Complications and outcomes of gastrostomy versus nasogastric tube feeding in paediatric allogeneic bone marrow transplant: a prospective cohort study

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Abstract

Background & Aims: The intensive conditioning regimens administered during bone marrow transplant (BMT) frequently cause mucositis, gastrointestinal toxicity and reduced oral intake. Children are consequently at risk of malnutrition. First-line nutrition support is recommended as enteral nutrition (EN). Nasogastric tube (NGT) is the mainstay for administration. Gastrostomies provide an alternative, but there is limited evidence of their efficacy and safety in paediatric BMT. This study aimed to compare enteral tube complications and nutritional and clinical outcomes between children with a gastrostomy versus NGT throughout BMT.

Methods: A prospective cohort study was conducted at a single centre in the United Kingdom. During pre-admission consultations families were offered choice of a prophylactic gastrostomy or NGT. Children undergoing allogeneic BMT were recruited from April 2021 to April 2022. Data compared between children with either tube included: tube complications, change in weight, body mass index and mid-upper-arm circumference, calorie, protein and fluid intake, timing and use of EN and parenteral nutrition, survival, graft-versus-host disease and length of admission. Following BMT, data were collected weekly for the first six weeks from electronic records, monthly thereafter from 3-day averaged food diaries and clinic assessments, until six months post-BMT.

Results: Nineteen children with NGT were compared to 24 with a gastrostomy. Of gastrostomy complications, 94.2% (129/137) were minor, mechanical issues being most common (80/137). Dislodgement comprised 80.2% (109/136) of NGT complications. No significant differences were seen between tubes on nutritional, anthropometric and clinical outcomes.

Conclusions: Gastrostomies were popular with families, relatively safe, associated with mostly minor complications and similarly effective as NGTs in supporting children's nutritional intake and status. Where an NGT may not be tolerated, a prophylactic gastrostomy could be considered. Placement of either tube requires balancing their risks, benefits, the child's nutritional status, conditioning, expected duration of EN and family preferences.

Keywords: Pediatric; bone marrow transplant; gastrostomy; nasogastric tube; complication; enteral nutrition.

Abbreviations: BMI, body mass index; BMR, basal metabolic rate; BMT, bone marrow transplant; CI, confidence interval; CNS, clinical nurse specialist; EN, enteral nutrition; GvHD, graft-versus-host disease; IQR, interquartile range; MDT, multidisciplinary team; MUAC, mid-upper-arm circumference; NGT, nasogastric tube; PN, parenteral nutrition; SACN, Scientific Advisory Committee on Nutrition; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; UK, United Kingdom; WHO, World Health Organisation.

1. Introduction

Intensive conditioning regimens used during bone marrow transplant (BMT) frequently lead to mucositis and gastrointestinal toxicity [1]. Following BMT, patients are at risk of developing malnutrition due to deterioration in oral intake [2,3] and weight loss [4]. Malnutrition has been negatively associated with overall survival, transplant-related mortality, relapse risk [5] and graft-versus-host disease (GvHD) [6]. Proactive initiation of nutrition support is required to circumvent these adverse outcomes.

The American Society for Parenteral and Enteral Nutrition and European Society for Clinical Nutrition and Metabolism recommend enteral nutrition (EN) first-line [7,8]. Observational studies in paediatric BMT have shown preferential outcomes of first-line EN over parenteral nutrition (PN), including better overall survival, less acute GvHD, faster platelet engraftment and shorter admission [9,10]. Nasogastric tubes (NGT) have historically been the mainstay to provide EN [9–13], yet are susceptible to complications including dislodgement, irritation with mucositis and refusal [14].

Gastrostomy use can be considered in paediatric BMT [15]. A recent systematic review concluded that whilst gastrostomy complications occur frequently, they are mostly minor and easily treated [16]. Gastrostomy feeding has also been associated with improvement of nutritional status [16], less use of PN compared to NGT [17] and cosmetic acceptability [18] in paediatric cancer/BMT. Gastrostomies are useful when long-term EN is required; highly relevant given 82% of children have been shown to require EN beyond discharge following BMT [17]. However, gastrostomy use remains less common than NGT in United Kingdom (UK) BMT centres due to the perceived risk of infectious complications [19].

A paucity exists of prospective, long-term studies comparing complications and outcomes of NGT versus gastrostomy feeding in paediatric BMT. A recent systematic review [16] found most studies were retrospective with many not specifying complication occurrence beyond discharge when families must manage issues independently of round-the-clock nursing support. This study aimed to compare the frequency and nature of tube complications, and nutritional and clinical outcomes between children with a gastrostomy versus NGT throughout BMT.

2. Materials and methods

2.1. Design, setting, recruitment and follow up

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [20]. Families and clinicians were involved in the conception, design and outcomes [21]. A prospective cohort study was conducted at a single UK centre. Children were recruited consecutively between April 2021-April 2022 during usual meetings prior to BMT and followed from BMT admission to six months post. Data were collected weekly from day -7 pre-BMT to six weeks post-BMT (to cover most of admission), monthly thereafter until six months post-BMT. Ethical approval was granted (reference 281830).

2.2. Participants

All children received allogeneic BMT from related or unrelated donors, bone marrow, peripheral or cord blood stem cells, for malignant and non-malignant diseases, following reduced intensity or myeloablative conditioning. During pre-admission consultations families were provided nutrition counselling and information regarding nutrition support from dietitians, consultants and clinical nurse specialists (CNS), and offered choice of an NGT to be placed during admission or prophylactic gastrostomy placed prior to admission. Following balanced verbal and written information parents made an informed choice in collaboration with the multidisciplinary team (MDT). Those receiving first-line PN (typically cords) and CAR T-cell therapy were excluded.

