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

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ABSTRACT

Background: 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 vs. PN provided during admission to children ≤18 years undergoing HSCT. Primary outcomes considered efficacy in relation to various nutritional parameters, and secondary outcomes included a range of post-transplantation parameters.

Methods: 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 grey literature searched using EThOS and Open Grey. Randomized and observational studies comparing any forms of EN vs. PN in children ≤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. As included studies were observational, risk of bias was assessed using ROBINS-I.

Results: As 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.

Discussion: A paucity of studies were 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.

Conclusions: 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.

Keywords: Pediatric; hematopoietic stem cell transplantation; enteral nutrition; parenteral nutrition; systematic review.

INTRODUCTION

Rationale

Hematopoietic stem cell transplantation (HSCT) has become a well-recognized treatment for malignant and non-malignant 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) following 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 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, recent American and European adult guidelines (10,11), have recommended first-line enteral nutrition (EN) due to 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 centres lacking nutrition support protocols (18) and continuing to use first-line PN (19).

Despite no international pediatric guidelines for nutrition support in HSCT, two 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), the second focused on pediatrics but included those with cancer who had, and had not, received HSCT (21). Across both reviews only three 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 vs. 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 (non-systematic) review including observational studies in adult and pediatric HSCT is now ten years old (25).

This highlights the absence of a review including randomized and non-randomized 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 two 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.

Objectives

The objective of this review is to determine, through randomized and observational studies, the efficacy of any forms of EN vs. PN provided during admission to children (≤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, including mortality, infections and GvHD.

MATERIALS AND 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 (non-randomized) clinical trials, quasi-RCTs, prospective and retrospective cohort studies, cross-sectional studies, case-control studies and case series. Grey literature and abstracts were included, if appropriate. In the latter case, we planned to contact authors to obtain full reports. 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 or Google translate, but only included if they could be fully translated.

Participants

Participants included children (≤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 was 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 as 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 vs. PN.

Outcomes

In the absence of standardised outcomes, and consequently a diverse range of endpoints reported across the literature (28), outcomes from the 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 (VOD) (31), diarrhea and vomiting (as defined by study authors), infections including positive blood cultures, oral mucositis (measured by National Cancer Institute-Common Terminology Criteria (NCI-CTC) (32)),

functional or perceived health status, such as Lansky Performance Status (33), and changes in liver function tests, such as gamma-glutamyltransferase (GGT).

Information sources

Databases searched via OVID were MEDLINE (1946 onwards), EMBASE (1974 onwards), Cochrane Central Register of Controlled Trials, AMED (1985 onwards) and CINAHL (via EBSCO). Grey 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 3 July 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 (non-systematic) 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) (Supplementary Appendix Search Terms) 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 resolved by consensus. The full-text of eligible and potentially eligible studies was retrieved as required.

Data items and extraction

(1) General information: author, title, country, aims, funding sources, conflicts of interest.
(2) Population: inclusion/exclusion criteria, patient demographics, sample size, between group differences.
(3) Confounders and co-interventions: transplantation modalities and procedures including conditioning.
(4) Outcomes: outcome measurements, results of dichotomous, continuous and time-to-event data.
(5) Conclusions: conclusions and limitations.

A data extraction form was developed and piloted on two included studies. Extracted data was checked by a second reviewer.

Risk of bias assessment

The search identified only observational studies and one quasi-randomized trial. Therefore, the 'Risk Of Bias In Non-randomised Studies of Interventions' (ROBINS-I) (36), was used. Risk of bias was assessed by one author on domains including: 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 67 remaining studies was examined, of which 61 did not meet the inclusion criteria. Six studies were finally included including two abstracts, of which the full-text could not be retrieved despite literature searches and attempts to contact authors via email. A flow diagram showing the study selection process is displayed in Figure 1 with a summary of included studies in Table 1.

