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Impact of Allogeneic Hematopoietic Stem Cell Transplantation on Nutritional Status and Intake in Children

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ABSTRACT

Objectives: This study aimed to describe the impact of allogeneic/haploidentical hematopoietic stem cell transplantation on nutritional status and intake in a group of children aged 2 to 18 years.

Methods: In an observational study, data were collected prospectively. Patients were prescribed individual nutritional support by hospital routines. Anthropometrics were measured pre-transplant at hospital admission and weekly from the day of transplant (day 0) until day +28. *z* scores for weight, height, and BMI were calculated using Norwegian growth references to assess nutritional status. Pre-transplant diet was assessed on the day of hospitalization. Nutrient provision from enteral nutrition (EN = oral and tube) and parenteral nutrition (PN) was assessed by daily records from day +1 until day +28, or previous discharge, and compared with recommendations (RI) from the Nordic Nutrition Recommendations and ESPGHAN guidelines. Total energy intake was presented as the percentage (%) of basal metabolic rate (BMR) calculated by the Schofield equation. Macro- and micronutrient provisions were presented as medians (interquartile range) and the % of RI.

Results: Twenty-eight patients, mean age 10.3 years (range 3.5–16.6), were included. Two-thirds (n = 18) had malignant diseases. At admission, mean weight Z-score was −0.3, height *z* scores −0.7, and BMI Z-score 0.1. Eighteen percent (n = 5) were stunted and 25% (n = 7) had overweight. At admission, 25% (n = 7) had established tube feeding, and 7% (n = 2) also had PN. No significant changes in weight *z* scores were detected during the studied weeks ($P = 0.454$). The median daily energy provision was 115% (110–123) of BMR and proteins 1.5 (1.3–1.8) g/kg. EN was provided during a median of 93% of the studied days and provided 21% of the energy. PN was given on a median of 96% of the studied days and provided 79% of energy. RI for vitamins, magnesium, and zinc was met. Provision of copper, iodine, selenium, calcium, and phosphate was below RI.

Conclusions: Combined EN and PN providing 115% of BMR and 1.5 g/kg protein ensured stable weight by day +28 and covered RI, except for trace elements and minerals.

Key Words: energy requirement, enteral nutrition, micronutrients, parenteral nutrition, protein

What Is Known

- Gastrointestinal toxicity and feeding problems are frequent during hospitalization for allogeneic hematopoietic stem cell transplantation (HSCT).
- Enteral nutrition is first-line therapy.
- Malnutrition is negatively associated with treatment outcomes, yet nutritional requirements and provision are not well studied in HSCT.

What Is New

- Energy provision of median 115% of basal metabolic rate and 1.5 g/kg protein ensured a stable weight by day +28 post-transplant, indicating low energy requirement.
- Even though enteral nutrition was first-line therapy, 79% of energy provision was from parenteral nutrition.
- Recommendations for macronutrients and vitamins were met. Copper, iodine, selenium, calcium, and phosphate were below the recommended values.

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative treatment for many patients with treatment-resistant malignant diseases, such as acute leukemias, and non-malignant diseases, such as immunodeficiencies, bone marrow failures, and metabolic conditions (1). Pre-transplant conditioning therapy consists

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of high doses of chemotherapy and sometimes total body irradiation. The aim is to eradicate all bone marrow cells, provide an immunosuppressed environment for donor cell engraftment, prevent rejection of donor stem cells and graft-versus-host disease (GvHD), and provide stem-cell niches in the host for the new stem cells (2). The second stage is the transplant (day 0), where donor stem cells are infused. Post-transplant, days are counted from day +1. In this stage, the goal is a reconstitution of hematopoiesis, immune function, and patient rehabilitation (3). The joint burden of the pre-transplant chemotherapy/irradiation, the transplant regimen, and numerous challenges in the post-transplant period put patients at risk of many complications. Patients are hospitalized for weeks to months post-transplant for medical and supportive treatment (4, 5). Gastrointestinal toxicity, infections, GvHD, pain, and psychological factors can induce feeding difficulties, and underlying diseases might aggravate nutritional risk. Children often require nutritional support post-transplant (5–16).

Studies have revealed that most children undergoing HSCT have normal BMI at admission (13, 17). However, low BMI, overweight, and weight loss during the post-transplant weeks have been detected (6, 17–19). Malnutrition, before or during HSCT, has been found to be an independent risk factor for complications and mortality (17, 19, 20). For that reason, nutritional treatment should be prioritized in pediatric patients. However, several questions regarding best practices to optimize supportive nutritional treatment remain unanswered.

Nutritional requirements during the post-transplant weeks are not well studied. However, a decline in resting energy expenditure during the first weeks post-transplant has been found in children undergoing HSCT (9, 21).

Acute GvHD (aGvHD) is the major cause of mortality during the first year after HSCT and is a process in which the donor-derived T-cells damage the host's healthy tissue (22). Studies have found that EN might contribute to preventing GvHD (23–25) and emphasizes the importance of using the gastrointestinal tract. EN is recommended as first-line therapy, but ESPEN also highlights that parenteral nutrition (PN) will be necessary for some situations, such as allogeneic transplantations (26).

Another critical but less studied aspect of nutritional therapy in HSCT is the provision of micronutrients and if recommendations are met. Micronutrient status has been found to influence clinical outcomes of pediatric cancer patients (27), which might imply that micronutrients also can be essential for HSCT patients.

