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Optimising Nutrition Delivery During Haploid Identical Stem Cell Transplant

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ABSTRACT:

A17yr old male with relapsed ALL ,height 174 cm , weight 55 kg presented with 10kg weight loss in a month, moderate oral intake and excessive fatigue.His BMI was 17kg/m2 and PGSGA score -7 (mild malnutrition). Patient was anaemic and had low counts. Energy requirement was calculated using Schofield Equation -1595 kcals, protein 80g at 1.5g/BW. During conditioning therapy, due to poor oral intake,high protein ONS suggested along with neutropenic high protein diet. From -D1 to -D8 an average of 55% calorie and 40% protein met. A further 3% weight loss and muscle loss noted. On D0 of stem cell transfusion patient was NPO.On+D1to+D5 due to poor oral intake RTF@100ml 3rd hourly with trial oral was initiated.Feeds were prepared under laminar floor.95% of calorie and 85% of protein met.+D6 patient kept on NPO due to Melina.TPN@50ml/hr initiated on +D7with on demand RTF@100ml 3rd hourly .Patient met 147% of calorie and 126% of protein requirement.+D13 to+D17 patient was on oral antibacterial liquid diet and met 75% of nutrition requirement.+D18 till discharge(+D26) encouraged neutropenic high protein vegetarian diet with ONS. He met 100% of calorie and protein requirement in immediate post-HSCT period. At time of discharge, after 34 days, egg and whole fruit were introduced along with high protein neutropenic oral diet and ONS. Post discharge telephonic follow-up was done for adherence to antimicrobial diet and high protein intake. Assessment at first visit post discharge revealed a weight gain of 1 kg.

This case illustrates that nutritional requirement of HSCT patients could be met adequately by optimising nutrition delivery through enteral and parenteral route. Dedicated nutritional counselling and multi model nutrition intervention is crucial to combat significant risk of malnutrition

Background: Bone marrow transplant (BMT) is a sophisticated procedure consisting of the administration of high-dose chemoradiotherapy followed by intravenous infusion of hemopoietic stem cells to reestablish marrow function when bone marrow is damaged or defective. BMT is used in the treatment of solid tumors, hematologic diseases, and autoimmune disorders. Artificial nutrition, total parenteral nutrition in particular, is provided to patients undergoing BMT to minimize the nutritional consequences of both the conditioning regimens (eg, mucositis of the gastrointestinal tract) and complications resulting from the procedure (eg, graft versus host disease and venoocclusive disease of

the liver). Although artificial nutrition is now recognized as the standard of care for BMT patients, defined guidelines for the use of artificial nutrition in this clinical setting are lacking

1. Introduction

Malnutrition, or undernutrition, is an imbalance between the required nutrient intake and the actual intake, leading to deficiencies in caloric energy, protein, and micronutrients [1]. Chronic disease in children contributes to malabsorption and increased metabolic demands [2], which, in turn, make many children, adolescents, and young adults with cancer or disorders of the blood and immune systems particularly vulnerable to malnutrition [3]. These patients often receive prolonged and intensive therapy, which impacts their optimal nutritional status and overall health [4]. The malnutrition rates in children with malignancies treated in developed countries vary widely: various articles report rates of 0–20% in leukemia patients, 0–31% in solid tumor patients, and up to 50% in high-risk neuroblastoma patients [5,6,7,8,9,10,11]. Malnutrition is also seen in children with transfusion-dependent anemias [12] and primary immunodeficiencies [13].

The BMT procedures are curative for many of these malignant and non-malignant conditions, including hemoglobinopathies, bone marrow failure syndromes, immunodeficiencies, immune dysregulatory syndromes, and metabolic disorders [14]. A preparative or "conditioning" regimen is given prior to the infusion of blood or bone marrow-derived stem cells. These regimens serve to make space in the patient's bone marrow cavity for the incoming donor cells, weaken the patient's immune system to allow for the acceptance of the donor graft and, in the case of malignant disorders, provide additional anti-cancer therapy. The combination of chemotherapy and/or radiation therapy often results in the development of nausea, vomiting, diarrhea, mucositis, and decreased appetite in transplant recipients [11,15]. The incidence and severity of these symptoms directly correlate with the conditioning regimen's intensity. Regardless of whether the conditioning intensity is high or reduced, the effects on the patient are significant, setting the stage for malnutrition to be a common finding in pediatric BMT patients [5]; the rates of malnutrition range from 1–47% prior to and 19–20% after BMT [3,16,17]. Importantly, unaddressed malnutrition in this context can lead to significant consequences, including poor growth, development, immune dysregulation, increased hospital length of stay, and increased healthcare costs [2,18,19,20,21].