2.3. Nutrition support

The aim was to meet the child's energy requirements for age, sex and weight based on the Scientific Advisory Committee on Nutrition (SACN) (2011) guidelines [22] using a combination of oral intake, EN and/or PN. Macro and micronutrient requirements were based on Department of Health (1991) dietary reference values [23]. Fluid requirements were calculated as 150 ml/kg for children 0-6 months old, 120 ml/kg 7-12 months old, and over 10 kg using the Holliday-Segar formula [24].

Children were encouraged to maintain their oral intake, as able. During admission food was provided from the BMT menu adhering to the centre's food safety principles and children could drink cooled, boiled water and individual cartons of juice. Following discharge, children were allowed home-cooked food and drinks whilst still adhering to food safety rules. Throughout admission the child's oral intake, EN and PN were recorded daily by nurses on electronic records. Intakes were compared to the child's requirements by the ward dietitian 2-3 times weekly until discharge. Families were advised on interventions to make up the deficit between intake and requirement. Post-discharge children received weekly dietetic review for the first month, tapering to monthly reviews thereafter.

2.3.1 Enteral and parenteral nutrition

Enteral nutrition was initiated when oral intake became insufficient to meet >50% energy requirements over 2-3 days, or weight reduced over 2-3 consecutive days. Children without a gastrostomy were encouraged to have an NGT placed no later than day +1 post-BMT before mucositis developed. Support with placement came from the MDT, especially play specialists. If dislodged, NGTs were replaced if clinically safe (child not thrombocytopenic) and allowed by the family. Children in the gastrostomy group received EN via percutaneous endoscopic gastrostomy.

Initially EN was provided using an age-appropriate hydrolysed protein formula to pre-empt gastrointestinal intolerance, providing: 0.66 kcal/1 mL, 1.8 g protein/100 mL for children <1 year old; 1 kcal/1 mL, 3 g protein/100 mL for children >1 year. In cases of gastrointestinal intolerance including intractable diarrhoea and vomiting, amino acid products were utilised, providing 0.67 kcal/1 mL, 1.8 g protein/100 mL for children <1 year old; 1 kcal/1 mL, 2.8 g protein/100 mL for children >1 year.

Enteral feeding regimens included daytime bolus feeds, given via gravity or pump over 30-60 minutes to promote gastrointestinal tolerance. Boluses were continued if tolerance was established or extended to continuous 12–20-hour feeds if vomiting and/or diarrhoea were problematic. Alternatively, children commenced continuous 9-12-hour overnight feeds. EN was gradually increased over 2-3 days to aid tolerance and make up the deficit between oral intake and requirements. Once oral intake ceased, having initially commenced on day or night-time feeds, children were provided a combination of both methods aiming to provide 100% requirements. Following engraftment, continuous pump feeds were transitioned to daytime boluses in preparation for discharge. Once home, children fed via NGT

continued, if needed, on daytime boluses as overnight feeding was prohibited due to risk of tube dislodgement and aspiration. Overnight gastrostomy feeding was permitted, so children received overnight feeds with daytime boluses, if required. EN was continued until the child could consume >70% energy requirements orally over 4-5 consecutive days.

Parenteral nutrition was initiated in cases of grade 3-4 mucositis (World Health Organisation (WHO) grading [25]), gastrointestinal GvHD, NGT refusal, or malabsorption of EN due to intractable vomiting/diarrhoea. Glucose and nitrogen solutions were administered over 24 hours, lipid over 20 hours. EN was re-introduced gradually over five days following engraftment and PN simultaneously weaned and eventually stopped prior to discharge.

2.4 Tube complications

During admission, complications with NGTs and gastrostomies were monitored daily by the MDT, with gastrostomy CNS referral made if required. Complications including blockages and dislodgements, aspiration and NGT refusal, stoma site leakage, granuloma, and infection with gastrostomies, were recorded. JE consulted families weekly to ensure no complications were missed. Discrepancies between parent and clinician reports were settled between JE and the child's nurse. Beyond discharge, tube complications were assessed via medical examination at monthly clinic, alongside weekly community nursing review. Following training by JE, parents also recorded tube complications in a diary, to ensure completeness of data. Parents received bi-weekly emails and/or telephone contact from JE to support and remind them to complete their diary.

Gastrostomy complications were informed by recent studies [16,26,27] and categorised as: 1) Infectious: gastrostomy site inflammation defined by presence of clinical signs including redness, inflammation or swelling. In cases of inflammation a skin swab was taken for microorganism assessment and infection confirmed by positive culture. Neutrophil count and treatment were noted; 2) Mechanical: damage to tube or components, occlusion and buried bumper syndrome; 3) Stoma: granuloma or leakage of gastric contents. Major complications were defined as infection/inflammation requiring intravenous antibiotics, surgical intervention to remediate the complication, a life-threatening complication or death. Other complications were classified minor. Nasogastric tube complications were categorised as: 1) Dislodgement: removal by any means; 2) Mechanical: damage to tube or

components or occlusion; but were not classified major/minor. Complications not falling under these categorises were classified as 'Other' for both tubes. Numbers of children developing any complication and frequency of complications (episodes), were recorded.

