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Enteral nutrition optimization program for children undergoing blood & marrow transplantation: A quality improvement project

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ABSTRACT

Background: Malnutrition in children and young adults undergoing blood and marrow transplantation (BMT) increases morbidity and mortality. Addressing this via optimization of enteral nutrition can potentially improve outcomes.
Methods: This Quality Improvement project utilized pre-post-intervention design and post-intervention survey to evaluate a novel program optimizing enteral nutrition support in children undergoing BMT. All patients aged 0–18 who were admitted during the 16-week implementation period followed the Enteral Nutrition Optimization Program from pre-BMT through discharge. Data on biometric indicators, complications, and post-transplant milestone time markers were evaluated via Mann-Whitney U, Fisher's exact, and Chi-square tests as indicated using SPSS™ Version 27. A separate sample of clinical providers completed a post-intervention survey to evaluate the feasibility and acceptance of the intervention.
Findings: Six patients received the intervention, with 12 patients evaluated. There were no statistical differences between groups on measured evaluations of weight loss (0.15 kg vs +0.4 kg, $p = 0.39$), malnutrition (2 vs 3, $p = 0.545$), graft-versus-host-disease (2 vs 2, $p = 1$), time to engraftment (platelets day 22 vs 20.5, $p = 0.589$), infections ($p = 0.368$), and length of stay (32.5 days vs 31 days, $p = 1$). The provider sample of 45 participants showed overall feasibility and acceptance of the intervention (88.9% agreed or strongly agreed).
Discussion: Feasibility and acceptance were high, resulting in increased use of nasogastric and gastrostomy tubes. Though no clinical significance, interpretation is limited due to the small sample size.
Practice implications: Implementing a novel nutritional support program resulted in a culture shift towards enteral nutrition optimization. Further studies are needed to determine clinical impacts.

Introduction

Background

Nutrition is vital for children to grow and thrive. Nutrition is also essential in children with conditions requiring blood and marrow transplantation (BMT) who receive prolonged, intensive therapy (Baumgartner et al., 2017). Malnutrition, used here as synonymous with undernutrition, is an imbalance between nutrient intake and requirement leading to energy, protein, and micronutrient deficiencies (Mehta et al., 2013) and is common in BMT patients (Liu, Wang, Yan, Cai, & Wang, 2016). The BMT preparative regimen is associated with nausea, vomiting, diarrhea, poor appetite, taste changes, mucositis (Rogers, 2015), and increased catabolic demands (McMillen, Coghlin-Dickson, & Adintori, 2020). Collectively, these clinical signs and symptoms put a previously well-nourished child at risk for malnutrition or worsen malnutrition already present (Koç et al., 2017).

Global malnutrition rates in children with malignancies vary widely and are estimated to be 5–10% in leukemia patients, 15–36% in solid tumor patients, and up to 50% in high-risk neuroblastoma patients (Brinksma et al., 2011). Malnutrition is also seen in children with transfusion-dependent anemias (Goldberg, Neogi, Lal, Higa, & Fung, 2018) and primary immunodeficiencies (Zemrani et al., 2019). Among BMT patients, malnutrition rates range from 1 to 47% before and 19–20% after BMT (Koç et al., 2017; Liu et al., 2016). Poor nutritional status can have significant consequences. Chemotherapy metabolism is altered, leading to delayed clearance (Rogers, 2015) and decreased tolerance of treatment regimens (Brinksma et al., 2011), resulting in

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dose modifications and undertreatment. Moreover, health-related quality of life in pediatric oncology patients and their parents is negatively impacted by a child's poor nutritional status (Brinksma et al., 2015). Malnutrition during BMT can increase morbidity and mortality by enhancing the risk of acute graft-versus-host-disease (GVHD) of the gut, infection, and non-relapse mortality survival (Hirose et al., 2019; Kerby et al., 2018). Altered nutrition is also associated with decreased progression-free survival (Hirose et al., 2019; Kerby et al., 2018). Furthermore, complications can lead to prolonged hospitalizations and increased healthcare costs. Although the exact impact is unknown, the cost of global disease-associated malnutrition exceeds $15.5 billion annually in the United States (Goates, Du, Braunschweig, & Arensberg, 2016).

When patients cannot meet their nutritional needs orally, support via enteral nutrition (EN) or parenteral nutrition (PN) is considered. The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends the use of EN over PN to "the greatest extent possible" and reserves PN for cases of medical contraindication to EN (Becker et al., 2015; Corkins et al., 2013). Following BMT however, PN has historically been more frequently utilized when oral intake declines (McMillen et al., 2020). The use of PN has been associated with increased infection rates, electrolyte imbalances, and liver dysfunction (Baumgartner et al., 2017). Absence of EN has been associated with a loss of microbial biodiversity in the gut (Ralls, Miyasaka, & Teitelbaum, 2014). The use of algorithms to clearly state indications for EN and PN has been suggested to increase the utilization of appropriate support (Corkins et al., 2013; McMillen et al., 2020).

Data was reviewed for children and young adults who underwent BMT at a children's academic hospital in the Mid-Atlantic area of the US in 2019, and the incidence of malnutrition was 47% (medical chart review via Epic, retrieved July 3, 2020). The diagnosis of "Inadequate Oral Intake" was given to 81% of patients at some point during BMT admission; however, EN via tube feeding (TF) was only utilized in roughly half (51%) of patients and four patients (9%) with a malnutrition diagnosis did not receive any nutritional support (medical chart, retrieved July 3, 2020).

Problem statement

Many pediatric, adolescent, and young adults who undergo BMT experience malnutrition, contributing to morbidity and mortality. Moreover, standard-of-care measures are lacking to reduce these rates and enhance nutritional support. Improvement in the nutritional status of BMT recipients via optimization of enteral nutrition can potentially decrease infection rates, graft-versus-host-disease, length of hospital stay (LOS), and healthcare costs.

Purpose

This Quality Improvement (QI) project aimed to evaluate the impact of an evidence-based, nutritional support program to optimize the use of enteral nutrition for children and young adults undergoing BMT. This project was implemented for patients aged 0–18 years within the pediatric oncology division of an academic children's hospital over a 16-week period. Outcomes were compared to a similar group of BMT patients before the implementation period.

Project aims

The four aims were to determine the impact of an enteral nutrition program on (1) nutritional status through assessment of weight for length z-score, weight loss, mid-upper arm circumference (MUAC), and malnutrition rates; (2) rates of transplant-associated complications (infection, GVHD); (3) patient outcomes post-transplant (time to platelet and neutrophil engraftment, LOS); and (4) to determine the feasibility and acceptance to establish the program as the standard operating procedure (SOP) by measuring satisfaction scores of clinical providers utilizing a post-intervention survey.