How malnutrition is addressed varies by BMT center. Generally, two options are considered, with either nutrition (EN) or parenteral nutrition (PN) being introduced. Historically, PN, which is intravenous nutritional supplementation, has been more frequently utilized to address poor nutritional status when oral intake declines during BMT [22]. However, the use of PN has been associated with increases in infection rates, liver dysfunction, and electrolyte imbalances [4,23]. Prior studies have shown the feasibility of enteral nutrition usage in pediatric BMT [24]. The absence of EN, thus bypassing the gastrointestinal (GI) tract, can lead to a loss of microbial biodiversity in the gut [25,26], leading to increased infection rates. The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends the use of EN as the first-line approach over PN and advises PN use only for cases associated with a medical contraindication to EN, including peritonitis, bowel obstruction, or severe GI symptoms [27,28,29]. When patients are unable to orally meet the EN goals, the placement of a temporary feeding tube such as a nasogastric (NG-tube) or gastrostomy (G-tube) is recommended [28,30,31,32].

Many pediatric patients requiring prolonged hospitalization for BMT experience malnutrition, which has been shown to contribute to morbidity, mortality, and prolonged length of stay, and there is a lack of standard-of-care measures to address this problem. Improvement in the nutritional status of these patients can potentially lead to reduced infection and GVHD rates, along with decreased length of stay and healthcare costs. This integrative review aims to evaluate the optimal nutritional support approach for children, adolescents, and young adults (AYA) during BMT admissions.

Methodology :

case description :

A 17 years old male, previously treated for ETP – T- ALL in 2019. He was on follow up and in May 2024, he had complaints of lethargy & excess fatigue for 2 weeks with history of weight loss (10 kg) in 1 month. Primary investigations done which revealed Hb: 5.4g/dL, TC: 14h40/cu. mm, Platelet count: 1,53,000/cu. mm. BMA and BM biopsy done on 28.05.2024 showed 81% blasts and biopsy showed relapsed ALL. BM biopsy for geneXpert- MTB not detected . Flow cytometry report shows dim positive for CD34, CD 38 and CD 117 with diagnosis of Relapsed Early T- cell precursor Acute Lymphoblastic leukemia (ETP- ALL). He was started on induction chemotherapy for 4 weeks. End of induction BMA for MRD: M3 marrow Induction failure. Consolidation phase was started . Patient achieved Molecular remission CR2 after consolidation phase . Fitness was obtained from Cardiologist, Nephrologist, Dentist and pulmonologist opinion and planned for Haploidentical allogenic stem cell transplant.

MEDICAL MANAGEMENT:

Neutropenic at relapse diagnosis; CNS 1 status; Karyotyping: Normal, Testes: Normal

No bulky disease; No mediastinal nodes was assessed NGS: IGLL1 exon 3 mutation positive, compound heterozygous, AR, Agammaglobulinemia-2, Uncertain significance were al the immunology were tested which reviled IgA Total: 196.90 mg/dL (Normal), IgG total: 839 mg/dL(Normal), IgM Total: 12.20 mg/dL (Low) MRD sampled was done which showed ; Pre-BMT PETCT Whole body: No active disease; CT Chest: Normal

Nutritional management : A17yr old male with relapsed ALL ,height 174 cm , weight 55 kg presented with 10kg weight loss in a month, moderate oral intake and excessive fatigue.His BMI was 17kg/m2 and PGSGA score -7 (mild malnutrition). Patient was anaemic and had low counts. Energy requirement was calculated using Schofield Equation -1595 kcals, protein 80g at 1.5g/BW. During conditioning therapy,due to poor oral intake,high protein ONS suggested along with neutropenic high protein diet. From -D1 to -D8 an average of 55% calorie and 40% protein met. A further 3% weight loss and muscle loss noted. On D0 of stem cell transfusion patient was NPO.On+D1to+D5 due to poor oral intake RTF@100ml 3rd hourly with trial oral was initiated.Feeds were prepared under laminar floor.95% of calorie and 85% of protein met.+D6 patient kept on NPO due to Melina.TPN@50ml/hr initiated on +D7with on demand RTF@100ml 3rd hourly .Patient met 147% of calorie and 126% of protein requirement.+D13 to+D17 patient was on oral antibacterial liquid diet and met 75% of nutrition requirement.+D18 till discharge(+D26) encouraged neutropenic high protein vegetarian diet with ONS. He met 100% of calorie and protein requirement in immediate post-HSCT period. At time of discharge, after 34 days, egg and whole fruit were introduced along with high protein neutropenic oral diet and ONS. Post discharge telephonic follow-up was done for adherence to antimicrobial diet and high protein intake. Assessment at first visit post discharge revealed a weight gain of 1 kg.