2.5 Anthropometry

Anthropometric measurements were taken during admission and clinic appointments. Weight was measured to the nearest 0.01 kg using a standing, sitting or baby scale. Infants <1 year were weighed naked, children >1 without shoes, wearing minimal clothing. Height was measured with the child standing (without shoes) to the nearest 0.1 cm using portable mechanical stadiometer for children >2 years. A measuring mat was used to measure recumbent length for younger children to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) /height (meters)^2. Measures were converted to Z-scores using WHO standards [28].

Mid-upper-arm circumference (MUAC) was measured by JE to avoid inter-person variability, using flexible paper tape measures following British Dietetic Association guidelines [29]. The mid-point between the acromion and olecranon process of the non-dominant arm was initially measured with arm bent at 90 degrees in front of the body. Two consecutive measurements were taken at the mid-point with the arm hanging loosely by the child's side and the mean calculated. MUACs were converted to Z-scores using PediTools [30].

2.6 Nutritional intake

Children's calorie, protein, fluid, copper, selenium, zinc, vitamin A and E intake was assessed over three days (two weekdays, one weekend), weekly from admission to six weeks post-BMT, monthly thereafter during the last week of each month (giving a snapshot of intake). This dietary recall method is considered acceptably accurate to estimate energy and macronutrient intake in children [31]. Intake was split by that provided orally, via EN (NGT or gastrostomy) and PN. During admission, nurses recorded daily intake from oral, EN and PN. Nurses and parents jointly kept a food diary, following training by JE, to record oral intake as accurately as possible. Beyond discharge, parents kept 3-day food diaries as per the above schedule, receiving bi-weekly contact from JE as support. Parents

recorded what and how much their child ate, drank, and EN volume and formula provided, including water flushes. This included recording weights of snacks on packaging, volumes of drinks, naming brands and describing portions consumed e.g. in spoons, bowls, plate and jar sizes. Parents were not expected to weigh foods to reduce burden and missing data.

2.7 Use of nutritional interventions and clinical outcomes

Data were collected on EN and PN commencement and duration. Use of NGT and gastrostomies were categorised as administering medications, EN and/or fluids. Clinical outcomes including: overall survival, non-relapse mortality and GvHD (acute: graded I-IV using Glucksberg criteria [32]; chronic: graded according to National Institutes of Health [33]), were recorded as incidence at day 100 and six months post-BMT, alongside admission length.

2.8 Statistics

Sample size was determined pragmatically as children that could be recruited over 12 months. Continuous variables were considered normally distributed by observing a bell-shaped histogram, described using mean and standard deviation (SD) with independent samples t-tests applied between groups, paired t-tests within groups. Otherwise, data were considered skewed, described using median and interquartile range [IQR] with Mann-Whitney U-test applied between groups, Wilcoxon Signed-Rank test within. Categorical variables were described using frequency and percentages and compared between groups using Chi-square or Fisher's exact. Episodes of tube complications were described as counts and compared using Poisson regression. Time to initiate/cease interventions and survival were analysed using Cox regression. As numerous children who started with NGT required a gastrostomy post-BMT, analyses were undertaken as 'intention-to-treat' and compared 'as treated' and 'per protocol'. Sensitivity analyses were undertaken. Missing data were dealt with using pairwise deletion. Food diaries were analysed using Dietplan version 7.00.65 [34], pre-installed with UK food tables [35]. Manufacturer's data on EN products and PN prescriptions were used to calculate nutritional intake. Data were analysed using SPSS Version 27.0.1.0 [36]. $P < 0.05$ was considered statistically significant.

3. Results

3.1 Participants

An 88% recruitment rate (43/49) was achieved; 24 children had a gastrostomy, 19 NGT. Throughout follow up: six children required a reactive gastrostomy due to failure of NGT feeding; four no longer required an NGT as they became able to take medications and sufficient nutrition orally; one child with NGT died (Fig. 1). Children were demographically comparable, except more with a gastrostomy had non-malignancies, those with NGT had more malignant diseases (Table 1). Tubes were placed a median [IQR] days pre-BMT: NGT -8.0 [-10.0, -7.0]; gastrostomy -38.5 [-49.3, -27.0]. Three children entered the study having had an NGT for > 2.5 months and six a gastrostomy for >5 months (five as their BMT was delayed, one receiving long-term EN). Reactive gastrostomies (n = 6) were placed a median [IQR] 38.5 [28.0, 71.5] days post-BMT.

Table 1

Children's characteristics and transplant modalities.