This study aimed to describe the impact of HSCT on nutritional status and intake in children. We hypothesized that combined nutritional provision from EN and PN ensured a stable weight and covered nutrient recommendations. Secondary, we report transplantation outcomes by day +28.

MATERIALS AND METHODS

Design and Subjects

We performed an observational, prospective study of children undergoing HSCT at the Department of Pediatric Hematology and Oncology, Oslo University Hospital (OUH). The study period was from hospital admission until day +28 post-HSCT or earlier discharge. All available patients aged 2 to 18 years with malignant and nonmalignant conditions were invited. We recruited a convenience sample from April 2018 to November 2020. Exclusion criteria were language difficulties (not able to read and write Norwegian), Down syndrome, previous HSCT, or diagnosed anorexia nervosa. Clinical information, such as diagnoses, aGvHD, infections, s-glucose, and demographic data, was obtained from medical records.

Anthropometry

Patient weight (kg) was measured by Seca weight (model 7701321004, Seca gmbh & co. kg, Germany) and height (cm) by a stadiometer (Holtain Limited, Britain). Measurements were done without shoes, in light clothing and by standard procedures on the day of hospital admission (28). Daily morning weight on the day of transplantation (day 0) and post-HSCT days +7, +14, +21, and +28 were used. *z* scores for weight-for-age, height-for-age, and BMI-for-age were calculated based on the Norwegian reference population (29). Stunting was defined as height *z* scores <–2, undernutrition (thinness) as BMI *z* scores <–2, overweight as BMI *z* scores >1, and obesity as BMI *z* scores >2 (30, 31). In the results, overweight and obesity were combined and presented as overweight.

Nutritional Therapy

Nutritional therapy was provided by the Department's standard nutritional treatment routines (32). Energy requirement in children depends on age, gender, and weight. Therefore, the percent (%) of basal metabolic rate (BMR) was used to describe energy requirement and provision. BMR was calculated by the Schofield equation (33) at admission. The total energy requirement was estimated to be 120% of BMR. To prevent overfeeding, an adjusted weight corresponding to the 75-percentile for BMI was used to calculate energy requirements for participants with obesity.

Post-transplant, EN was first-line therapy, and PN was added to reach energy requirements if necessary (26). The medical team initiated, regulated, and discontinued tube and PN according to estimated needs from day +1 based on daily evaluation of oral intake, tube feeding, PN, and the patient's clinical status (eg, fluid balance, blood values, gastrointestinal function, and tolerance of EN). Patients were encouraged an oral intake. Early placement of a nasogastric tube was routinely used to ensure EN via the gastrointestinal tract if oral intake was low or to ease the oral medication burden (32). Contraindications to EN were conditions needing total bowel rest, for example, grade 4 gut GvHD or typhlitis (34).

Nutritionally complete, age-appropriate ready-to-use tube feeds were used. In cases of impaired enteral tolerance, the infusion rate was reduced, or the type of product changed. If the tube was lost, it was reinserted based on clinical judgment. PN was initiated at the earliest on post-transplant day +1. A weight-appropriate, ready-to-use multi-chamber PN bag was prescribed. PN was supplemented with parenteral multivitamins (Vitalipid Infant and Soluvit, Fresenius Kabi) and trace elements (Peditrace, Fresenius Kabi) products (35, 36). Peditrace was chosen to limit iron provision since HSCT patients are at risk of iron overload (37). Individual tailored PN solutions were used if metabolic complications (38).

Nutrient Intake

A diet record was kept from day +1 to +28, or until the day before discharge, if earlier (39). Patients, parents, and nurses recorded oral intake bedside by household measures (e.g., teaspoons). Dietary supplements, tube feeds (products, volumes), and PN (products, additives, volumes) were registered in the patient's medical records. Two assigned pediatric dietitians ensured all records' quality and did nutritional calculations. DietistPro, a software for dietary analysis based on the Norwegian Food Composition Table (40), was used by the dietitians to calculate participants' mean nutrient provision for all recorded days. Separate calculations were made for oral diet (including supplements), tube feeds, PN, and total provision. Oral and tube feeds were combined to assess EN. The median % of BMR was used to describe energy provisions for the total diet record period and each of the 4 weeks. The provision of macro- and micronutrients from EN and PN was compared with the respective RI from the Nordic Nutrition Recommendations and ESPGHAN guidelines (35, 36, 41–46). Macro-, and micronutrients were presented as medians [interquartile range (IQR)] and % of RI. The percentage (%) of participants reaching RI was presented.

Transplantation Outcomes by Day +28

We report survival and engraftment. Engraftment was defined as the first of 3 consecutive days of achieving a sustained peripheral blood neutrophil count of $>0.5 \times 10$ E^9/L (47). Acute GvHD was graded according to Glucksberg criteria (48). Skin aGvHD grade II to IV treated with systemic corticosteroids >3 days, and gut aGVHD grade IV were reported. Fluid overload was assessed by the use of diuretics during hospitalization. Fluid overload was defined as relevant if diuretics were provided during >3 consecutive days. Use of diuretics or clinically relevant edema were used to assess fluid overload at the last measured weight. Mean s-glucose was calculated from daily measurements, and values >8 mmol/L were defined as hyperglycemia. We report verified infections assessed by bacteria in blood culture, catheter-related infection, typhlitis, bacteria, virus in feces, and maximum c-reactive protein (CRP).

