($P = .10$) [19]. Grades III to IV aGVHD was more common in PN groups within day 100 ($P = .033$) [19] and during admission ($P = .004$) [39]. Gut aGVHD was less frequent among EN groups ($P = .011$ [39] and $P = .014$ [19]).

Neutrophil engraftment was achieved by most patients in both groups by day 100 ($P = .1$) [19] and during admission [39]. No differences in time to neutrophil engraftment were seen ($P = .06$ [37] and $P > .05$) [39]; hazard ratio, .81; 95% confidence interval, .62 to 1.04) [19]. Platelet engraftment was more frequent in the EN than PN group within day 100 ($P < .0001$) [19], but no difference was found during admission ($P > .05$) [39]. Platelet engraftment was faster in EN groups ($P = .01$) [39] (hazard ratio, 1.79; 95% confidence interval, 1.37 to 2.33) [19].

Septicemia ($P > .05$ [39] and $P = .37$ [19]), viral infections ($P > .05$ [39] and $P = .86$ [19]), positive blood cultures ($P = .6$) [37], and oral mucositis ($P > .05$ [39] and $P = .9$ [19]) were no different between groups.

More vomiting and diarrhea episodes were found in the EN group (no P) [37]. The percent of days a child vomited > 100 mL or >2 a day and had >2 watery defecations per day were lower in the EN group (no P) [38]. Vomiting duration (>2 a day) was no different between groups ($P = .7$), but diarrhea (>3 loose stools a day) was shorter in the EN group ($P = .03$) [37].

Admissions were shorter in EN groups ($P < .001$ [39] and $P < .0001$) [19]), but another study found no difference ($P = .3$) [37].

A higher maximum γ-glutamyltransferase ($P = .012$) and longer duration above normal range ($P < .0001$) were found in the PN group as well as a correlation between PN duration and γ-glutamyltransferase level ($r = .50$, $P < .0001$) [19].

Well-being using Lansky scoring [33] was measured in 1 study [37]. Oral mucositis led to worse well-being at the start of PN compared with the start of EN ($P < .0001$). Development of diarrhea in the PN group led to worsening well-being ($P = .002$), but this improved by the end of PN ($P < .0001$). No changes in well-being were observed in the EN group during nutrition support ($P = .7$) or between groups at the end of nutritional support ($P = .3$).

DISCUSSION

To our knowledge this is the first systematic review investigating the efficacy of EN versus PN in pediatric HSCT. Included studies were clinically heterogeneous and at moderate to serious risk of bias. Conflicting results in favor of either method of nutrition support or no difference between methods were seen for duration of interventions, nutritional intakes, biochemical and anthropometric changes, mortality, infections, admission length, and neutrophil engraftment. However, results support the growing body of increasingly higher quality pediatric evidence [19,39] that EN is feasible and may provide favorable benefits over PN regarding aGVHD and platelet engraftment.

EN was well tolerated, with 70% to 100% of the EN groups maintained exclusively on EN [19,37,39]. Conflicting evidence regarding duration of EN and PN was reported by 2 studies [19,38]. However, studies initiated and stopped nutrition support on incomparable criteria. There remains no consensus on the optimal indication for nutrition support [16].

Inconsistent reporting of nutritional intakes and anthropometric measurements made comparing intakes and nutritional status difficult. Nutrition support route seemed not to influence intakes. Most children were normally nourished on admission, typically defined as a Z-score of any anthropometric parameter within ±2 standard deviations. On commencement of treatment, regardless of nutrition support route or anthropometric measure, most children maintained a satisfactory nutritional status either during nutrition support [37] or until discharge [19,38,39]. Although weight and body mass index were widely used, they are crude markers of nutritional status and do not provide details of body composition, which is an important consideration for survival [40]. Future studies should use MUAC or bioelectrical impedance as more sensitive markers of nutritional status [41]. Malnutrition is an independent risk factor for nonrelapse mortality [42]. The maintenance of nutritional status could reflect a proactive approach to nutrition support across studies. However, because no studies compared nutritional interventions with control groups receiving no nutrition support, it cannot be said whether malnutrition is modifiable through nutrition support [8].