	Gastrostomy (n = 24)	Nasogastric tube (n = 19)	P value
Age (years), median [interquartile range]	3.5 [1.6, 4.9]	4.5 [1.0, 8.4]	0.980 [a]
Sex, Male/Female, n	14/10	14/5	0.349 [b]
Ethnicity, n (%)			
White	18 (75.0)	11 (57.9)	0.384 [c]
Asian	4 (16.7)	5 (26.3)	
Mixed race	2 (8.3)	1 (5.3)	
Black	0 (0)	2 (10.5)	
Disease type, n (%)			
Non-malignant	22 (91.7)	10 (52.6)	**0.005** [c]
Malignant	2 (8.3)	9 (47.4)	
Diagnoses, n (%)			
Non-malignant			
Severe combined immunodeficiency	3 (12.5)	2 (10.5)	
Chronic granulomatous disease	4 (16.7)	0 (0)	
Activated PI3K delta syndrome	3 (12.5)	0 (0)	
Hurler syndrome	3 (12.5)	0 (0)	
Wiskott-Aldrich syndrome	2 (8.3)	1 (5.3)	
Adrenoleukodystrophy	0 (0)	3 (15.8)	
Other	7 (29.2)	4 (21.1)	
Malignant			
Acute myeloid leukaemia	1 (4.2)	4 (21.1)	
Acute lymphoblastic leukaemia	0 (0)	2 (10.5)	
Juvenile myelomonocytic leukaemia	0 (0)	2 (10.5)	
Other	1 (4.2)	1 (5.3)	
Disease status at transplant, n (%)			
Stable	21 (87.5)	12 (63.2)	0.079 [c]
Partial remission	1 (4.2)	1 (5.3)	>0.999 [c]
Complete remission 1	2 (8.3)	5 (26.3)	0.211 [c]
Complete remission ≥ 2	0 (0)	1 (5.3)	0.442 [c]
Transplant number, n (%)			
1st	22 (91.7)	18 (94.7)	>0.999 [c]
≥ 2nd	2 (8.3)	1 (5.3)	
Stem cell source, n (%)			
Bone marrow	14 (58.3)	12 (63.2)	0.765 [b]
Peripheral blood	8 (33.3)	2 (10.5)	0.145 [c]
Cord	2 (8.3)	5 (26.3)	0.211 [c]
Donor, n (%)			
Matched unrelated donor	11 (45.8)	5 (26.3)	0.189 [b]
Matched sibling donor	7 (29.2)	5 (26.3)	0.836 [b]
Cord	2 (8.3)	5 (26.3)	0.211 [c]
Mismatched unrelated donor	4 (16.7)	3 (15.8)	>0.999 [c]
Matched related donor	0 (0)	1 (5.3)	0.442 [c]
Sex mismatch (male recipient, female donor), n (%)	5 (20.8)	6 (31.6)	0.495 [c]
Cytomegalovirus disparity (between donor and recipient), n (%)	4 (16.7)	3 (15.8)	>0.999 [c]
Conditioning regimens, n (%)			
Myeloablative	16 (66.7)	15 (78.9)	0.500 [b]
Reduced intensity	8 (33.3)	4 (21.1)	
Total body irradiation	2 (8.3)	1 (5.3)	0.575 [c]
Number of CD 34+ cells infused, median [interquartile range]	7.1 [2.2, 10.1]	4.6 [1.2, 10.0]	0.448 [a]

Comparison using: [a] Mann-Whitney; [b] Chi-Square; [c] Fisher's exact.

P values < 0.05 are marked bold.

3.2 Tube complications

Based on their original tube (intention-to-treat): 100% (19/19) children with NGT, 95.8% (23/24) with gastrostomy developed ≥1 complication ($p > 0.999$); the NGT group experienced a median [IQR] 5.0 [3.0, 10.0] episodes, gastrostomy 5.0 [3.3, 7.8] ($p = 0.023$, β 1.3, 95% CI 1.0-1.7). Of gastrostomy complication episodes, 93.9% (122/130) were minor, 6.2% (8/130) major, the latter encountered in 25.0% (6/24) children. Of all 30 children who had a gastrostomy: 86.7% (26/30) developed ≥1 complication and had a median [IQR] 4.0 [3.0, 6.3] episodes, of which 94.2% (129/137) were minor, 5.8% (8/137) major, the latter experienced by 20% (6/30) children.

More children with NGT than gastrostomy developed a complication during weeks 4 and 6 post-BMT (47.4% v 8.3%, $p = 0.005$; 47.1% v 11.5%, $p = 0.014$ respectively), and had more episodes during week 4 (84.6% v 15.4% of total episodes, $p = 0.012$), week 6 (77.8% v 22.2%, $p = 0.003$), and month 6 (56.7% v 43.3%, $p < 0.001$) (Table 2).

Most frequent NGT complications were being pulled or vomited out, encountered by 79.0% (15/19) and 57.9% (11/19) children, making up 58.8% (80/136) and 20.6% (28/136) episodes respectively (Table 3). Most frequent gastrostomy complications were mechanical, totalling 58.4% (80/137) episodes, with device leakage occurring most often in 53.3% (16/30) children, making up 23.4% (32/137) episodes. Site inflammation with no positive culture was the most common infectious complication, experienced by more children than any other complication (66.7%, 20/30), comprising 20.4% (28/137) episodes, with 71.4% (20/28) occurring within four weeks post-BMT, the child being neutropenic (<1.0 x 10^9/L) in 46.4% (13/28) episodes, 21.4% (6/28) treated with intravenous antibiotics, 78.6% (22/28) monitored without treatment prescribed.

Table 2

Frequency and time points at which tube complications occurred.