NUTRITIONAL ASSESSMENT :

ASSESSMENT ON ADMISSION : PG-SGA score: 7(mild malnourished)

- Weight loss : 3 kgs in 1months 11 kgs in 6months
- Metabolic Demand: Yes
- Physical Exam: Muscle loss yes (shoulder)
- Clinical Symptoms: Fatigue
- Food Intake: Less than usual
- Functional Capacity: Normal with no limitation

ASSESSMENT ON DISCHARGE : PG-SGA score: 14 (severely malnourished)

- Weight Loss: 4kgs (7.5%)
- Metabolic Demand: Yes
- Physical Exam: Muscle loss yes (rib, shoulder, clavical)
- Clinical Symptoms: nausea, diarrhea, vomiting)
- Food Intake: Less than usual
- Functional Capacity: Normal

MACRO NUTRIENT REQUIREMENT:

- Calorie – 1595 kcal
- Protein – 80 g@1.5 gm
- Carbs – 239 g
- Fat – 44 g
- Fluid requirement: 2120 ML / DAY

MEDICAL NUTRITION THERAPY FOLLOW UP PROGRESS

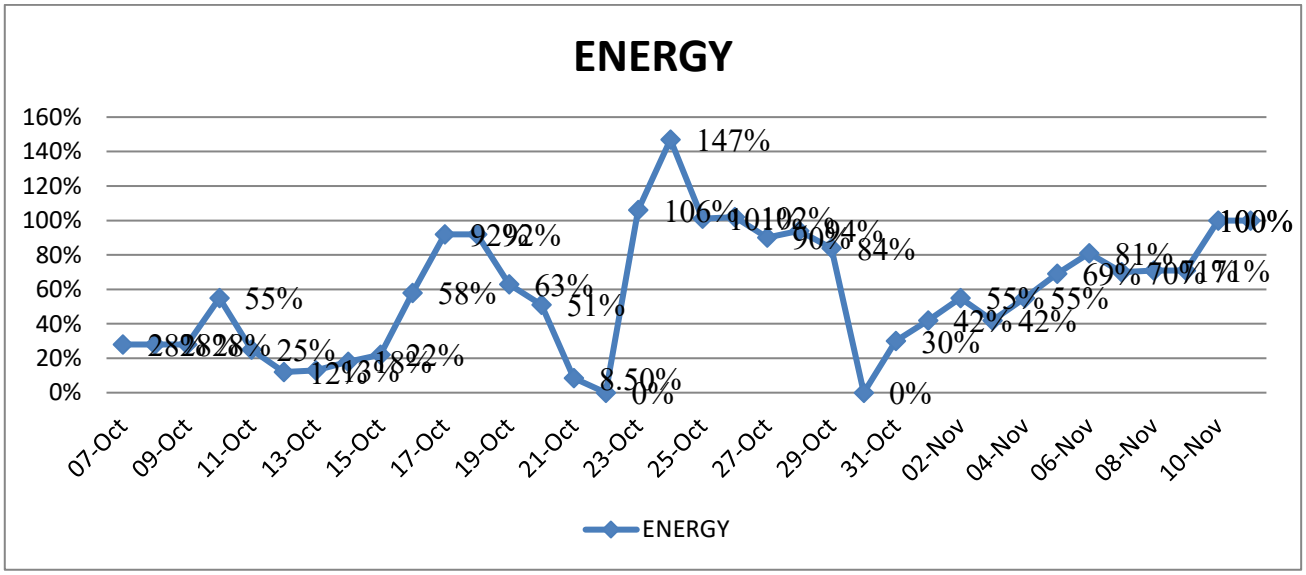
DATE	DIET PROGRESSION	VOLUME	CALORIE	PROTEIN	Calorie meet %	Protein meet %
18/10/24 #2	RTF 100ML 3RD HRLY	1330ML	1483	68	92%	85%
19/10/24 #3	RTF 100ML 3RD HRLY + ORAL STARTED	850ML	1017	40	63%	50%
20/10/24 #4	RTF 100ML 3RD HRLY	600	821	32	51%	40%
21/10/24 #5	RTF 100ML 3RD HRLY	100	136	5	8.5%	6%
22/10/24 #6	NBM				0%	0%
23/10/24 #7	STARTED ON RTF @100ML/H HRLY + TPN	1900	882+812(1694)	38+33(71)	106%	89%
24/10/24 #8	RT@150ML 3RDHRLY+TPN	1600+900(2500)	1114+1231(2345)	52+69(101)	147%	126%
25/10/24 #9	RT@150ML 3RDHRLY+TPN	1050+250(1300)	1437+185(1622)	57+9(66)	101%	82%
26/10/24 #10	RT150 ML 3RD HRLY + ORAL DIET	1050	1437+200(1637)	57	102%	71%
27/10/24 #11	RTF 150ML 3RD HRLY	1050	1437	57	90%	71%