Statistical Considerations

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (Armonk, NY). Normally distributed data were presented as means (SD), and non-normally distributed data and nutrient intakes were presented as medians and IQR. Associations between normal weight or overweight and clinical outcomes were tested with Chi-square or Fishers exact tests. Differences between weekly weight *z* scores from admission until day +28 were tested with one-way repeated measures ANOVA. Mann-Whitney *U* test was used to assess %-weight change between overweight and normal weight participants from admission until the end of the study. The Friedman Test analyzed the difference across weekly energy provisions. Wilcoxon signed rank test with Bonferroni correction was used to analyze differences in weekly energy provisions, and the level of significance was set to $P < 0.001$ due to multiple analyses (49). Missing variables were excluded pairwise, and the level of significance was two-sided and set to $P < 0.05$ for all the other analyses.

Ethical Considerations

Informed consent was given by participants aged above 16 years and all parents. The Helsinki Declaration was followed. The Regional Ethics Committee South-East (2016/391/REK sør-øst B) and the Data Protection Officer, OUH, approved the study. The study was registered in Clinical Trials (AEV2017/1).

RESULTS

Participants

During recruitment, 66 patients underwent HSCT. Out of these, we excluded 30 (20 young age, 3 with poor language skills, 1 admitted for a second HSCT, 1 with Down syndrome, 1 with anorexia nervosa, and 4 due to logistical issues). We invited all 36 eligible to participate, and 29 gave consent. One died during conditioning and was excluded from the analyses. Our final study group consisted of 28 children, corresponding to 78% participation.

Baseline Characteristics

Characteristics of participants are presented in Table 1. The mean age was 10.3 years (SD 4.0) (range 3.5–16.6), two-thirds were boys, and two-thirds had malignant diseases. Six patients (86%) with immunodeficiency also had inflammatory bowel disease, regarded as immunodeficiency related. One patient (4%) was previously diagnosed with celiac disease.

TABLE 1. Patient characteristics at admission

Characteristics	Participants (N = 28)	
Age, y, mean (SD)	10.3	(4.0)
Gender, N (%)		
Female	9	(32)
Male	19	(68)
Anthropometrics, mean (SD)		
Weight, kg	37.7	(18.9)
Weight *z* score	−0.3	(1.2)
Height, cm	139.1	(26.5)
Height *z* score	−0.7	(1.2)
BMI, kg/m^2	18.1	(3.2)
BMI *z* score	0.1	(1.2)
Diagnosis, N (%)		
Malignant	18	(64)
Acute myeloid leukemia	9	
Acute lymphoblastic leukemia	7	
Myelodysplastic syndrome	2	
Non-malignant	10	(36)
Immunodeficiency*	7	
Combined immunodeficiency	2	
CGD	1	
STAT3-GOF mutation	1	
Specific granuladefect type 2	1	
ALPS	1	
Congenital neutropenia	1	
Bone marrow failure	2	
Severe aplastic anemia	1	
Diamond-Blackfan anemia	1	
Neurometabolic disease	1	
X-linked adrenoleukodystrophy	1	
HSCT conditioning, N (%)		
Myeloablative conditioning (MAC)	24	(86)
TBI-containing	7	
Reduced-intensity conditioning (RIC)	4	(14)
Type of donor, N (%)		
Matched unrelated	20	(71)
Matched related	7	(25)
Haploidentical	1	(4)
Stem-cell source, N (%)		
Bone marrow	24	(86)
Peripheral blood stem cells (PBSC)	4	(14)

ALPS = autoimmune lymphoproliferative syndrome; BMI = body mass index; CGD = chronic granulomatous disease; SD = standard deviation, TBI = total body irradiation. * Six were diagnosed with immunodeficiency-related inflammatory bowel disease.

Nutritional Status and Diet at Hospital Admission for HSCT

The group had a normal BMI *z* score at hospital admission, Table 1. Overweight was found in 25% (n = 7) of patients, 18% (n = 5) were stunted, and none had BMI *z* score <−2.

At hospital admission, 25% (n = 7) received supportive nutritional therapy. They all had tube feeding, and 2 (7%) also had supplemental PN. Eleven percent (n = 3) had a gastrostomy, and 14% (n = 4) had a nasogastric tube. They all had normal BMI *z* scores, but 2 of them (29%) had stunted growth.

Weight Change by Day +28

All patients had weight measurements on day +21. Due to earlier discharges, the weight at day +28 was available for 19 (68%) participants. No significant changes in weight *z* scores were detected during the studied weeks, $P = 0.454$. The patients' mean weight change during the study was 0.2%, with a variation from −8.0% to 6.1%. During the post-transplant period, 25% (n = 7) of participants had a fluid overload for >3 consecutive days. Two (7%) had a fluid overload at the end of the study period. Both were on diuretics and had edema, and weight gain from admission was 2.6% and 5.3%. Weight loss >5% was found in 2 (7%) teenage boys losing 6.9% and 8% of admission weight. Two overweight participants lost weight, and the prevalence of overweight was reduced to 18% (n = 5) at the end of the study. None of the participants had BMI *z* score <−2 at any time point. No significant difference in %-weight change was found between participants that were overweight and normal weight at admission, $P = 0.474$.

Nutritional Therapy

From the day of hospital admission until the last studied day, tube feeding was used for 1 or more days by 82% (n = 23) of participants. It was first initiated before transplantation in 48% (n = 11), and at day 0 or during the first week post-transplant in 52% (n = 12). PN was initiated in all except 1, and all were started during the first post-transplant week. Twenty-two percent (n = 6) of participants did not require nutritional support by tube or PN on day +28 or at earlier discharge.