Time period	Total complication episodes, n †	Gastrostomy					Nasogastric tube			Comparison of episodes between groups [b]				P comparing children developing ≥1 complication between groups
		Children with gastrostomy, n [a]	Episodes, n (% total episodes)	Major episodes, n (% gastrostomy total)	Minor episodes, n (% gastrostomy total)	Children developing ≥1 complication, n (% with gastrostomy)	Children with NGT, n [a]	Episodes, n (% total episodes)	Children developing ≥1 complication, n (% with NGT)	P value	Exp(β)	95% CI Lower	95% CI Upper	
Conditioning week (Day -7 to 0)	45	24	21 (46.7)	2 (9.5)	19 (90.5)	15 (62.5)	19	24 (53.3)	13 (68.4)	0.219	1.44	0.80	2.59	0.686 [c]
Week 1 post-BMT (Day +1 to +7)	12	24	6 (50.0)	1 (16.7)	5 (83.3)	4 (16.7)	19	6 (50.0)	5 (26.3)	0.686	1.26	0.41	3.92	0.477 [d]
Week 2 post-BMT (Day +8 to +14)	18	24	10 (55.6)	2 (20.0)	8 (80.0)	8 (33.3)	19	8 (44.4)	8 (42.1)	0.982	1.01	0.40	2.56	0.555 [c]
Week 3 post-BMT (Day +15 to +21)	20	24	10 (50.0)	0 (0)	10 (100)	6 (25.0)	19	10 (50.0)	7 (36.8)	0.601	1.26	0.53	3.04	0.401 [c]
Week 4 post-BMT (Day +22 to +28)	13	24	2 (15.4)	0 (0)	2 (100)	2 (8.3)	19	11 (84.6)	9 (47.4)	**0.012**	6.95	1.54	31.34	**0.005** [d]
Week 5 post-BMT (Day +29 to +35)	10	25	3 (30.0)	0 (0)	3 (100)	3 (12.0)	18	7 (70.0)	4 (22.2)	0.088	3.24	0.84	12.53	0.427 [d]
Week 6 post-BMT (Day +36 to +42)	18	26	4 (22.2)	0 (0)	4 (100)	3 (11.5)	17	14 (77.8)	8 (47.1)	**0.003**	5.35	1.76	16.26	**0.014** [d]
Month 2 post-BMT (Day +43 to +61)	29	28	17 (58.6)	1 (5.9)	16 (94.1)	11 (39.3)	12	12 (41.4)	8 (66.7)	0.186	1.65	0.79	3.45	0.112 [c]
Month 3 post-BMT (Day +62 to +91)	29	29	15 (51.7)	1 (6.7)	14 (93.3)	10 (34.5)	11	14 (48.3)	6 (54.5)	0.051	2.46	0.91	5.10	0.295 [d]
Month 4 post-BMT (Day +92 to +122)	25	30	17 (68.0)	1 (5.9)	16 (94.1)	13 (43.3)	9	8 (32.0)	4 (44.4)	0.294	1.57	0.68	3.64	>0.999 [d]
Month 5 post-BMT (Day +123 to +152)	24	30	19 (79.2)	0 (0)	19 (100)	12 (40.0)	8	5 (20.8)	4 (50.0)	0.979	0.99	0.37	2.64	0.698 [d]
Month 6 post-BMT (Day +153 to +183)	30	30	13 (43.3)	0 (0)	13 (100)	9 (30.0)	8	17 (56.7)	5 (62.5)	**<0.001**	4.90	2.38	10.10	0.117 [d]
During BMT admission *	146	24	75 (51.4)	7 (9.3)	68 (90.7)	23 (95.8)	19	71 (48.6)	18 (94.7)	0.064	1.35	0.98	1.85	>0.999 [c]
Post-discharge to month 6 post-BMT **	113	29	61 (54.0)	1 (1.6)	60 (98.4)	21 (72.4)	12	52 (46.0)	9 (75.0)	0.054	2.03	0.93	2.93	>0.999 [c]

Abbreviations: BMT, bone marrow transplant; CI, confidence interval; Day 0, day of transplant; NGT, nasogastric tube.

† Total episodes throughout follow up from conditioning to month 6 = 273 (gastrostomy = 137; NGT = 136).

* Analysed as intention-to-treat (tube child originally had); ** Analysed as treated: six children changed from NGT to gastrostomy, excluding one who died with NGT, one not discharged by end of follow up in the gastrostomy group. Total episodes during admission and post-discharge do not add up to total episodes (273) as different numbers of children are analysed during these time periods.

[a] numbers with either tube changed throughout the study as shown in Fig. 1.; comparison using [b] Poisson regression; [c] Chi-Square; [d] Fisher's exact.

P values < 0.05 are marked bold.

Table 3

Tube complications experienced throughout the study, including children who had a reactive gastrostomy.