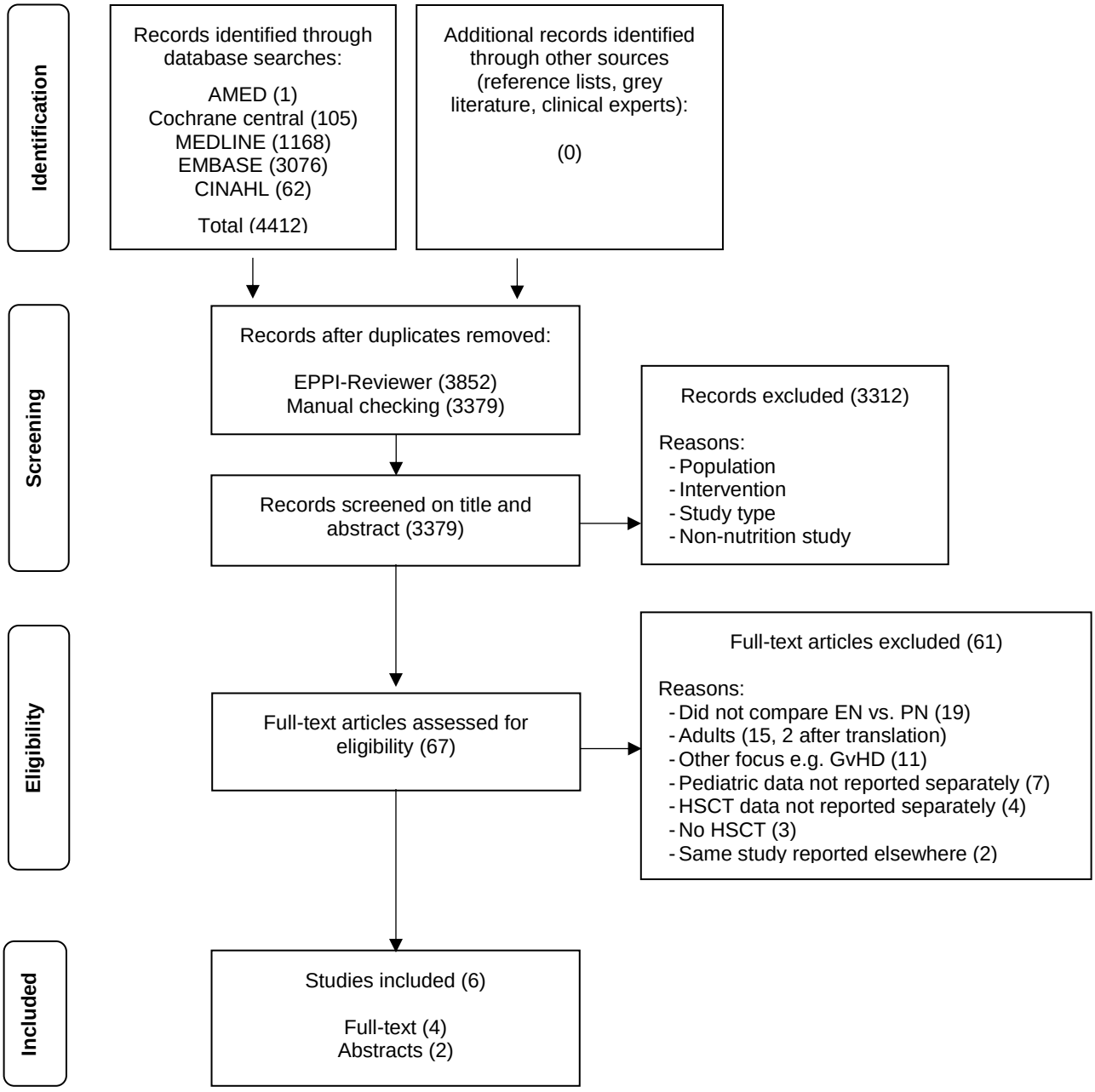

Figure 1. PRISMA flow diagram showing the number of studies included and excluded (with reasons) at each stage of the systematic review.