Review of the literature

ASPEN has advocated using EN as the first line of nutritional support over PN for all children with malnutrition (Corkins et al., 2013). However, this has not been uniformly instituted in the pediatric BMT population (McMillen et al., 2020). Barriers to implementation include concerns for intolerance and perceived risks in the presence of neutropenia or mucositis despite the lack of solid evidence to support these concerns (Andersen, Brown, Kennedy, & Banks, 2014).

A literature search for manuscripts on nutritional support during pediatric BMT published within the previous ten years was performed to support the proposed intervention. Enteral nutritional support via nasogastric or gastrostomy tube placement was found to be feasible in children undergoing BMT in several studies (Azarnoush et al., 2012; Bicakli et al., 2012; Evans, Green, Connor, Lanigan, & Gibson, 2022; Evans, Needle, & Hirani, 2019; Gonzales et al., 2018; Lewandowski, Daudt, Jochims, Paz, & Mello, 2019; Zama et al., 2020; Zemrani et al., 2019). The use of EN alone or in combination with PN in pediatric BMT recipients was associated with decreased LOS (Azarnoush et al., 2012; Evans, Hirani, & Needle, 2019; Gonzales et al., 2018; Zama et al., 2020; Zemrani et al., 2019), infection rates (Zama et al., 2020), incidence and severity of acute GVHD (Azarnoush et al., 2012; Evans, Needle, & Hirani, 2019), and incidence of sinusoidal obstructive syndrome (Alsalamah et al., 2021) along with earlier platelet engraftment (Alsalamah et al., 2021; Azarnoush et al., 2012; Gonzales et al., 2018) and improved overall survival (Gonzales et al., 2018) when compared to the use of PN alone.

Enteral support pathways to guide decisions related to nutritional optimization have been described in the literature for pediatric oncology patients (Steele, Salazar, & Rypkema, 2016) and adult BMT patients (Andersen et al., 2014). Unfortunately, despite clear evidence of benefit, adoption into pediatric BMT programs is lacking (McMillen et al., 2020). As noted above, barriers include institutional culture regarding the feasibility of NG placement/EN support and a lack of standardized algorithms to optimize EN regimens (McMillen et al., 2020). Pediatric BMT programs with successful, proactive NG placement strategies have dedicated multidisciplinary support to this approach and provide early counseling to patients and families to overcome these obstacles (Evans et al., 2022).

Methods

Design

This quality improvement project utilized a pre-post intervention design, a historical "usual practice" group, and an intervention group. Outcomes of interest were defined above and included the project's impact on nutritional markers, transplant-associated complications, and patient outcomes. Using a post-intervention survey, the feasibility and acceptability of the program was evaluated.

Setting

This project was implemented within the pediatric oncology division of a children's hospital in a large, urban academic center in the Mid-Atlantic area of the US from October 2021 to January 2022. This division is comprised of nurses (RNs), advanced practice providers (APPs), attending and fellowship-trainee physicians (MDs), overnight resident physician coverage, registered dieticians (RDs), social workers (SWs), and support staff. Approximately 50 BMTs are performed annually for patients with various diagnoses in patients under the age of 25.

Sample

Participants in the intervention group included a convenience sample of all children and young adults (ages 0 to 18 years) admitted for BMT during the 16-week project implementation period. Patients who already had feeding tubes on admission and those who refused NG tube replacement initially were included, as it was anticipated that EN use might be intermittent for some participants due to GI toxicities. Exclusion criteria consisted of patients aged 19–24; even though these patients are seen in the pediatric BMT division at this institution, results from this age group would better correlate with adult data. Participants who declined all tube feeding support throughout admission were excluded from this project. Chart review was utilized to compare results from enrolled patients to those of a paired sample of patients that underwent a BMT within the two years before the intervention period (usual practice group). Clinical providers (RNs, APPs, MDs, RDs, and SWs) within the division were the sample for the fourth aim, with all invited to participate.

Recruitment

During their pre-BMT evaluation clinic visits, BMT patient participants were engaged in the nutritional support program via face-to-face communication with a BMT APP and RD. Recruitment of clinical staff to complete an anonymous post-implementation survey occurred via email, QR code postings displayed throughout the division, and face-to-face recruitment.

Intervention/procedures

Before the initiation of this QI project, a 30-min information session was held at a weekly BMT multidisciplinary meeting regarding the upcoming project. Discussion points included the scope and significance of malnutrition in pediatric BMT patients, the evidence behind the project's interventions, and discussion of the algorithm to be used to guide patient care decisions [see Fig. 1 for algorithm]. The presentation was later recorded into a 10-min video and distributed via email to the division. In addition, the BMT Enteral Nutrition Optimization Program algorithm was uploaded into each patient's electronic medical record (EMR), and a copy was kept at the nurse's station.

All upcoming BMT patients were referred to an RD during the intervention period as part of their pre-BMT evaluations. At this appointment, patients underwent nutritional screening and received education on anticipated post-BMT health effects, including but not limited to the need for feeding tube placement. Before this project, an RD did not see patients until admission, and feeding tube discussions and placements were sporadic and provider dependent. Child life specialists, child psychologists, and the patient's attending physician also discussed the need for feeding tube placement and support surrounding this approach at pre-BMT clinic visits and throughout their hospitalization, which were all new interventions related to this project.

If patients were found to be malnourished at the RD visit, NG tube or gastrostomy (G) tube placement and initiation of EN support before admission was strongly advised to their primary team. Patients deemed high nutritional risk (age < 1 year, underlying severe malnutrition, multiple myeloablative transplants planned, or patients with immunodeficiencies) were referred to surgery for G-tube placement after discussion with their primary team. If patients required central line placement at the time of BMT admission, the recommendation was to place an NG (or G) tube while in the operating room. Otherwise, an NG tube was placed no later than one day following the completion of their chemotherapy (typically Day −1 or Day +4, depending on their preparative regimen).

Children's Oncology Group (COG)/ASPEN guidelines and literature review were synthesized to create an enteral feeding algorithm (Fig. 1) which was verified by two content experts. This algorithm included malnutrition criteria, indications to initiate or reduce feeds, feeding tube tips, signs and symptoms of intolerance (and how to address them), criteria to start TPN, and when to use trophic feeds, including feeding contraindications. This algorithm was uploaded into the patient's EMR via the media tab within Epic™. Daily progress notes indicated that the patient was following the BMT Enteral Nutrition Optimization Program, and an order was placed for bedside nurses to notify the APP/resident if feeds needed to be held for more than two hours. Upon NG tube dislodgement, the goal was immediate replacement if clinically appropriate. Platelet transfusions were given before replacement if the platelet count was below 20×10^9/L, and replacement of NG tubes was limited to two per nursing shift. If patients were expected to be unable to tolerate EN for 7–10 days, PN would be recommended, with trophic feeds encouraged unless contraindicated. Nutrition was addressed daily during multidisciplinary rounds, and RDs were readily available for consultation if not present at rounds.