Post-transplant, any oral diet was used for a median of 48% (18–62) of studied days. Tube feeding was provided for a median of 70% (18–87) of studied days. Hence, in total, any EN was provided for a median of 93% (86–100), and PN for 96% (84–100) of the post-transplant days by day +28. For >5 days, no EN was found in 18% (n = 5) of participants, all treated for leukemia. Reasons for prolonged lack of EN were that 1 refused tube, 2 did not tolerate the tube, and 2 were prescribed "nil by mouth" due to gut aGvHD or typhlitis.

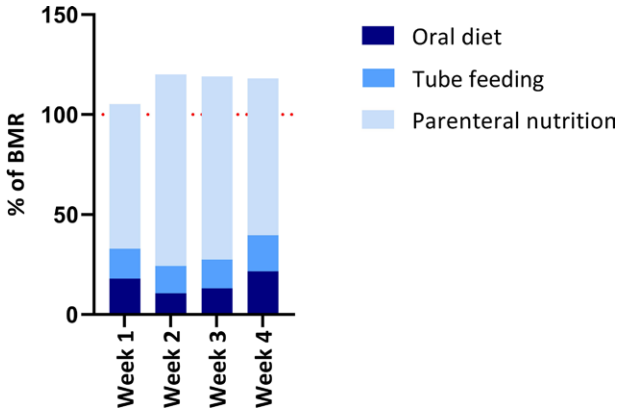

FIGURE 1. Weekly median energy provision in pediatric patients after allogeneic hematopoietic stem cell transplantation.

Nutrient Provision

Diet was recorded for a median of 28 days (26-28) with a range from 22 to 28 days (mean 26.7 days, SD 1.8). Median energy provision during the whole diet registration period was 115% (110–123) of BMR. Median energy provision the first post-transplant week was 105% (99–122) of BMR. Figure 1 illustrates weekly energy provision. A significant difference across the 4 weeks was found, $P = 0.029$. Further analyses revealed a significant difference between week 1 and week 2, $P < 0.001$.

Table 2 presents the provision of energy and macronutrients during all studied days. PN contributed to a median of 79% (69–90), and EN contributed to 21% (11–31) of energy provision. The median total supply of proteins was 1.5 g/kg (1.3–1.8). The participants' oral intake was low, contributing to a median of 5.7% (1.4–15.7) of energy provision with 322 kJ/day (99–1032) [77 kcal/day (23–246)]. Tube feeds contributed to a median of 9.5% (1.8–14.7) of energy provision with 565 kJ/day (155–899) [135 kcal/day (37–214)].

The tube-fed patients (n = 23) all got liquid, ready-to-feed formulations. Oligopeptides were used by 78% (n = 18), polymeric formulas by 4% (n = 1), and 18% (n = 4) used both. An energy density of 1 kcal/mL was used in 52% (n = 12), a more energy-dense product in 9% (n = 2), and 39% (n = 9) received both. All PN

TABLE 2. Daily provision (median, IQR) of energy and macronutrients in pediatric patients after allogeneic hematopoietic stem cell transplantation

	Total		Enteral nutrition*		Parenteral nutrition		Guideline enteral†	Guideline parenteral‡
	Median	IQR	Median	IQR	Median	IQR		
kJ	5814	4864–7024	1130	603−2022	4161	3516–5513		
Kcal	1389	1162–1678	270	144–483	994	840–1317		
kJ/kg	147	110–195	39	18–64	116	103–162		
Kcal/kg	35.0	26.3–46.5	9.4	4.4–15.2	27.8	24.6–38.8		
Protein, g	60.6	35.9–72.8	8.6	5.2–14.2	39.4	26.1–60.7		
Protein, g/kg	1.5	1.3–1.8	0.3	0.1–0.5	1.2	1.0–1.4	>0.9	2.0–1.0
Carbohydrates, g	173.5	161.0–207.6	34.4	20.3–69.8	130.0	114.8–158.0		
Carbohydrates, g/kg	5.1	4.1–7.4	1.2	0.6–2.1	3.7	2.8–4.9		8.6–1.4
Lipids, g	48.0	39.9–57.9	10.8	5.4–17.1	33.6	26.4–44.5		
Lipids, g/kg	1.4	1.2–1.7	0.3	0.2–0.6	1.0	0.8–1.3		<3

IQR = interquartile range. *Enteral nutrition = oral diet and tube feeds. †The Nordic Nutrition Recommendations (41). ‡ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition (42–45).

patients (n = 27) got ready-to-use 3-chamber PN bags. Changes to individually prescribed PN were done in 15% (n = 4).

Forty-six percent (n = 13) used oral vitamin D, 54% (n = 15) used magnesium, one (4%) got phosphate, and one (4%) used calcium as dietary supplements. Parenteral multivitamins and trace elements were added to all PN solutions. RI for vitamins, magnesium, and zinc was met. The provision of copper, iodine, selenium, calcium, and phosphate was below RI (Figure 2A, Table 1 (Supplemental Digital Content, *http://links.lww.com/MPG/C912*), Table 2 (Supplemental Digital Content, *http://links.lww.com/MPG/C912*). Iron was below RI, but this was considered adequate due to the risk of iron overload (37). Vitamin E was also considered adequate even below RI due to extra content in the lipid emulsions of PN solutions (35). Figure 2B illustrates the % of participants reaching RI for micronutrients. None of the participants reached RI for iron or iodine. The number of participants that reached RI from oral diet, tube feeds and PN were 4% (n = 1) for selenium, 7% (n = 2) for copper, 7% (n = 2) for calcium, 11% (n = 3) for vitamin E, 32% (n = 9) for vitamin D, 46% (n = 13) for vitamin C, and 46% (n = 13) for phosphate. RI for magnesium, vitamin B2, niacin, folate, vitamin B1, zinc, vitamin A, vitamin B6, and vitamin B12 were met for most participants.