Complications	Children,** n (%)	Episodes,** n (% of subtotal)
	Gastrostomy (n = 30)	
Mechanical		
Device leakage	16 (53.3)	32 (23.4)
ENFit connector broke during use	15 (50.0)	23 (16.8)
Tube occlusion (unblocked without removing gastrostomy)	6 (20.0)	11 (8.0)
ENFit connector broke by child	4 (13.3)	5 (3.6)
Fast release clamp broke	3 (10.0)	3 (2.2)
External fixation plate broke	3 (10.0)	3 (2.2)
Tube occlusion requiring surgery to replace gastrostomy *	2 (6.7)	2 (1.5)
Change of device due to ongoing leaking, not under surgery	1 (3.3)	1 (0.7)
Infectious		
Site inflammation (no positive culture), no treatment	15 (50.0)	22 (16.1)
Site inflammation (no positive culture), intravenous antibiotics *	5 (16.7)	6 (4.4)
Stoma		
Granuloma	11 (36.7)	14 (10.2)
Peristomal leakage	8 (26.7)	10 (7.3)
Other		
Device caught (without dislodgement) causing pain/redness	3 (10.0)	3 (2.2)
Device dislodged during play, replaced without surgery	2 (6.7)	2 (1.5)
Subtotal, n (% of: children with PEG; total episodes 273)	**26 † (86.7)**	**137 (50.2)**
Major,* n (% of gastrostomy total)	**6 (20.0)**	**8 (5.8)**
Minor, n (% of gastrostomy total)	**26 (100)**	**129 (94.2)**
	Nasogastric tube (n = 19)	
Dislodgement		
Pulled out by child	15 (79.0)	80 (58.8)
Vomited out	11 (57.9)	28 (20.6)
Dislodged (caught on toy)	1 (5.3)	1 (0.7)
Mechanical		
Unable to aspirate and test pH, needed repositioning	5 (26.3)	8 (5.9)
Tube occlusion, later unblocked	4 (21.1)	5 (3.7)
Tube occlusion, tube replacement needed	3 (15.8)	3 (2.2)
Tube cap broke	3 (15.8)	3 (2.2)
Tube cap stuck from medicines, eventually unstuck	2 (10.5)	2 (1.5)
Hole in tube, tube replacement needed	1 (5.3)	1 (0.7)
Other		
Blister on ear	2 (10.5)	2 (1.5)
Placement refusal	1 (5.3)	1 (0.7)
Epistaxis	1 (5.3)	1 (0.7)
Accidentally cut	1 (5.3)	1 (0.7)
Subtotal, n (% of: children with NGT; total episodes 273)	**19 (100)**	**136 (49.8)**

Abbreviations: NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy.

* Major complication requiring intravenous antibiotics or surgery to replace the gastrostomy.

** Children could experience multiple complications therefore numbers exceed total children in each group.

† Only 26/30 children with a gastrostomy experienced the complications listed.

3.3 Anthropometry

Under intention-to-treat, as treated, per protocol and sensitivity analysis (in and excluding a child with growth retardation in the gastrostomy group with measurements >7-9 SD below the mean), no significant differences were seen in weight or MUAC between NGT v gastrostomy groups at any time during follow up (Fig. 2 and Supplementary Table 1). When analysing all children's BMI, no differences were seen between groups, but on removing the child with growth retardation, the gastrostomy v NGT group had a significantly higher mean (SD) at: day -7, 1.00 (1.11) v 0.10 (1.52), p = 0.033, 95% CI -1.71 to -0.08; day 28, 0.71 (1.01) v -0.08 (1.29), p = 0.030, -1.51 to -0.08; day 62, 0.78 (0.93) v 0.05 (1.32), p = 0.043, -1.45 to -0.03; which became non-significant from day 91 onwards.

3.4 Nutritional intake

Fifteen food diaries were unreturned. Under intention-to-treat, as treated and per protocol analysis, no significant differences were found between groups at any time on percentage of calorie, protein, fluid, copper, selenium, zinc, vitamin A and E requirements met from oral, EN or PN (Fig. 3 and Supplementary Table 2). During engraftment, median calorie intake compared to basal metabolic rate (BMR) based on Schofield equations [37] in the NGT v gastrostomy group met: 151.0% v 87.0% conditioning; 157.6% v 163.1% week 1; 151.3% v 183.5% week 2; 160.5% v 167.0% week 3; 157.3% v 161.4% week 4; all p > 0.10.

3.5 Use of nutritional interventions and clinical outcomes

No significant differences were seen between tubes regarding use of EN and PN, length of admission, overall survival, GvHD (Table 4), nor use to administer medications, EN or fluids (Supplementary Table 3). One child with NGT died due to multiorgan failure; three with NGT developed chronic GvHD (two mild, one moderate); by day 100 one with NGT and two with gastrostomy developed grade II acute gut GvHD, two with gastrostomy had grade III; by month 6 GvHD resolved for all except two with gastrostomy with grade III persisting (one remained an inpatient throughout follow up).

All children were discharged with a tube in situ: NGT n = 12, gastrostomy n = 29. Beyond discharge, 82.8% (24/29) with gastrostomy, 66.7% (8/12) NGT required ongoing EN. Six months post-BMT: 100% (30/30) with gastrostomy, 66.7% (8/12) NGT still had their tube in situ to administer medications as a minimum; 50.0% (15/30) with gastrostomy, 25.0% (3/12) NGT still required EN.

Table 4

Timing and use of nutritional interventions and clinical outcomes.

	Gastrostomy (n = 24)	**Nasogastric tube (n = 19)**	**P value**
EN initiation (days pre-BMT), median [IQR]	4.0 [7.0, 2.0]	2.0 [7.5, 0.8]	0.430 [a]
EN duration during admission (days), median [IQR]	35.0 [23.0, 44.0]	29.0 [23.0, 52.0]	0.875 [b]
Percent of days EN provided during admission, median [IQR]	63.0 [44.2, 82.2]	55.5 [46.5, 67.5]	0.605 [b]
Children requiring PN at any time during admission, n (%)	16 (66.7)	14 (73.7)	0.619 [c]
PN initiation (days from BMT), median [IQR]	Day 0.5 post-BMT [-1.8, 2.8]	Day -2.5 pre-BMT [-2.0, 7.0]	0.991 [a]
PN duration (days), median [IQR]	49.0 [43.3, 57.8]	42.5 [23.8, 57.5]	0.360 [b]
Day 100 overall survival, n (%)	24 (100)	18 (94.7)	0.593 [a]
Month 6 overall survival, n (%)	24 (100)	18 (94.7)	0.593 [a]
Day 100 grade I-II acute GvHD, n (%)	8 (33.3)	6 (31.6)	0.903 [c]
Month 6 grade I-II acute GvHD, n (%)	4 (16.7)	1 (5.6) *	0.371 [d]
Day 100 grade III-IV acute GvHD, n (%)	2 (8.3)	0 (0)	0.489 [d]
Month 6 grade III-IV acute GvHD, n (%)	2 (8.3)	0 (0)	0.489 [d]
Day 100 gut GvHD, n (%)	4 (16.7)	1 (5.3)	0.363 [d]
Month 6 gut GvHD, n (%)	2 (8.3)	0 (0)	0.489 [d]
Length of admission (days), median [IQR] **	48.0 [32.0, 65.0]	43.5 [35.0, 67.3]	0.927 [b]