Following the 16-week implementation period, a post-implementation survey via Qualtrics™ was distributed to clinical staff via email and QR codes posted around the unit to encourage participation.

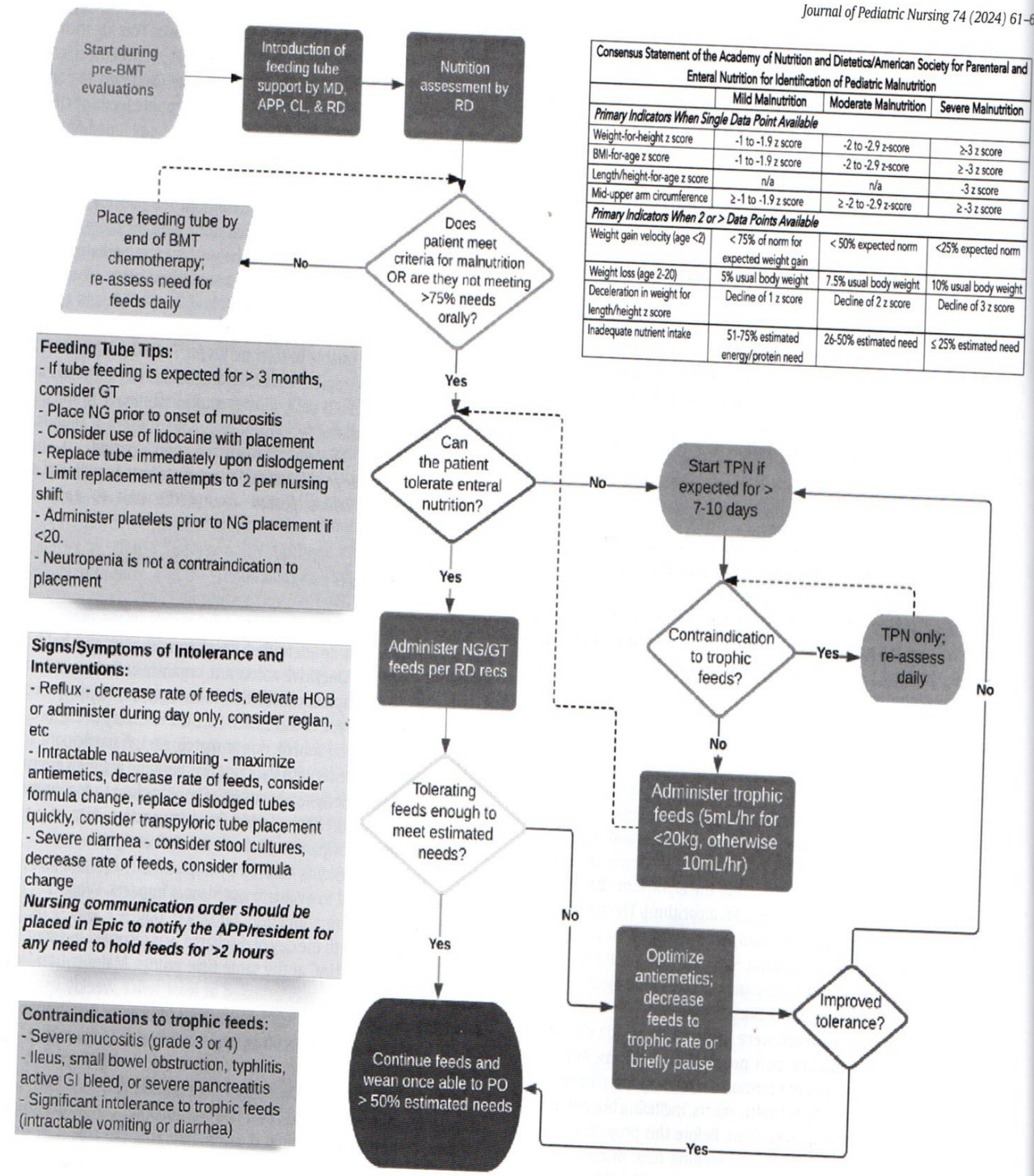
Instruments/measures & data collection

Chart review via Epic™ was utilized throughout the project. Data was exported into a de-identified Excel spreadsheet and held in a password-protected OneDrive account to organize and store collection data. Patient demographics collected included age, sex, ethnicity, underlying diagnosis, and type of transplant (i.e., the intensity of chemotherapy regimen, stem cell source, donor match, etc). A participant from within the past two years with the same conditioning regimen intensity, stem cell source, underlying diagnosis, who was close to the intervention participant's age was selected for comparative data as a pre-implementation participant to evaluate for clinical significance.

Various measurements entered by RNs and RDs into the patients' EMRs were obtained to evaluate nutritional impacts. Weight at Pre-BMT evaluation, upon admission, on Day 0, Day +7, Day +14, Day +21, Day +30, or until the day of discharge was recorded in kilograms. An RD performed MUAC at the same time points. Malnutrition (incidence of and severity) was assessed at least twice weekly using the guidelines outlined in the Academy/ASPEN Indicators Recommended for the Identification and Documentation of Pediatric Malnutrition (Undernutrition) (Becker et al., 2015) and World Health Organization's Weight for length anthropometric z-scores as calculated via Epic™. Although the Academy/ASPEN tool has no reliability or validity studies to date, content experts view it as reliable. It is the sole nutritional assessment tool utilized within the dietary division of this children's hospital; therefore, it is incorporated within the EMR.

A chart review was utilized to evaluate rates of transplant-associated complications and outcomes. Infection rates were quantified by assessing the occurrence of bacteremia or culture-negative sepsis. Incidence of GVHD was estimated with GVHD screening weekly starting Day +7 utilizing the MAGIC Criteria (Harris et al., 2016), which is deemed reliable via a position statement published by GVHD experts from the European Society for Blood and Marrow Transplantation, the National Institutes of Health, and the Center for International Blood and Marrow Transplant Research (Schoemans et al., 2018). LOS was quantified by calculating the days from admission, or start of chemotherapy preparative regimen if patients were admitted for reasons other than planned BMT start, until discharge. Time to engraftment was quantified using definitions from the Center for International Blood and Marrow Transplant Research® (CIBMTR, 2022).