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 following MAC. Malignant and non-malignant diseases.	Prospective cohort.	NGT day one post-graft, polymeric feed.	EN supplemented by PN if poor EN tolerance, gut aGvHD.	Various nutritional and post-transplant parameters.
Couec et al. (2010)	EN (n=42) PN (n=39)	No detail.	Retrospective cohort.	No detail.		Duration of nutritional interventions and change in nutritional status.
Gonzales et al. (2017)	EN (n=97) PN (n=97)	All received allogenic HSCT following MAC. Children matched on age, disease, donor, stem cell source, conditioning.	Matched retrospective cohort.	NGT day one post-graft, polymeric feed until eating >60% requirements.	Initiated day one 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 non-malignant 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.
Koerich et al. (2010)	TF (n=14) PN (n=22)	No detail regarding HSCT type or conditioning. Malignant and non-malignant diseases.	Retrospective observational.	No detail.		Use of nutritional interventions and intakes.
Papadopoulou et al. (1998)	EN (n=20) PN (n=19)	Allogenic and autologous. Malignant and non-malignant 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.

Abbreviations: aGvHD, acute graft-versus-host-disease; EN, enteral nutrition; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative conditioning; MUAC, mid-upper-arm circumference; NGT, nasogastric tube; OS, overall survival; PN, parenteral nutrition; TF, tube feeding.

Settings and designs

All studies were in English with two 15-20 years old (37,38), and ranged from one year (38), to 11 (19) in duration. All were single-centre studies conducted in Europe, except one multi-centre study (19), and one undertaken in Brazil (39).

Designs were mostly cohort studies conducted prospectively (37,40), or retrospectively (19), with the latter matching children on relevant covariates. One study attempted an RCT, but due to 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 three who received autologous transplant (37). Children had malignant and non-malignant diseases and received various conditioning regimens, except in two studies which focused on those receiving myeloablative conditioning (19,40). No studies reported sample size calculations and samples were generally small, from 34 (38) to 194 (19), with 449 participants included in this review.

Interventions

Studies typically compared those who received EN vs. PN. However, within each study there were patients that received a mixture of interventions, as expected, with none including a control group. Intervention details were absent in two studies (39,41), but EN was provided similarly across other studies. Although two studies only mentioned 'tube feeding' without stating the tube type (38,39), most used nasogastric tubes. However, differences existed is timing of EN initiation, which was either started systematically the day after HSCT (19,40), when oral intake provided ≤75% requirements on three consecutive days (38), or when a child lost >5% of admission weight and/or ≥10% decrease in mid-upper-arm circumference (MUAC) (37).

PN was initiated systematically the day following 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 (38,40), 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±EN±PN (38). Changes in nutritional status were also reported in varying ways, from changes in body mass index (BMI) (19,40), MUAC (37), and triceps skinfold thickness (TST) (38). Albumin was reported as numbers having hypoalbuminaemia (40), or

change from start to end of nutrition support (37).

Post-transplantation outcomes included OS at day 100 (19,40), and discharge (38), length of admission (19,37,40), aGvHD (19,38,40), VOD (40), positive blood cultures (37), time to neutrophil and platelet engraftment (19,40), oral mucositis measured using NCI-CTC (19), but not defined (37), vomiting and diarrhea (varying definitions) (37,38), days GGT 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.

Table 2.

Risk of bias summary using domains from the ROBINS-I assessment tool for each included study.

	Gonzales et al. (2017)	*Azarnoush et al. (2012)*	*Papadopoulou et al. (1998)*	*Hopman et al. (2003)*	*Koerich et al. (2010)*	*Couec et al. (2010)*
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	L	L
Measurement of outcomes	M	M	M	M	M	M
Selection of the reported result	M	M	M	M	M	M
Overall	M	S	S	S	?	?

L : Low risk of bias. Study is comparable to a well performed randomized trial.

M : Moderate risk of bias. Study provides sound evidence for a non-randomized trial, but cannot be considered comparable to 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.

? : No information. Insufficient information provided to determine risk of bias.

Overall risk of bias: Equal to the most severe level of bias found in any domain.

Confounding

The most detail regarding transplant modalities were provided by (19,40), with one study matching participants on five modalities (19). This detail, including statistical control, was largely absent in other trials. Therefore, one study was considered moderate risk of confounding (19), compared to serious in other studies.