Abbreviations: BMT, bone marrow transplant; EN, enteral nutrition; GvHD, graft-versus-host disease; IQR, interquartile range; PN, parenteral nutrition; SD, standard deviation.

Comparison using: [a] Cox regression; [b] Mann-Whitney; [c] Chi-Square; [d] Fisher's exact.

* One child who died excluded from analysis.

** Excluding a child who died during admission (nasogastric tube), one not discharged by end of follow up (gastrostomy).

4 Discussion

Gastrostomies were used heavily up to six months post-BMT, associated with mostly minor complications and similarly effective to NGT in supporting children's nutritional intake and status.

Given both tubes were used so frequently complications are inevitable. Although gastrostomy complications occurred frequently in 87% children with gastrostomy, 94% were minor. A systematic review [16] found 55% of children developed gastrostomy complications with 77% being minor, yet many studies were retrospective limiting accuracy of findings. Classification of complications as major/minor is somewhat arbitrary given a local infection in an immunocompromised child could be a major event. NGT complications are not categorised in this way. Dislodgement was the most common NGT complication; a persistent risk by their nature, even up to month six post-BMT when emetic effects of conditioning have subsided. Replacement was undertaken promptly and rarely contraindicated yet can cause child and parent distress [38]. Qualitative exploration would illuminate the impact on families.

Most common gastrostomy complications were mechanical (58% episodes) and easily remedied through replacement of damaged parts. A systematic review found inflammation (52%) and infection (42%) most frequent [16]. Despite no positive cultures, site inflammation was prominent in this study (20% episodes), often occurring during the neutropenic phase. Given the seriousness of infectious complications in BMT there may be overcompensation by clinicians to gastrostomy care, and selection bias (parents chose this intervention and may be more diligent to their upkeep), which could have contributed to low incidence. Parents also received gastrostomy CNS training prior to discharge. Education is vital in empowering parents to prevent and rectify complications.

Weight and BMI are traditionally used to assess nutritional status but are affected by hydration, oedema and organomegaly [39]. MUAC is considered more sensitive being independent of such factors [40]. Addition of MUAC to BMI has shown increased sensitivity of nutritional assessment in paediatric cancer [41]. In paediatric BMT, MUAC $<5^{th}$ percentile has been associated with poorer event-free survival, relapse and non-relapse mortality 3-years post-BMT compared to higher percentiles, with MUAC seen as a stronger predictor of outcomes than BMI [42]. Given MUAC is an easy bedside measure, recommended by the International Society of Pediatric Oncology [40], it should be used routinely in paediatric BMT. Optimal nutritional assessment methods are essential given malnutrition is an independent risk factor for poorer outcomes post-BMT [5,6,43].

Children entered BMT adequately nourished with anthropometric measures within ±1 SD of the mean; similar findings to others [10,44,45]. Over follow up, the NGT group narrowed the baseline

difference in weight, MUAC and BMI, with weight and BMI in this group the only measures to exceed baseline. The gastrostomy group's weight was the only measure significantly lower at month six than baseline. Other studies have shown weight stabilisation with NGT and gastrostomy 1-2 months post-BMT [17], others weight loss [10,46,47].

Anthropometric measures generally declined or stabilised despite total calorie intake in both groups meeting 87-184% BMR during the first four weeks post-BMT and >75% SACN requirements throughout six months, with protein exceeding 100% SACN requirements throughout. Impaired nutrient absorption and gastrointestinal toxicity post-BMT [8] and overreporting in food diaries could explain this. Whilst recommendations exist for calorie requirements in adult cancer [8], surveys have shown centres aim for different targets [48,49]. Requirements for children post-BMT are not well studied [44]. Previous research has shown declines in resting energy expenditure in the month post-BMT [50–52] and overestimation of calorie needs using Schofield, Harris-Benedict and WHO equations [50]. Another study supports this, finding 115% BMR and 1.5 g/kg protein stabilised weight to day 28 post-BMT, suggesting lower requirements to healthy children are suitable [44]. Post-BMT, children experience numerous factors altering energy expenditure, including mucositis and catabolic effects of GvHD [53], whilst usually inactive often requiring analgesia [52]. To ensure optimal nutrition support, sufficient to preserve or improve children's nutritional status, yet not excessive risking metabolic complications, it is important to accurately determine energy requirements [52,54]. Further research is needed.