To evaluate the feasibility and acceptance by staff to integrate this project as standard practice for the division, a survey for clinical providers was created and distributed via Qualtrics after the 16-week



Consensus Statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition for Identification of Pediatric Malnutrition			
	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Primary Indicators When Single Data Point Available			
Weight-for-height z score	-1 to -1.9 z score	-2 to -2.9 z-score	≥-3 z score
BMI-for-age z score	-1 to -1.9 z score	-2 to -2.9 z-score	≥ -3 z score
Length/height-for-age z score	n/a	n/a	-3 z score
Mid-upper arm circumference	≥ -1 to -1.9 z score	≥ -2 to -2.9 z-score	≥ -3 z score
Primary Indicators When 2 or > Data Points Available			
Weight gain velocity (age <2)	< 75% of norm for expected weight gain	< 50% expected norm	<25% expected norm
Weight loss (age 2-20)	5% usual body weight	7.5% usual body weight	10% usual body weight
Deceleration in weight for length/height z score	Decline of 1 z score	Decline of 2 z score	Decline of 3 z score
Inadequate nutrient intake	51-75% estimated energy/protein need	26-50% estimated need	≤ 25% estimated need

References:
Becker, P., Carney, L. N., Corkins, M. R., Monczka, J., Smith, E., Smith, S. E., Spear, B. A., & White, J. V. (2014). Consensus statement of the Academy of nutrition and Dietetics/american society FOR parenteral and enteral nutrition.*Nutrition in Clinical Practice*,*30*(1), 147–161. https://doi.org/10.1177/0884533614557642
Corkins, M. R., & Balint, J. (2015).*The A.S.P.E.N. Pediatric nutrition support core curriculum*. American Society for Parenteral and Enteral Nutrition.
McMillen, K. K., Coghlin-Dickson, T., & Adintori, P. A. (2020). Optimization of nutrition support practices early after hematopoietic cell transplantation.*Bone Marrow Transplantation*,*56*(2), 314–326. https://doi.org/10.1038/s41409-020-01078-9
Sondheimer, J. (2004). A critical perspective on trophic feeding.*Journal of Pediatric Gastroenterology and Nutrition*,*38*(3), 237–238. https://doi.org/10.1097/00005176-200403000-00001
Steele, C., Salazar, A., & Rypkema, L. (2016). Utilization of a nutrition support algorithm reduces unnecessary parenteral nutrition use in pediatric oncology inpatients.*Journal of the Academy of Nutrition and Dietetics*,*116*(8), 1235–1238. https://doi.org/10.1016/j.jand.2015.12.007

Abbreviations: MD = BMT Attending Physician, APP = BMT Advanced Practice Provider (NP, PA), CL = Child Life Specialist, RD = Registered Dietician, RN = Registered Nurse, NG = nasogastric tube; GT = gastrostomy tube

Fig. 1. Pediatric BMT enteral feeding optimization program algorithm.

implementation period. This survey consisted of five questions, utilizing a 5-point Likert Scale to assess the subjective success of the project and the desire to integrate this as the standard of care. Two content experts validated the survey. The demographic of the provider role was also collected.

Ethical review

Ethical review approval for this project was obtained from the Johns Hopkins School of Nursing Project Ethical Review Committee (PERC) and deemed QI; therefore, full IRB review was not required. Informed

voluntary consent was gained by patients/caregivers allowing feeding tube placement and formula rate adjustments, and patients and/or their caregivers were able to request modifications to or refuse interventions at any time during this QI project.

Data analysis

Data analysis plan

Descriptive and frequency statistics were used to analyze participant demographics, including age, gender, ethnicity, diagnosis requiring BMT, type of preparative regimen, stem cell source and donor match, and the occupation of clinical staff participants. Data were analyzed using the IBM SPSS™ Version 27 statistical software program. Patient data was evaluated between pre-and post-intervention groups for aims 1–3 using various statistical measures to assess for significance. Aim four, regarding feasibility and acceptance from post-intervention survey results of clinical providers, was analyzed and compared using descriptive statistics and frequencies.

For Aim one regarding nutritional biomarkers, change in weight from admission to discharge was calculated and compared between groups using a Mann-Whitney *U* test. The incidence of malnutrition was evaluated using Fisher's exact test, and the maximum severity of malnutrition was using a Chi-squared test. For Aim two regarding post-transplant complications, the rates of infection and incidence of GVHD were evaluated with a Fisher's exact test. The maximum severity of GVHD was analyzed via the Mann-Whitney U test. Aim three regarding post-transplant-related indicators, LOS, platelet engraftment, and neutrophil engraftment was analyzed with a Mann-Whitney U test.

Results

Sample characteristics

There was an enrollment of 12 patients (6 receiving the intervention) in this QI project, with a mean age in the pre-intervention group of 5.4 years (IQR 2–11) and 7.6 years (IQR 1–15) in the intervention group. Diagnoses included leukemia, solid tumors, brain tumors, and immunodeficiencies. As noted, both groups were well matched with respect to BMT type, donor match, stem cell source, and conditioning regimen intensity (See Table 1). The provider sample included 45 participants who completed the survey fully and were mostly nurses (RNs) ($n = 27$, 42.9%), followed by attendings ($n = 7$, 11.1%), then Advanced Practice Providers (APPs) ($n = 5$, 7.9%), fellows ($n = 4$, 6.3%), and other groups (See Table 2).

Table 1
Patient Sample Characteristics.

	Pre-Implementation (usual practice) sample, $N = 6$	Post-Intervention sample, N = 6	*p*-value
Age in years, mean (SD)	5.4 (5)	7.6 (7.28)	0.35
Male, N (%)	2 (33.3%)	3 (50%)	0.343
Female, N(%)	4 (66.7%)	3 (50%)	
Race, N (%)			0.878
White	3 (50%)	2 (33.3%)	
Black	1 (16.7%)	1 (16.7%)	
Hispanic	1 (16.7%)	1 (16.7%)	
Asian	1 (16.7%)	1 (16.7%)	
Bi-Racial	0 (0%)	1 (16.7%)	
Underlying Diagnosis, N (%)			0
Leukemia	2 (33.3%)	2 (33.3%)	
Solid Tumor (non-CNS)	1 (16.7%)	1 (16.7%)	
Brain Tumor	1 (16.7%)	1 (16.7%)	
Immunodeficiency	2 (33.3%)	2 (33.3%)	
Type, N (%)			0
Autologous	2 (33.3%)	2 (33.3%)	
Allogeneic	4 (66.7%)	4 (66.7%)	
Donor Match			1.333
Haploidentical	2 (33.3%)	2 (33.3%)	
Matched Related	0 (0%)	0 (0%)	
Matched Unrelated	2 (33.3%)	1 (16.7%)	
Mismatched Unrelated	0 (0%)	1 (16.7%)	
N/A (autologous)	2 (33.3%)	2 (33.3%)	
Stem Cell Source, N (%)			0
Bone Marrow	2 (33.3%)	2 (33.3%)	
Peripheral Blood	4 (66.7%)	4 (66.7%)	
Intensity, N (%)			0
Myeloablative	3 (50%)	3 (50%)	
Reduced-Intensity	2 (33.3%)	2 (33.3%)	
Non-myeloablative	1 (16.7%)	1 (16.7%)	