Transplant Outcomes by Day +28

One participant died during conditioning therapy and was excluded from analyses since no data on nutritional intake was available. All the other patients survived by day +28. Engraftment of neutrophils was detected by day +28 for 26 patients. Table 3 (Supplemental Digital Content, *http://links.lww.com/MPG/C912*) presents results by day +28 for aGvHD, infections, CRP, and s-glucose. Mean s-glucose was normal, and values above 8.0 mmol/L for >3 consecutive measurements were not detected. Five (18%) patients were treated with Defibrotide due to prophylactic, suspected, or clinically proven veno-occlusive-disease/sinusoidal obstructive syndrome; none severe. No significant associations were found between participants with normal BMI or overweight at admission and aGvHD ($P = 0.396$), infections ($P = 0.551$), or use of Defibrotide ($P = 0.574$).

DISCUSSION

This observational, prospective study describes the impact of HSCT on nutritional status and intake. Most participants had normal BMI and height. From admission until day +28, we found no significant change in the patients' weights. Energy intake was median 115% of BMR, and proteins 1.5 g/kg. PN was the primary energy and nutrient source, but EN was provided most days. The provision of macronutrients and vitamins was in line with RI, yet copper, iodine, selenium, calcium, and phosphate were below.

In line with other studies, we found a normal mean BMI for the group at hospitalization (7, 8, 16, 18). However, one-fourth of participants were overweight, and one-fifth were stunted. Stunted growth has previously also been found in children with immunodeficiency undergoing HSCT (7). Stunting is a marker of chronic malnutrition and is related to underlying diseases (31). An association between stunting and increased use of nutritional support before and during hospitalization was previously described (20, 50). Overweight/obesity has been associated with decreased survival in HSCT patients (19, 51). Hence, nutrition support is essential before and during HSCT for undernourished and overweight/obese patients to prevent under- and overfeeding.

We found no significant change in the participants' weight *z* score during this study. Results might indicate that combined EN and PN providing a median supply of 115% of BMR and 1.5 g protein/kg was adequate in our group. Weight was chosen as it was used in clinical practice, although not ideal since hydration status can affect results (31). Fluid overload may mask weight loss, although it was unlikely to have a major impact on our results as only 2 patients had clinically observed edema and were treated with diuretics on the last studied day. Other studies have reported no change (10, 15) or weight loss (6, 13, 14, 16, 18) during the first period after HSCT. Weight gain on PN versus loss on EN was reported in a retrospective study where edema was found in 58% of PN versus 20% of the EN group (13), indicating an increased risk of fluid overload with PN. However, another explanation could be a higher energy provision in the PN group (13), and overfeeding could be suspected. Another limitation is that a stable weight could mask loss of lean body mass and increase in fat mass (31). A combination of weight loss and a profound loss of lean body mass was reported despite an energy intake of 130% to 150% of the resting energy requirement in adolescent HSCT patients post-transplant (18). Muscle loss has been associated with fatigue, impaired physical function (52), and adverse health outcomes later in life (53). Importantly, loss of lean body mass can be aggravated if nutritional treatment is inadequate (54). Our results indicate lower energy requirements post-transplant compared to healthy children (41), and support findings from previous studies (9, 21). Therefore, patients might be at risk of overfeeding. However, individual differences in physical activity, stress, inflammation, body composition, or loss of nutrients are likely. Low energy requirements and provision increase the risk of an inadequate supply of protein and micronutrients, and the quality of nutritional support must be emphasized.

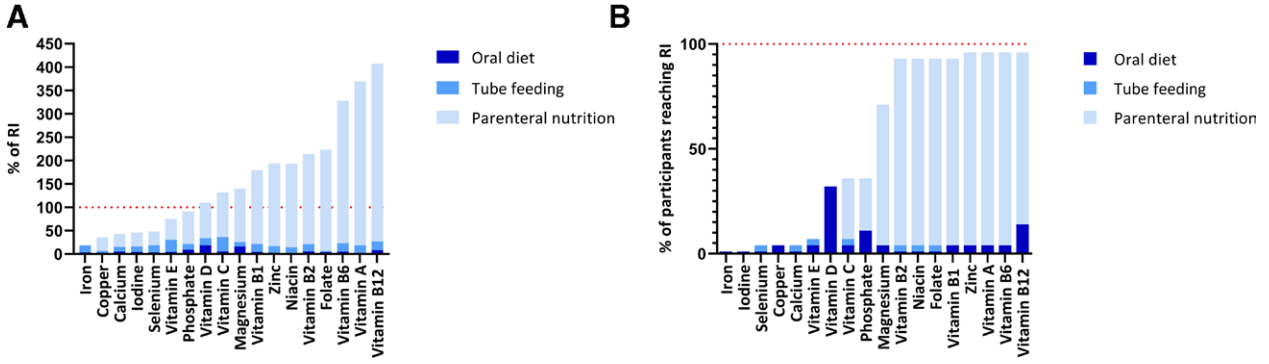

FIGURE 2. Micronutrient provision in children after allogeneic hematopoietic stem cell transplantation presented as (A) median % of RI and (B) % of participants reaching RI. RI = recommended intake.