Participant selection

One study included all eligible participants and started EN or PN day one post-graft, and was therefore considered low risk of bias (19). Two studies demonstrated selection bias (37,40). In the first, all patients initially started EN, but patients received PN who developed oral mucositis (37). In the second, patients received EN-PN because of poor tolerance or gut aGvHD (40). These groups were subsequently compared to 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 two studies and considered low risk of bias (19,40), but not in one study which was therefore considered serious risk of bias (38).

Deviation from intended interventions

From groups where EN was provided first-line, 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 first-line, 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.

Outcome measurement

One study acknowledged that differences in local practices between the EN group managed in one centre, and PN managed across three others, may have influenced outcomes, and was considered moderate risk of bias (19). Across the remaining studies certain outcomes required assessor judgement (e.g. GvHD), and as 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 pre-registered protocols, there is 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. Due to the clinical heterogeneity of studies, results frequently omitting confidence intervals, continuous data reported as median [IQR] and mean (SD), and some time-to-event data not analyzed using survival analysis with hazard ratios (HR), it was felt inappropriate to conduct meta-analyses, and results are reported as a qualitative synthesis.

Primary outcomes

Five studies reported duration of nutrition support, but only two reported *P* values. One found a longer duration of EN than PN (median [IQR] 43 days [25-51] vs. 27 [6-44], p=0.001) (38), whilst another found the opposite (EN median [IQR] 23 days [20-29], PN 44 [32-57], p<0.0001) (19). Two studies reported EN requirement post-discharge. One found more in the EN than the PN group required this (10% vs. 5%, no significance reported) (37), whilst the other found no difference (6% vs. 9%, p=0.40) (19).

One study found 55% in the EN vs. 95% in the PN group achieved a sufficient oral intake after 22 and 23 days respectively (37), but did not define how this was measured. Higher energy intakes (kcals/kg/day) were reported in the PN vs. EN groups by two studies (19,39). Another reported significantly higher oral intakes in the PN group for energy (17 vs. 28 kcals/kg/day), protein (0.5 vs. 1.0 g/kg/day) and fluid (19 vs. 28 ml/kg/day) (all p<0.05), but when oral intakes were combined with EN in the EN group, or PN in the PN group, intakes of energy (66 vs. 57 kcals/kg/day), protein (1.6 vs. 1.4 g/kg/day) and fluid (86 vs. 70 ml/kg/day) were significantly higher in the EN group (all p<0.05) (38).

No differences were found in children losing ≥10% weight (8% EN group vs. 7% PN, p>0.05) (40).

Weight-for-height Z-scores increased significantly from HSCT to day 100 only in the EN group (41), whilst another study found no difference from start to end of EN or PN (0.09 vs. 0.14, p=0.6) (37). Significance of the change in the same measure between groups was not reported by another study (38). However, the EN group had a significantly lower weight-for-height Z-score than the PN group at admission (-0.01 vs. 1.5) and day 30 (0.4 vs. 1.6) (both $p<0.05$) (38). MUAC Z-scores were reported in two studies. One found no difference in change during nutrition support between EN and PN groups (0.09 vs. 0.16, p=0.6) (37), the other did not report the significance of change between groups, but again the EN group had a significantly lower MUAC Z-score than the PN group at admission (-1.0 vs. -0.04) and day 30 (-0.5 vs. 0.4) (both $p<0.05$) (38). TST was measured in one study which found this significantly increased from admission (0.5) to day 30 (1.2) only in the PN group ($p<0.05$) (38). Temporal evolution of BMI Z-scores reported weekly from admission to discharge were reported by two studies. One showed no difference between groups (40), the second found the EN group experienced a significant loss compared to the PN group ($p<0.0001$), but the different length of admissions prevented a direct comparison (19). One study found significant correlations between duration of EN, but not PN, and improvements in weight and MUAC ($p<0.0001$) (37).

Hypoalbuminaemia ≤30g/L (40) and ≤35g/L (19) was more frequent in PN groups (p=0.02, $p<0.0001$ respectively). The lowest albumin during admission was not different between groups (p=0.27) (19), but was lower in the PN group during nutrition support (EN 31.5g/L, PN 28.7g/L, p=0.03) (37). One study reported both groups experienced a significant albumin reduction from the start of nutrition support to the lowest value, but both groups experienced a significant increase by the end of nutrition support (37).