Despite frequent NGT dislodgement, both tubes contributed similarly to nutritional requirements; EN contributed 11-57% calorie, 22-99% protein, 23-92% fluid requirements, demonstrating their key role in supporting intake up to six months post-BMT. Other studies have reported EN contributing a median 10% to children's calorie requirements (based on BMR) in weeks 1-4 post-BMT [44], and mean 78% (based on WHO) during various admissions after transplant [55]. Oral intake declined to a nadir by week two post-BMT, similar findings to others [56]. Interestingly, oral calorie and protein intake increased more throughout follow up than fluid so both tubes played a more prominent role in helping meet fluid requirements. PN made up the shortfall in requirements during the period of maximum gut toxicity following conditioning, contributing 33-70% calorie requirements. Others have shown PN to provide 79% of energy during BMT admission based on BMR [44] and Schofield [57].

Micronutrient intake has received little attention in BMT [58]. Studies investigating various minerals, water- and fat-soluble vitamins found total micronutrient intake (not split by feeding route) did not meet children's requirements at various times from cancer diagnosis to 18 months post [59], nor in adults from BMT to day 100 post [58]. This cohort also struggled to meet 100% copper, selenium and zinc

requirements until month two post-BMT. Plasma micronutrient deficiencies have also been found in paediatric cancer with low selenium [59,60] and copper [59] identified as independent predictors of relapse, event-free and overall survival. Given the prevalence of micronutrient abnormalities and associations with poorer outcomes, further research is needed. Micronutrient status should be routinely assessed and monitored in paediatric BMT.

Whenever possible, EN should be used first-line [7,8] given its association with better survival, shorter admission [10], reduced incidence of bloodstream infections [46], faster platelet engraftment and less GvHD [61,62], than exclusive PN. The protective effects of EN on GvHD could be attributable to improved gut microbiota observed post-BMT [63,64]. Given emerging evidence associating gut microbiome modifications and GvHD, this requires further research.

Between tubes, similar incidence of GvHD and use of EN and PN were observed. Both tubes were used heavily during follow up; 91% still required their tube six months post-BMT. Whilst in situ tubes were always used to administer medications; especially important given poor oral medication adherence is associated with greater infection risk in paediatric BMT [65]. Many children required long-term EN; 78% post-discharge, 47% at month six. Although others have shown shorter EN requirement [9,10], duration of need is likely a significant factor in parent's decision making when choosing a tube.

A prior study found earlier PN initiation among children with NGT than gastrostomy [17]. Due to pre-existing IV access and children often refusing NGT placement [66,67], PN rather than EN has been preferred by clinicians [19,68]. NGT refusal was rarely encountered in this study. Comprehensive pre-admission preparation of families for tube feeding and MDT support, including dietitians; aspects crucial to success of NGT feeding [68], could explain this. However, due to persistent dislodgement, NGT feeding failed for six children and reactive gastrostomies were required. With hindsight these families would have benefited from prophylactic gastrostomy placement to avoid this failure. During pre-admission consultations, if NGT feeding is deemed unrealistic, a gastrostomy should be considered. This would save families stress of prolonging admission, waiting for count recovery to enable safe gastrostomy placement following an already difficult period. Despite this, admission length was no different between groups, similar to previous findings [17].

4.1 Limitations

Children were not randomised to either tube nor was economic evaluation undertaken. From prior work [17] lower gastrostomy uptake was anticipated and from practice we know how passionately families feel about their choice. Thus, randomisation was not deemed appropriate. Sample size was small so statistical power was low. A multicentre study was considered but from previous work [19] this would not have greatly increased numbers with a gastrostomy. Children with gastrostomies mostly had non-malignancies thus limiting generalisability to malignancies. Timing of gastrostomy placement for those undergoing chemotherapy prior to BMT is challenging. The accuracy of some food diaries were poor, but conducting the study prospectively meant details could be clarified. Nutritional intake was measured only 3-days monthly from months 2-6 to minimise burden, a problem noted with 4-day diaries [59], but appreciate this compromised detail.

5 Conclusion

Gastrostomies were relatively safe, associated with frequent but mostly minor complications, utilised heavily up to six months post-BMT, with similar efficacy to NGT in supporting children's nutritional intake and status throughout transplant. When it is suspected an NGT may not be tolerated, a prophylactic gastrostomy could be an alternative. The decision to place either tube requires balancing their risks, benefits, the child's nutritional status, conditioning, expected duration of EN and family preferences, after all, parents will be the ones using it.

This study was part of a mixed methods project. The qualitative component explored why families chose an NGT or gastrostomy and how their experiences of either tube compared. We hope to report these findings in time to give a holistic picture of this phenomenon. Future multicentre studies should contain economic evaluation and randomise children to either tube to provide higher quality evidence and adequately powered samples. Research should explore optimal EN formulas, superior methods for nutritional assessment and correlations between nutrition support modalities, nutritional status and clinical outcomes.

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8 Author contributions

James Evans: Conceptualisation, Methodology, Formal analysis, Investigation, Data curation, Writing - Original draft, Visualisation, Project administration, Funding acquisition. Dan Green: Methodology, Formal analysis, Writing - Reviewing and editing, Supervision. Graeme O'Connor: Methodology, Writing - Reviewing and editing, Supervision. Julie Lanigan: Methodology, Writing - Reviewing and editing, Supervision. Faith Gibson: Methodology, Writing - Reviewing and editing, Supervision. All authors read and approved the final manuscript as submitted.

9 Conflict of Interest

The authors declare no conflict of interest.

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11 Figure legends

Figure 1. Inclusion and flow of children through the study.

Figure 2. Change in weight, mid-upper-arm circumference and BMI throughout follow up.

Figure 3. Contribution of oral, enteral and parenteral nutrition to calorie, protein and fluid requirements.