Outcomes

Aim 1: Health/Biometric Indicators

The overall change in weight for both groups combined was a median of 0.25 kg gained from BMT admission to discharge (IQR-0.8-0.95). For the pre-treatment group, the median was a loss of 0.15 kg (Min −0.6 to Max +1), whereas for the post-implementation group, the median was a gain of 0.40 kg (Min −2.3 to Max +2.2). Mann Whitney U test to compare means was not statistically significant at $p = 0.394$. Cohen's D test was performed to evaluate clinical significance and showed a small negative effect at −0.215. The incidence of malnutrition for all patients was 41.7% at the pre-BMT visit and 66.7% from BMT admission to Day +30 post-BMT. Incidence rates from BMT admission to the day of discharge were also compared between groups; three patients (50%) in the pre-implementation group and five patients in the post-implementation group (84%) met malnutrition criteria. Fisher's exact test showed that these results were not statistically significant ($p = 0.545$). Most patients with a malnutrition diagnosis during BMT admission (33%) were noted to have severe, acute malnutrition. In the pre-implementation group, there was one patient each (25%) with acute mild, moderate acute, severe acute, and severe chronic malnutrition, based on Academy/ASPEN Indicators. For the post-implementation group, two patients (40%) had severe acute, with one each (20%) with mild acute, moderate acute, and severe chronic malnutrition. These differences were not statistically significant using the Chi-square test for analysis ($P = 0.973$).

Overall MUAC weight-for-length z-score for the post-implementation group was 0.05 (SD 0.512), which would be classified as well nourished. Unfortunately, we could not calculate a MUAC z-score for the pre-implementation group as 100% of data was missing due to the COVID-19 pandemic; dieticians worked remotely throughout most of 2020–2021 and were not on-site to perform these evaluations. This impact was, therefore, unable to be determined. The remainder of the results are found in Table 3.

Aim 2: post-transplant related complications

Most patients (66.6%) had at least one infection during their initial BMT hospitalization. In the pre-implementation group, one patient

Table 2
Provider Sample Characteristics.

	Provider Sample, $N = 45$
RN, N (%)	27 (42.9%)
APP, N (%)	5 (7.9%)
Fellow, N (%)	4 (6.3%)
Attending, N (%)	7 (11.1%)
SW, N (%)	0 (0%)
RD, N (%)	1 (1.6%)
Child Life, N (%)	0 (0%)
Other, N (%)	1 (1.6%)

Table 3
Post-Transplant Biometrics, Complications, Indicators, and Outcomes.

	Pre-Implementation Group (n = 6)	Post-Implementation Group (n = 6)	p-value
Biometrics			
Change in weight, kg, median (IQR)	−0.15 (1.52).	0.4 (1.72)	0.394
Malnutrition			
Incidence on admission, n (%)	2 (33.3%)	3 (50%)	1
Incidence from BMT admission to discharge, n (%)	3 (50%)	5 (83.3%)	0.545
Maximum Severity			
mild acute, n (% of patients with malnutrition during BMT admission)	1 (25%)	1 (20%)	0.973
moderate acute, n (%)	1 (25%)	1 (20%)	
severe acute, n (%)	1 (25%)	2 (40%	
severe chronic, n (%)	1 (25%)	1 (20%)	
Infection			
Rates of infection			0.368
0 infections, n (%)	3 (50%)	1 (16.7%)	
1 infection, n (%)	1 (16.7%)	3 (50%)	
2 infections, n (%)	3 (33.3%)	2 (33.3)	
Acute GVHD			
Incidence, n (% of allo BMTs)	2 (50%)	2 (50%)	1
Acute GVHD Maximum Severity			0.667
Grade I, n	0	0	
Grade II, n	2	1	
Grade III, n	0	1	
Grade IV, n	0	0	
Engraftment			
Platelet engraftment, day, median (IQR)	22 (16)	20.5 (16)	0.589
Neutrophil engraftment, day, median (IQR)	14 (7)	15.5 (6)	0.818
Length of stay			
Days of hospitalization, median (IQR)	32.5 (13)	31 (21)	1

(16.7%) had one infection, and two patients (33.3) had two, compared to the post-implementation group in which three patients (50%) had at least one infection, and two patients (33.3%) had two. Although there was a trend towards higher infection rates in the post-implementation group, this was not statistically significant using Chi-square analysis ($p = 0.368$).

Rates of GVHD for the eight patients who received allogeneic BMT was 50% overall, and this was distributed evenly between the pre-and post-implementation groups with the incidence of two patients (50% of allogeneic patients) in each group. This was not statistically significant with Fisher's exact test ($p = 1.0$). The severity of GVHD was predominantly grade 2. Both patients in the pre-implementation group ($n = 2$, 100%) had a grade of 2, with one patient with a grade of 2 (50%) and one with a grade 3 (50%) in the post-implementation group. The difference between groups in GVHD severity was not statistically significant via the Mann-Whitney *U* test ($p = 0.667$). See Table 3 for results.

Aim 3: post-transplant related indicators

The length of stay for all participants was found to have a median of 31 days. The minimum stay was 19 days, and the maximum was 52 days (outlier). There was a slight variance between groups, with a median of 32.5 days (Range 26–50) for the pre-implementation group and a median of 31 days (Range 19–52) post-implementation. This was not statistically significant (Mann-Whitney U, p = 1).

Table 4
Participant Feasibility and Acceptability Rankings (n = 45).