Hypophosphataemia <35mg/L was found to be more frequent in the EN-PN than EN group (34% 73%, p=0.02) (40), but no difference was found between groups in another study (p=0.063) (19). However, this latter study found a difference in the lowest value during admission in the PN vs. EN group (21.2mg/L vs. 23.8, p=0.007) (19). Another study found significant reductions in the PN group, not EN, in zinc, selenium and phosphate from pre-HSCT to the lowest level (37).

Secondary outcomes

Day 100 OS was lower in the EN than PN group (99% vs. 86%, HR 0.73, 95% CI 0.01-0.57, p=0.013) (19), whereas another study found no difference (100% vs. 100%) (40). Day 100 non-relapse

mortality (NRM) was no different between EN vs. PN groups (1% vs. 7%, HR 0.14, 95% CI 0.02-1.14, p=0.066) (19). Another study reported OS during admission (tube feed 58% vs. PN group 68%) and NRM (tube feed 33% vs. PN group 23%) (38). Time from admission to death was median [IQR] 90 [26-210] days in the tube feed vs. 150 [53-180] in the PN group, but was not reported using time-to-event analysis (38).

Incidence of aGvHD grades I-IV were no different between groups (p=0.07) (38), but grades III-IV were more common within day 100 in the PN than EN group (25% vs. 16%, HR 0.49, 95% CI 0.25-0.95, p=0.033) (19), and during admission in the EN-PN than EN group (47% vs. 10%, p=0.004) (40). Incidence of skin and liver aGvHD were no different between groups (p=0.49 and 0.10 respectively) (19), but gut aGvHD was less frequent in the EN vs. PN groups (4% vs. 40%, p=0.011) (40), (16% vs. 32%, p=0.014) (19). No difference in VOD was found between groups, (p>0.05) (40).

Neutrophil engraftment defined by (29), was achieved by most patients in both EN and PN groups by day 100 (99% vs. 99%, p=0.1) (19), and during admission (100% vs. 100%) (40). No differences in time to neutrophil engraftment were seen (mean (SD) EN 13.6 (4.0) days, PN 18.4 (11.1), p=0.06) (37), (median [IQR], EN 23 [12-41] days, PN 24 [16-60], p>0.05) (40), (HR 0.81, 95% CI 0.62-1.04) (19). Successful platelet engraftment $\geq 50x10^9$/L was more frequent in the EN than PN group within day 100 (92% vs. 78%, p<0.0001) (19), but no difference was found during admission (76% vs. 60%, p>0.05) (40). Time to platelet engraftment was faster in EN than PN groups (median [IQR], EN 23 [11-40] days, PN 29 [17-63], p=0.01) (40), (HR 1.79, 95% CI 1.37-2.33) (19).

Incidence of septicaemia p>0.05 (40), p=0.37 (19), viral infections p>0.05 (40), p=0.86 (19), positive blood cultures p=0.6 (37), and oral mucositis p>0.05 (40), p=0.9 (19), were no different between groups.

One study reported no difference in diarrhea or vomiting between tube feed and PN groups (39). Another reported more episodes of vomiting >2/day for >2 days in the EN than PN group (four vs. 11), and diarrhea (>3 loose stools/day) (four vs. 19) (37), but did not report significance. The percent of days a child vomited >100ml or >2/day and had >2 watery defecations/day, were lower in the EN than PN group (vomiting, 23% vs. 24%; diarrhea, 19% vs. 27%, no significance reported) (38). Vomiting duration (days >2/day) was no different between groups (p=0.7), but diarrhea (days >3 loose stools/day), was significantly shorter in the EN than PN group (mean (SD), 4.2 (1.5), 11.9 (10.8), p=0.03) (37).

Admission lengths (median [IQR]), were shorter in the EN than PN groups (29 [20-60] days vs. 40

[27-76], p<0.001) (40), (28 [25-41] vs. 52 [41-66], p<0.0001) (19), but no difference was found in another study (27 [14-39] vs. 30 [21-122], p=0.3) (37).