PN was the primary energy source, and PN energy provision seemed higher than in another study of pediatric HSCT patients (14). Myeloablative pretreatment was provided to 86% (n = 24) of participants and might explain the frequent need for supportive PN. In line with our results, most studies have found frequent use of PN during the first month after HSCT in children (6–8, 13–15, 18). In the present study, oral intake was low and supports results from a previous study (8). However, EN was provided in small amounts on most studied days since tube feeding was frequently used. Other studies have concluded that EN was feasible for a high proportion of HSCT patients (11–13). Importantly, the quality of nutrient provision was not assessed in these studies. Whether gastrostomies could improve the amount of EN and reduce the need for supplemental PN is unknown, though a study found it improved nutritional outcomes (55). A recent systematic review and meta-analysis concluded that in combination with PN, EN provided favorable benefits over PN alone regarding the risk of aGvHD (24). One could speculate that the major risk factor could be the lack of EN rather than supplemental PN. One explanation could be that the gut microbiome is affected by multiple challenges during HSCT (e.g., antibiotics) (25). Changes in the microbiome and immune markers during treatment were seen in children after HSCT (56), and in adults, microbiota disruption was associated with mortality (57). Recovery of gut microbiome homeostasis was promoted by EN in a pediatric study (58), emphasizing the importance of EN (25, 59, 60). However, the amount and type of EN required to get effects should be further studied.

Combined nutritional therapy provided RI for vitamins, but copper, iodine, selenium, calcium, and phosphate were below (35, 36, 41, 46). Whether the requirements of HSCT patients differ from healthy children is unknown. Inadequate provision of calcium and phosphate was related to the composition of ready-to-use PN bags and support results from a study of children dependent on home parenteral nutrition (61). Concerns about bone mineralization must be highlighted in children dependent on PN (46, 61, 62), and low BMD is a known late effect after childhood HSCT (63). Vitamin D intake was within RI, but vitamin D deficiency has previously been frequently described in HSCT patients (64). Vitamin D is important for bone health, and has also been associated with other health outcomes and immunoregulatory effects, which could be relevant for this group of children (65). Our study found a low provision of most trace elements. However, a study of intestinal failure patients on long-term home parenteral nutrition found that serum selenium and vitamin E were adequate despite lower dietary provision compared with RI. Noteworthy, a high prevalence of iodine insufficiency was found even though PN doses were higher than in the present study (66). Our study support that trace element solutions should be revised to improve content (67). Nutritional status is difficult to assess in illness since biomarkers can be affected by inflammation, and the lack of disease-specific references is a challenge. Dietary assessment can give information on nutritional status, but is suboptimal on its own (68, 69). The combination of nutrient provision and biomarkers of micronutrient status should be investigated in HSCT patients. Further studies are necessary to make firm recommendations on vitamins, trace elements, and minerals for pediatric HSCT patients. Hence, we suggest individual follow-up by anthropometrics, diet records, and biomarkers to assess nutritional status pre- and post-transplant. Follow-up should be performed in patients on PN for prolonged periods to ensure the provision of micronutrients.

We found normal s-glucose even if PN was the primary energy source. This could be due to PN administration of 16 to 20 hours/day, carbohydrate doses within recommendations, and a strictly regulated energy supply. A study comparing only PN to combined EN and PN found a higher risk of bloodstream infections in the only PN group (6), but other studies found no differences (10, 13). Preventive procedures, including hygiene, stable solutions, and safe administration, are essential to prevent PN complications (70).

The strength of this study is a high participation rate and detailed assessment of all nutrition provided over an extended period. However, the small and heterogeneous patient population, lack of nutritional biomarkers, and no measures of body composition are weaknesses. Due to different diagnoses, age groups, and differences in nutritional treatments, the results from the present study can not be generalized as representative of all patients undergoing HSCT. Performing a study might also improve the focus on nutritional support, and our results might be better than "real-world data." We encourage further studies to include nutritional assessment and evaluate the quality of nutrient provision.

CONCLUSIONS

In conclusion, this study found that combined EN and PN providing 115% of BMR and 1.5 g/kg protein ensured a stable weight and covered nutrient recommendations except for trace elements and minerals. We call for further studies to better target nutritional treatment regarding the patient's individual needs. Long-term follow-up studies are necessary to evaluate micronutrients and if stable weight during hospitalization might improve body composition and other HSCT outcomes.

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REFERENCES

1. Kanate AS, Majhail NS, Savani BN, et al. Indications for hematopoietic cell transplantation and immune effector cell therapy: guidelines from the american society for transplantation and cellular therapy. *Biol Blood Marrow Transplant* 2020;26:1247–56.
2. Nagler A, Shimoni A. Conditioning. In: Carreras E, Dufour C, Mohty M, Kröger N, editors. *The EBMT Handbook. Hematopoietic Stem Cell Transplantation and Cellular Therapies*. Cham, Switzerland: Springer Open; 2019;99–108.
3. Talekar MK, Olson T. Immune Reconstitution After Hematopoietic Stem Cell Transplantation. In: Brown VI, editor. *Hematopoietic Stem Cell Transplantation for the Pediatric Hematologist/Oncologist*. Cham, Switzerland: Springer International Publishing; 2018;371–383.
4. Ifversen M, Meisel R, Sedlacek P, et al. Supportive care during pediatric hematopoietic stem cell transplantation: prevention of infections. a report from Workshops on Supportive Care of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Front Pediatr* 2021;9:705179.
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;55:1126–36.
6. 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.
7. Zemrani B, Yap JK, Van Dort B, et al. Nutritional challenges in children with primary immunodeficiencies undergoing hematopoietic stem cell transplant. *Clin Nutr* 2020;39:2832–41.
8. Bechard LJ, Guinan EC, Feldman HA, et al. Prognostic factors in the resumption of oral dietary intake after allogeneic hematopoietic stem cell transplantation (HSCT) in children. *JPEN J Parenter Enteral Nutr* 2007;31:295–301.
9. Bechard LJ, Feldman HA, Venick R, et al. Attenuation of resting energy expenditure following hematopoietic SCT in children. *Bone Marrow Transplant* 2012;47:1301–6.