	Agreed or Strongly Agreed, N %
The BMT Enteral Nutrition Optimization Program (EN-Opt) was easy to follow	41 (91.1%)
The BMT EN-Opt increased my focus on nutritional support for our patients	43 (95.5%)
The BMT EN-Opt helped to increase enteral nutritional support during BMT admissions	38 (84.5%)
The BMT EN-Opt was beneficial to our patients	42 (93.4%)
The BMT EN-Opt should be adopted as the standard of care approach for our patients	40 (88.9%)

Time to count recovery was also not statistically different between groups. For platelet engraftment recovery, defined as the first day of three consecutive days of platelets $>20 \times 10^9$/L, untransfused for the past seven days, the median was Day +20.5 (Range 12–29). The minimum time was 12, with a maximum of 41. There were no missing values, but 41 was an outlier. The median for the pre-implementation group was Day +22 (Range 15–41), and the post-implementation group was Day +20.5 (IQR 16), with Mann-Whitney U analysis of $p = 0.589$. Neutrophil recovery, defined as the first of three consecutive days of absolute neutrophil count $\geq 0.5 \times 10^9$/L occurred at a median of Day +15 (Minimum 10; maximum 25). The post-implementation group had a slighter shorter time with a median Day +14 (Range 10–17) compared to Day +15.5 (Range 10–25) in the pre-implementation group, but this was also not found to be significant via Mann-Whitney U analysis ($p = 0.818$).

Aim 4: feasibility & acceptance

Out of a staff of approximately 100 BMT-focused providers, 45 completed the post-implementation survey (participation rate 45%). A total score of 20 or higher indicated agree or strongly agree with survey questions, and the median summary score of the post-implementation survey evaluating provider acceptance of the QI project methods was 22.2 (out of 25; SD 3.32)—one outlier with a score of five self-identified as an APP. However, there were only four APPs on staff, making this data questionable. Further exploration revealed that the RD and fellows gave the highest rankings with mean of 25 and 24 (SD 1.41), respectively. All provider groups' mean total scores indicated agreement except for the APP group. Subtracting the questionable outlier from that group, the total score would indicate acceptance at a mean total score of 22.2 (out of 25). At least 88.9% of all providers agreed or strongly agreed with this project, indicating overall feasibility and acceptability. See Table 4 for details.

Discussion

In this Quality Improvement (QI) project, a novel, evidence-based, nutritional support program to optimize the use of enteral nutrition for children undergoing BMT was created within a division that previously had no standardized nutrition support strategy. Malnutrition during a BMT is a modifiable risk factor for poor outcomes (Kranjčec et al., 2020; McMillen et al., 2020), and when clinically appropriate, EN is recommended as first-line support over PN (Corkins et al., 2013; Nava et al., 2020). Similar enteral support pathways and decision guides have been described in the literature for pediatric oncology patients (Steele et al., 2016) and adult BMT patients (Andersen et al., 2014; Lazarow et al., 2020), but literature specifically on nutritional support pathways within the pediatric BMT population is sparse. Azarnoush

et al. (2012) discussed their program's standardized pre-BMT education on NG tubes and universal tube placement on Day +1, with noted feasibility and tolerance of support. This QI project also showed high feasibility, although tolerance was not evaluated.

Findings were insignificant between pre-implementation and post-implementation groups on biometric indicators, complications, and outcome measures. This was primarily driven by the small sample size in each group. However, the overall feasibility and acceptability of this program was high. Parents, patients, and staff received increased education on the importance of nutritional support and the means to address this. Williams-Hooker et al. (2015) found that caregivers and healthcare providers prefer to receive education about nutritional support and the associated pros and cons of different strategies before implementation. Without this information, many prefer PN due to ease of administration (Williams-Hooker et al., 2015). Similar studies have documented utilizing pre-BMT interviews with patients and families to discuss EN and NG tubes and found high levels of feasibility and acceptance of EN (Azarnoush et al., 2012; Zama et al., 2020). All patients admitted during this project's 16-week implementation period had a feeding tube at some point. Two patients, who were deemed high risk for prolonged malnutrition, underwent prophylactic gastrostomy tube placement prior to their BMT admission coupled with their surgery for central line placement. The algorithm aided discussion and support for the need for these surgical tubes. Importantly, the overall culture of the division was noted to change during this implementation, which was critical to the success of this project.

The increased use of surgically placed gastrostomy tubes was an unexpected result of this QI project. Two patients from this project refused NG tube replacement after repeated dislodgements, a problem not experienced by those with g-tubes. ASPEN consensus guidelines recommend surgical feeding tube placement for patients expected to require EN support for longer than 4–6 weeks (Boullata et al., 2017). With this information, all patients at the project site who require tandem, myeloablative, autologous BMTs are now routinely referred for prophylactic, surgically placed, feeding tubes. A survey of pediatric BMT divisions in 2021 showed that only 42% of centers offered prophylactic g-tube placement (Evans et al., 2022). G-tube use within pediatric BMT has been associated with less PN use (Evans, Needle, & Hirani, 2019). However, surgically placed G-tubes are not without risks, so decisions for use should be patient-specific (Evans et al., 2021).

Limitations

There were several limitations in this study. Most notedly, this study was underpowered to evaluate for efficacy significance due to the small number of patients in each group. The overall admission rate during the implementation of this project was markedly decreased due to the COVID-19 pandemic, which limited travel for a large contingent of international patients and directly limited research studies as well as transplants for non-malignant disorders. The pandemic also affected the ability to evaluate MUAC in the post-implementation group, which would likely have been more accurate than weight gain to assess nutritional status. Refusal of feeding tube replacement after repeated dislodgements was noted. Hence, lack of secure NG tubes was a limitation, and further investigation into the use of securement devices for NG tubes in the pediatric BMT population is needed. While two content experts reviewed the survey created for this project to evaluate feasibility and acceptance, it was not previously assessed for validity and reliability. Due to the small patient sample size, it was difficult to see the impacts of this program on all of the outcome parameters. Importantly, and despite these limitations, the nutritional support program continued to have strong stakeholder buy-in post-implementation, and its interventions have continued beyond the completion of this project. Future studies will be done to evaluate the impacts over 12 months and, therefore, on a larger sample size.

Implications to practice

The importance of shifting the divisional culture towards the urgent, unmet need to optimize nutritional support and using EN as the first line cannot be understated. Before the start of this project, formal nutritional screening rarely occurred pre-BMT, and the approach to address weight loss and associated malnutrition varied on a day-to-day basis depending on the treatment team. Evans et al. (2022) surveyed 12 pediatric BMT centers to evaluate nutritional support practices and found most (92%) provided nutritional counseling and nutritional screening (83%) before admission. However, the majority (58%) did not have a standardized guideline or protocol for monitoring or addressing nutritional status. Following the implementation of this project, a standardized operating procedure (SOP) was created at our institution and has continued to remain in place. The need for multidisciplinary support was vital for this project's support, which has been emphasized within the literature (McMillen et al., 2020). Institutional culture, such as lack of RD involvement within the interdisciplinary team and failure to adequately educate patients, caregivers, and providers, are known barriers to routine EN use (McMillen et al., 2020). Addressing these barriers early and often helped the success of this project. As the largest and most frontline group of providers, pediatric nurses are in a pivotal position to develop and implement similar evidence-based nutritional support pathways within their own unit.