Among PN groups, even though falls in nutritional biochemistry were more significant and hypoalbuminemia more common [19,37,39], decreases in these parameters were also seen in EN groups. The etiology of these changes are multifactorial, with hypoalbuminemia attributable to fluid redistribution, protein losing enteropathy [43], and acute phase response to infections [44], with zinc reductions also attributable to the latter [45]. Zinc depletion has been found to correlate with more positive blood cultures [46], yet included studies found no differences between groups for infections, possibly because time periods of investigation were too short [19]. This is contrary to studies showing more infections associated with PN [15,47].

Neutrophil engraftment was no different between groups, but faster platelet engraftment was found among EN groups [19,39]. A possible explanation could be long-term administration of intravenous lipid emulsion inducing hyperactivation of the monocyte–macrophage system [48]. However, with thrombocytopenia a manifestation of GVHD, delayed platelet recovery could alternatively be a secondary finding to increased GVHD in PN groups. Any differences found in platelet recovery when comparing EN versus PN in autologous HSCT recipients where GVHD would not be expected would better support the lipid hypothesis.

Lower incidence of aGVHD grades III to IV and gut manifestation were observed in EN groups [19,39]. Damage to the gut after conditioning, coupled with increased mucosal atrophy and intestinal permeability from resting the gut during PN [49], leads to alterations in gut microbiota, which have been linked to aGVHD [50]. During periods of maximum gut toxicity, provision of even trophic EN can support the gut barrier function, prevent mucosal atrophy, and reduce the risk of bacterial translocation [51], which may explain the protective benefit of EN.

Limitations

This review highlights numerous limitations of the evidence base. Although many other studies investigating this population have shown EN to be feasible [52–54], they were excluded because no EN versus PN comparisons were made. We included non-English studies and set no date limits on searches to capture as much literature as possible. Studies were also generally old. The advancement of conditioning regimens and nutritional products over the past 20 years brings into question the comparability of older with more recent studies. Included studies were at moderate to serious risk of bias because of the absence of baseline confounding parameters, statistical control, retrospective designs, selection bias, randomization, and control groups. The heterogeneity of studies meant that meta-analyses were not conducted. The HSCT population is inherently heterogenous. The more specific the population becomes to optimize internal validity, the generalizability to the wider population becomes compromised. Researching more specific populations also makes obtaining adequate sample sizes, which were generally small across studies, difficult. Further heterogeneity was seen in nutritional interventions.

For example, among EN groups, 30% [19,37] and 75% [38] required additional PN. Thus, no studies compared children maintained exclusively on EN or PN. This may not be realistic because some deviation from intended interventions would be expected in practice. Finally, the range of outcomes, which varied in measurement, reporting, and analysis, made comparisons and meta-analyses difficult, and the number of included studies was too low for sensitivity and subgroup analyses to be undertaken.

Implications for Practice

Despite these limitations, nutrition support remains an integral part of clinical care and international guidelines [10,11]. The wide range of outcomes reported mostly no difference or conflicting results, between either method of nutrition support. However, results support the growing body of pediatric evidence that EN is feasible may provide similar benefits to PN regarding many nutritional and post-transplantation outcomes and could provide benefits above PN regarding aGVHD and platelet engraftment. We hope this review facilitates the decision-making of clinicians when providing nutrition support to these children.

Implications for Research

The paucity of studies highlights a need for more primary research. Methodologic studies are needed to match nutritional interventions and define pertinent outcomes that can be standardized across units. Following this, the current review supports previous reviews [8,21] in recommending that future studies should then conduct RCTs to provide higher quality evidence comparing the effectiveness of EN and PN, ideally including a control group, using these agreed on interventions and outcomes. Such studies should be multicenter to obtain larger sample sizes and ensure trials are adequately powered.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2019.02.023.

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