10. Papadopoulou A, Williams MD, Darbyshire PJ, et al. Nutritional support in children undergoing bone marrow transplantation. *Clin Nutr* 1998;17:57–63.
11. Papadopoulou A, MacDonald A, Williams MD, et al. Enteral nutrition after bone marrow transplantation. *Arch Dis Child* 1997;77:131–6.
12. Langdana A, Tully N, Molloy E, et al. Intensive enteral nutrition support in paediatric bone marrow transplantation. *Bone Marrow Transplant* 2001;27:741–6.
13. 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;37:2113–21.
14. Lewandowski CG, Daudt LE, Jochims AMK, et al. Nutritional aspects in allogeneic hematopoietic stem cell transplantation in children and adolescents in a tertiary hospital. *Nutr Hosp* 2019;36:20–4.
15. Cohen J, Maurice L. Adequacy of nutritional support in pediatric blood and marrow transplantation. *J Pediatr Oncol Nurs* 2010;27:40–7.
16. 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;47:1191–5.
17. 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.
18. Sharma TS, Bechard LJ, Feldman HA, et al. Effect of titrated parenteral nutrition on body composition after allogeneic hematopoietic stem cell transplantation in children: a double-blind, randomized, multicenter trial. *Am J Clin Nutr* 2012;95:342–51.
19. White M, Murphy AJ, Hallahan A, et al. Survival in overweight and underweight children undergoing hematopoietic stem cell transplantation. *Eur J Clin Nutr* 2012;66:1120–3.
20. Baumgartner A, Hoskin K, Schuetz P. Optimization of nutrition during allogeneic hematologic stem cell transplantation. *Curr Opin Clin Nutr Metab Care* 2018;21:152–8.
21. Duggan C, Bechard L, Donovan K, et al. Changes in resting energy expenditure among children undergoing allogeneic stem cell transplantation. *Am J Clin Nutr* 2003;78:104–9.
22. Holler E, Greinix H, Zeiser R. Acute Graft-Versus-Host Disease. In: Carreras E, Dufour C, Mohty M, Kröger N, editors. *The EBMT Handbook. Hematopoietic Stem Cell Transplantation and Cellular Therapies*. Cham, Switzerland: Springer Open; 2019:323–30.
23. 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:e252–9.
24. Zama D, Gori D, Muratore E, et al. Enteral versus parenteral nutrition as nutritional support after allogeneic hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Transplant Cell Ther*. 2021;27:180.e1–e8.
25. Masetti R, Zama D, Leardini D, et al. The gut microbiome in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation. *Pediatr Blood Cancer* 2020;67:e28711.
26. Muscaritoli M, Arends J, Bachmann P, et al. ESPEN practical guideline: Clinical Nutrition in cancer. *Clin Nutr* 2021;40:2898–913.
27. Revuelta Iniesta R, Gerasimidis K, Paciarotti I, et al. Micronutrient status influences clinical outcomes of paediatric cancer patients during treatment: a prospective cohort study. *Clin Nutr* 2021;40:2923–35.
28. World Health Organization. *Training Course on Child Growth Assessment*. Geneva, Switzerland, WHO, 2008.
29. Juliusson PB, Roelants M, Nordal E, et al. Growth references for 0-19 year-old Norwegian children for length/height, weight, body mass index and head circumference. *Ann Hum Biol* 2013;40:220–7.
30. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes* 2012;7:284–94.
31. Hulst JM, Huysentruyt K, Gerasimidis K, et al. A Practical approach to identifying pediatric disease-associated undernutrition: a position statement from the ESPGHAN Special Interest Group on Clinical Malnutrition. *J Pediatr Gastroenterol Nutr* 2022;74:693–705.
32. Oslo University Hospital. Nutritional treatment of children undergoing hematopoietic stem cell transplantation at the Department of Pediatric Hematology and Oncology. Web site: https://ehandbok.ous-hf.no/document/3079. Published October 2021. Accessed 01.06.2022.
33. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 1985;39:5–41.
34. Naymagon S, Naymagon L, Wong SY, et al. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. *Nat Rev Gastroenterol Hepatol* 2017;14:711–26.
35. Bronsky J, Campoy C, Braegger C, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Vitamins. *Clin Nutr* 2018;37:2366–78.
36. Domellof M, Szitanyi P, Simchowitz V, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. *Clin Nutr* 2018;37:2354–9.
37. Tenneti P, Chojecki A, Knovich MA. Iron overload in the HCT patient: a review. *Bone Marrow Transplant* 2021;56:1794–804.
38. Riskin A, Picaud JC, Shamir R. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Standard versus individualized parenteral nutrition. *Clin Nutr* 2018;37:2409–2417.
39. Baranowski T. *24-Hour Recall and Diet Record Methods. In: Willett W, editor. Nutritional Epidemiology*. 3rd edition. New York, USA: Oxford University Press; 2013. p. 49–69.
40. Norwegian Food Safety Authority, Norwegian Directorate of Health, University of Oslo. The Norwegian Food Composition Table, Oslo, 2018. Available from: www.matvaretabellen.no. [Accessed January 15, 2021]
41. Nordic Council of Ministers. *Nordic Nutrition Recommendations 2012 - Integrating nutrition and physical activity*. Copenhagen, Denmark: Nordic Council of Ministers Secretariat; 2014.
42. Joosten K, Embleton N, Yan W, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Energy. *Clin Nutr* 2018;37:2309–14.
43. van Goudoever JB, Carnielli V, Darmaun D, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Amino acids. *Clin Nutr* 2018;37:2315–23.
44. Mesotten D, Joosten K, van Kempen A, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Carbohydrates. *Clin Nutr* 2018;37:2337–43.
45. Lapillonne A, Fidler Mis N, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Lipids. *Clin Nutr* 2018;37:2324–36.
46. Mihatsch W, Fewtrell M, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: calcium, phosphorus and magnesium. *Clin Nutr* 2018;37:2360–5.
47. Wallhult E, Quinn B. Early and Acute Complications and the Principles of HSCT Nursing Care. In: Kenyon M., Babic A., editors.. *The European Blood and Marrow Transplantation Textbook for Nurses*. Cham, Switzerland: Springer Open; 2018:163–95.
48. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation* 1974;18:295–304.
49. Armstrong RA. When to use the Bonferroni correction. *Ophthalmic Physiol Opt* 2014;34:502–8.
50. Hecht C, Weber M, Grote V, et al. Disease associated malnutrition correlates with length of hospital stay in children. *Clin Nutr* 2015;34:53–9.
51. Doney K, McMillen K, Buono L, et al. Impact of body mass index on outcomes of hematopoietic stem cell transplantation in adults. *Biol Blood Marrow Transplant* 2019;25:613–20.
52. Ryan AM, Power DG, Daly L, et al. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc* 2016;75:199–211.
53. Orsso CE, Tibaes JRB, Rubin DA, et al. Metabolic implications of low muscle mass in the pediatric population: a critical review. *Metabolism* 2019;99:102–12.
54. Mehta NM, Corkins MR, Lyman B, et al. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *JPEN J Parenter Enteral Nutr* 2013;37:460–81.
55. Evans J, Needle JJ, Hirani SP. Early outcomes of gastrostomy feeding in paediatric allogenic bone marrow transplantation: a retrospective cohort study. *Clin Nutr ESPEN* 2019;31:71–9.
56. Ingham AC, Kielsen K, Cilieborg MS, et al. Specific gut microbiome members are associated with distinct immune markers in pediatric allogeneic hematopoietic stem cell transplantation. *Microbiome* 2019;7:131.

57. Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as Predictor of Mortality in Allogeneic Hematopoietic-Cell Transplantation. *N Engl J Med* 2020;382:822–34.
58. D'Amico F, Biagi E, Rampelli S, et al. Enteral nutrition in pediatric patients undergoing hematopoietic SCT promotes the recovery of gut microbiome homeostasis. *Nutrients* 2019;11:2958.
59. Köhler N, Zeiser R. Intestinal microbiota influence immune tolerance post allogeneic hematopoietic cell transplantation and intestinal GVHD. *Front Immunol* 2018;9:3179.
60. Braegger C, Decsi T, Dias JA, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN committee on nutrition. *J Pediatr Gastroenterol Nutr* 2010;51:110–22.
61. Kvammen JA, Thomassen RA, Kjeserud CN, et al. Bone mineral density and vitamin D in paediatric intestinal failure patients receiving home parenteral nutrition. *Clin Nutr ESPEN* 2020;39:234–41.
62. Bechard LJ, Gordon C, Feldman HA, et al. Bone loss and vitamin D deficiency in children undergoing hematopoietic cell transplantation. *Pediatr Blood Cancer* 2015;62:687–92.
63. Chow EJ, Anderson L, Baker KS, et al. Late effects surveillance recommendations among survivors of childhood hematopoietic cell transplantation: a children's oncology group report. *Biol Blood Marrow Transplant* 2016;22:782–95.
64. Ros-Soto J, Anthias C, Madrigal A, et al. Vitamin D: is it important in haematopoietic stem cell transplantation? A review. *Bone Marrow Transplant* 2019;54:810–20.
65. Soto JR, Anthias C, Madrigal A, et al. Insights into the role of vitamin D as a biomarker in stem cell transplantation. *Front Immunol* 2020;11:966.
66. Thomassen RA, Kvammen JA, Saeland C, et al. Micronutrients in paediatric Intestinal Failure Patients receiving home parenteral nutrition. *Clin Nutr* 2020;39:3452–60.
67. Zemrani B, McCallum Z, Bines JE. Trace element provision in parenteral nutrition in children: one size does not fit all. *Nutrients* 2018;10:1819.
68. Morello E, Guarinoni MG, Arena F, et al. A systematic review of the literature and perspectives on the role of biomarkers in the management of malnutrition after allogeneic hematopoietic stem cell transplantation. *Front Immunol* 2020;11:535890.
69. Gerasimidis K, Bronsky J, Catchpole A, et al. Assessment and interpretation of vitamin and trace element status in sick children: a position paper from the european society for paediatric gastroenterology hepatology, and nutrition committee on nutrition. *J Pediatr Gastroenterol Nutr* 2020;70:873–81.
70. Hartman C, Shamir R, Simchowitz V, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: complications. *Clin Nutr* 2018;37:2418–29.