Conclusion

This quality improvement project created a novel nutritional support program encompassing an algorithm widely supported by clinical providers, and a culture shift towards enteral nutrition optimization was the ultimate result. Malnutrition is a significant problem for children and young adults who undergo BMT and is a modifiable risk factor for poorer outcomes (Hirose et al., 2019; Kerby et al., 2018). Yet clinical guidelines are lacking to reduce these rates and optimize nutritional support, particularly with EN (McMillen et al., 2020). Enteral nutrition is recommended as the first line of nutritional support (Corkins et al., 2013); however, use tends to vary by provider and patient (McMillen et al., 2020). Using SOP guidelines and algorithms aids in systematizing nutritional support and provides at-bedside clinical decision support to ensure best practices are followed (Corkins et al., 2013). While the results of this QI project were not statistically significant, the feasibility and acceptance were high and shifted divisional culture.

CRediT authorship contribution statement

Jessica D. Murphy: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. **Kenneth R. Cooke:** Supervision, Writing – review & editing. **Heather J. Symons:** Supervision, Writing – review & editing. **Brigit VanGraafeiland:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. No funding was received for this project.

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References

Alsalamah, S., Alramyan, R., Alakel, R., Altheyeb, F., Alrashed, R., Masuadi, E., ... Essa, M. F. (2021). The outcome and complications of total parenteral nutrition in pediatric hematopoietic stem cell transplantation. *Pediatric Transplantation, e14198*. https://doi.org/10.1111/petr.14198.

Andersen, S., Brown, T., Kennedy, G., & Banks, M. (2014). Implementation of an evidenced-based nutrition support pathway for haematopoietic progenitor cell transplant patients. *Clinical Nutrition (Edinburgh, Scotland), 34*(3), 536–540. https://doi.org/10.1016/j.clnu.2014.06.006.

Azarnoush, S., Bruno, B., Beghin, L., Guimber, D., Nelken, B., Yakoub-Agha, I., & Seguy, D. (2012). Enteral nutrition: A first option for nutritional support of children following Allo-SCT? *Bone Marrow Transplantation (Basingstoke), 47*(9), 1191–1195. https://doi.org/10.1038/bmt.2011.248.

Baumgartner, A., Bargetzi, A., Zueger, N., Bargetzi, M., Medinger, M., Bounoure, L., Gomes, F., Stanga, Z., Mueller, B., & Schuetz, P. (2017). Revisiting nutritional support for allogeneic hematologic stem cell transplantation-a systematic review. *Bone Marrow Transplantation, 52*(4), 506–513. https://doi.org/10.1038/bmt.2016.310.

Becker, P., Carney, L. N., Corkins, M. R., Monczka, J., Smith, E., Smith, S. E., ... White, J. V. (2015). Consensus statement of the academy of nutrition and dietetics/american society for parenteral and enteral nutrition. *Nutrition in Clinical Practice, 30*(1), 147–161. https://doi.org/10.1177/0884533614557642.

Bicakli, D. H., Yilmaz, M. C., Aksoylar, S., Kantar, M., Cetingul, N., & Kansoy, S. (2012). Enteral nutrition is feasible in pediatric stem cell transplantation patients. *Pediatric Blood & Cancer, 59*(7), 1327–1329. https://doi.org/10.1002/pbc.24275.

Boullata, J. I., Carrera, A. L., Harvey, L., Escuro, A. A., Hudson, L., Mays, A., ... Guenter, P. (2017). ASPEN safe practices for enteral nutrition therapy. *JPEN Journal of Parenteral and Enteral Nutrition, 41*(1), 15–103. https://doi.org/10.1177/0148607116673053.

Brinksma, A., Huizinga, G., Sulkers, E., Kamps, W., Roodbol, P., & Tissing, W. (2011). Malnutrition in childhood cancer patients: A review on its prevalence and possible causes. *Critical Reviews in Oncology/Hematology, 83*(2), 249–275. https://doi.org/10.1016/j.critrevonc.2011.12.003.

Brinksma, A., Sanderman, R., Roodbol, P. F., Sulkers, E., Burgerhof, J. G. M., de Bont, E. S. J. M., & Tissing, W. J. E. (2015). Malnutrition is associated with worse health-related quality of life in children with cancer. *Supportive Care in Cancer, 23*(10), 3043–3052. https://doi.org/10.1007/s00520-015-2674-0.

CIBMTR (2022). Peripheral Blood Count Recovery. Retrieved 3/13/22, from https://www.cibmtr.org/manuals/fim/1/en/topic/4100q17-20.

Corkins, M. R., Griggs, K. C., Groh-Wargo, S., Han-Markey, T. L., Helms, R. A., Muir, L. V., & Szeszycki, E. E. (2013). *Standards for nutritional support: Pediatric hospitalized patients*. SAGE Publications. https://doi.org/10.1177/0884533613475822.

Evans, J., Gardiner, B., Green, D., Gibson, F., O'Connor, G., & Lanigan, J. (2021). Systematic review of gastrostomy complications and outcomes in pediatric cancer and bone marrow transplant. *Nutrition in Clinical Practice, 36*, 1185–1197. https://doi.org/10.1002/ncp.10724.

Evans, J., Green, D., Connor, G. O., Lanigan, J., & Gibson, F. (2022). Nutritional support practices and opinions toward gastrostomy use in pediatric bone marrow transplant centers: A national survey. *Nutrition, 95*, Article 111556. https://doi.org/10.1016/j.nut.2021.111556.

Evans, J., Needle, J. J., & Hirani, S. P. (2019). Early outcomes of gastrostomy feeding in paediatric allogenic bone marrow transplantation: A retrospective cohort study. *Clinical Nutrition ESPEN, 31*, 71–79. https://doi.org/10.1016/j.clnesp.2019.02.014.

Evans, J. C., Hirani, S. P., & Needle, J. J. (2019). Nutritional and post-transplantation outcomes of enteral versus parenteral nutrition in pediatric hematopoietic stem cell transplantation: A systematic review of randomized and nonrandomized studies. *Biology of Blood and Marrow Transplantation, 25*(8), e252–e259. https://doi.org/10.1016/j.bbmt.2019.02.023.

Goates, S., Du, K., Braunschweig, C. A., & Arensberg, M. B. (2016). Economic burden of disease-associated malnutrition at the state level. *PLOS ONE*. 11(9), e0161833. https://doi.org/10.1371/journal.pone.0161833.

Goldberg, E. K., Neogi, S., Lal, A., Higa, A., & Fung, E. (2018). *Nutritional deficiencies are common in patients with transfusion-dependent thalassemia and associated with iron overload*. Science and Education Publishing Co., Ltd. http://doi.org/10.12691/jfnr-6-10-9.