One study investigated GGT and found a higher maximum level in the PN than EN group (p=0.012), longer duration above normal range (median [IQR], 24 [13-44] days vs. 15 [6-24], p<0.0001), and a significant correlation between PN duration and GGT level (r=0.50, p<0.0001) (19).

Well-being using the Lansky performance scoring system (Lansky et al., 1987), was measured in one study (37). Well-being before HSCT was comparable between PN and EN groups, (median [IQR], 80 [50-90] vs. 70 [50-90], p=0.4). The development of oral mucositis led to well-being worsening by the start of nutrition support in the PN compared to EN group (median [IQR], 40 [20-75] vs. 70 [40-90], p<0.0001). Development of diarrhea in the PN group was associated with a further worsening of well-being compared to the start of PN (median [IQR] of the minimum score during PN was 40 [10-70], p=0.002). At the end of PN, well-being was better compared to the start (median [IQR] 60 [30-80], p<0.0001). In the EN group well-being was unaltered during its provision (median [IQR] at the end of EN was 60 [40-90], p=0.7). At the end of nutrition support no differences were found between PN and EN groups (median [IQR] 60 [40-90] vs. 60 [40-90], p=0.5).

DISCUSSION

To our knowledge, this is the first systematic review investigating the efficacy of EN vs. PN specifically 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 (19,40), that EN is feasible and may provide favorable benefits over PN regarding aGvHD and platelet engraftment.

EN was well tolerated with 70-100% of the EN groups maintained exclusively on EN (19,37,40), consistent with adult studies (42,43). Conflicting evidence regarding duration of EN and PN was reported by two 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).

The inconsistency in reporting of nutritional intakes and various anthropometric techniques measured at varying time points 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 SDs. This is a similar finding to adult studies (2,44). 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 (19,38,40). Although weight and BMI 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 (45). Future studies should consider using MUAC or bioelectrical impedance as more sensitive markers of nutritional status (46). Malnutrition is an independent risk factor for NRM (47). The maintenance of nutritional status could reflect a proactive approach to nutrition support across studies, but the absence of comparisons to any control group makes it difficult to say what the benefits would have been compared to no nutrition support. Until suitably powered trials comparing nutritional interventions to placebo are conducted, 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 hypoalbuminaemia more common (19,37,40), decreases in these parameters were also seen in EN groups. The aetiology of these changes are multifactorial, with hypoalbuminaemia attributable to fluid redistribution, protein losing enteropathy (48), and acute phase response to infections (49), with zinc reductions also attributable to the latter (50). Zinc depletion has been found to correlate with more positive blood cultures (51), 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 (15,52).

Neutrophil engraftment was no different between groups, contrary to results from an adult study (42). However, consistent with this study, and another (53), was the finding of faster platelet engraftment among EN groups (19,40). A possible explanation could be long-term administration of intravenous lipid emulsion inducing hyperactivation of the monocyte-macrophage system (54).

Lower incidence of aGvHD grades III-IV and gut manifestation were observed in EN groups (19,40), similar findings to those observed in adults (42,55). Damage to the gut following conditioning, coupled with increased mucosal atrophy and intestinal permeability from resting the gut during PN (56), leads to alterations in gut microbiota which have been linked to aGvHD (57). 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 (58), which may explain the protective benefit of EN.

CONCLUSIONS

Limitations

One limitation of this review was the inclusion of two abstracts of which the full-text was not identified. This review highlights numerous limitations of the evidence base. Whilst many other studies investigating this population have shown EN to be feasible (59–61), they were excluded as no EN vs. 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 to more recent studies. Included studies were at moderate to serious risk of bias due to 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 optimise internal validity, the generalisability 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 as 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 will facilitate 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. Methodological studies are needed to agree 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 interventions and outcomes. Such studies should be multi-centre to obtain larger sample sizes and ensure trials are adequately powered.

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AUTHORSHIP

JE drafted the protocol and final article, screened all records retrieved from the searches and assessed risk of bias for all included studies. JN and SH provided critical revision and feedback on the protocol and final article. All authors approved the final submitted article.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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