Gonzales, F., Bruno, B., Alarcón Fuentes, M., De Berranger, E., Guimber, D., Behal, H., Gandemer, V., Spiegel, A., Sirvent, A., Yakoub-Agha, I., Nelken, B., Duhamel, A., & Seguy, D. (2018). Better early outcome with enteral rather than parenteral nutrition in children undergoing MAC allo-SCT. *Clinical Nutrition, 37*(6), 2113–2121. https://doi.org/10.1016/j.clnu.2017.10.005.

Harris, A. C., Young, R., Devine, S., Hogan, W. J., Ayuk, F., Bunworasate, U., ... Levine, J. E. (2016). International, multicenter standardization of acute graft-versus-host disease clinical data collection: A report from the Mount Sinai acute GVHD international consortium. *Biology of Blood and Marrow Transplantation, 22*(1), 4–10. https://doi.org/10.1016/j.bbmt.2015.09.001.

Hirose, E. Y., de Molla, V. C., Gonçalves, M. V., Pereira, A. D., Szor, R. S., da Fonseca, A., ... Arrais-Rodrigues, C. (2019). The impact of pretransplant malnutrition on allogeneic hematopoietic stem cell transplantation outcomes. *Clinical Nutrition ESPEN, 33*, 213–219. https://doi.org/10.1016/j.clnesp.2019.05.005.

Kerby, E. H., Li, Y., Getz, K. D., Smith, E. C., Smith, L. T., Bunin, N. J., & Seif, A. E. (2018). *Nutritional risk factors predict severe acute graft-versus-host disease and early mortality in pediatric allogeneic hematopoietic stem cell transplantation*. Wiley. https://doi.org/10.1002/pbc.26853.

Koç, N., Gündüz, M., Tavil, B., Azik, M. F., Coşkun, Z., Yardımcı, H., ... Tunç, B. (2017). Beneficial effect of nutritional support in children who underwent hematopoietic stem cell transplant. *Experimental and Clinical Transplantation, 15*(4), 458–462. https://doi.org/10.6002/ect.2015.0298.

Kranjčec, I., Matijašić, N., Mašić, M., Švigir, A., Jakovljević, G., & Bolanča, A. (2020). Nutritional status as a predictor of adverse events and survival in pediatric autologous stem cell transplant. *Pediatric Hematology and Oncology, 37*(8), 717–731. https://doi.org/10.1080/08880018.2020.1797254.

Lazarow, H., Singer, R., Compher, C., Gilmar, C., Kucharczuk, C. R., Mangan, P., ... Landsburg, D. J. (2020). Effect of malnutrition-driven nutritional support protocol on clinical outcomes in autologous stem cell transplantation patients. *Supportive Care in Cancer, 29*(2), 997–1003. https://doi.org/10.1007/s00520-020-05571-1.

Lewandowski, C. G., Daudt, L. E., Jochims, A. M. K., Paz, A., & Mello, E. D. (2019). Nutritional aspects in allogeneic hematopoietic stem cell transplantation in children and adolescents in a tertiary hospital. *Nutrición Hospitalaria, 36*(1), 20–24. http://doi.org/10.20960/nh.2050.

Liu, P., Wang, B., Yan, X., Cai, J., & Wang, Y. (2016). Comprehensive evaluation of nutritional status before and after hematopoietic stem cell transplantation in 170 patients with hematological diseases. *Chinese Journal of Cancer Research, 28*(6), 626–633. http://doi.org/10.21147/j.issn.1000-9604.2016.06.09.

McMillen, K. K., Coghlin-Dickson, T., & Adintori, P. A. (2020). Optimization of nutrition support practices early after hematopoietic cell transplantation. *Bone Marrow Transplantation, 56*(2), 314–326. https://doi.org/10.1038/s41409-020-01078-9.

Mehta, N. M., Corkins, M. R., Lyman, B., Malone, A., Goday, P. S., Carney, L., ... Schwenk, W. F. (2013). Defining pediatric malnutrition. *Journal of Parenteral and Enteral Nutrition, 37*(4), 460–481. https://doi.org/10.1177/0148607113479972.

Nava, T., Ansari, M., Dalle, J., de Heredia, C. D., Güngör, T., Trigoso, E., ... Bader, P. (2020). 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 Transplantation, 55*(6), 1126–1136. https://doi.org/10.1038/s41409-020-0818-4.

Ralls, M. W., Miyasaka, E., & Teitelbaum, D. H. (2014). Intestinal microbial diversity and perioperative complications. *Journal of Parenteral and Enteral Nutrition, 38*(3), 392–399. https://doi.org/10.1177/0148607113486482.

Rogers, P. (2015). Importance of nutrition in pediatric oncology. *Indian Journal of Cancer, 52*(2), 176–178. https://doi.org/10.4103/0019-509X.175830.

Schoemans, H. M., Lee, S. J., Ferrara, J. L., Wolff, D., Levine, J. E., Schultz, K. R., ... Pavletic, S. Z. (2018). EBMT–NIH–CIBMTR task force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transplantation, 53*(11), 1401–1415. https://doi.org/10.1038/s41409-018-0204-7.

Steele, C., Salazar, A., & Rypkema, L. (2016). Utilization of a nutrition support algorithm reduces unnecessary parenteral nutrition use in pediatric oncology inpatients. *Journal of the Academy of Nutrition and Dietetics, 116*(8), 1235–1238. https://doi.org/10.1016/j.jand.2015.12.007.

Williams-Hooker, R., Adams, M., Havrilla, D. A., Leung, W., Roach, R. R., & Mosby, T. T. (2015). Caregiver and health care provider preferences of nutritional support in a hematopoietic stem cell transplant unit. *Pediatric Blood & Cancer, 62*(8), 1473–1476. https://doi.org/10.1002/pbc.25473.

Zama, D., Muratore, E., Biagi, E., Forchielli, M. L., Rondelli, R., Candela, M., ... Masetti, R. (2020). Enteral nutrition protects children undergoing allogeneic hematopoietic stem cell transplantation from blood stream infections. *Nutrition Journal, 19*(29), 1–9. https://doi.org/10.1186/s12937-020-00537-9.

Zemrani, B., Yap, J. K., Van Dort, B., Evans, V., Bartle, J., Shandley, D., ... Cole, T. (2019). Nutritional challenges in children with primary immunodeficiencies undergoing hematopoietic stem cell transplant. *Clinical Nutrition, 39*(9), 2832–2841. https://doi.org/10.1016/j.clnu.2019.12.015.