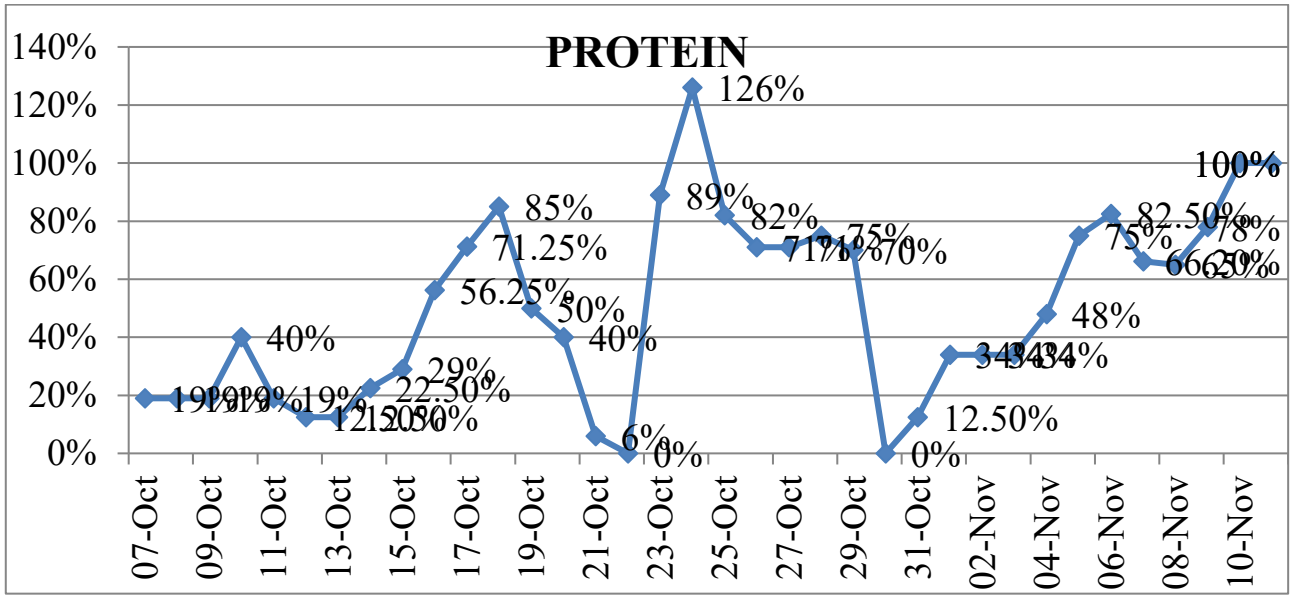
DIET	DIET PROGRESSION	WATER	CALORIE	PROTEIN	Calorie meet %	Protein meet %
28/10/24 #12	RTF 150ML 3RD HRLY	1050	1509	60	94%	75%
29/10/24 #13	RTF150ML MIDHRLY + TPN	450+630(1080)	646+702(1348)	25+31(56)	84%	70%
30/10/24 #14	NBM				0%	0%
31/10/24 #15	NUTROPENIC LIQUID DIET		320	10	20%	13%
01/11/24 #16	NUTROPENIC LIQUID DIET		675	27	42%	34%
02/11/24 #17	NUTROPENIC LIQUID DIET		675	27	42%	34%
03/11/24 #18	NETUROPENIC NORMAL DIET		675	27	42%	34%
04/11/24 #19	NETUROPENIC NORMAL DIET		885	39	55%	49%
05/11/24 #20	NETUROPENIC NORMAL DIET		1116	60	69%	75%
06/11/24 #22	NETUROPENIC NORMAL DIET		1305	66	81%	83%

DATE	DIET PROGESSION	CALORIE	PROTEIN	CALORIE MEET %	PROTEIN MEET %
07/10/24	NETUROPENIC NORMAL DIET	450	15	28%	19%
08/10/24	NETUROPENIC NORMAL DIET	450	15	28%	19%
09/10/24	NETUROPENIC NORMAL DIET	450	15	28%	19%
10/10/24	NETUROPENIC NORMAL DIET	800	30	55%	40%
11/10/24	NETUROPENIC NORMAL DIET	400	15	25%	19%
12/10/24	NETUROPENIC NORMAL DIET	200	10	12%	12%
13/10/24	NETUROPENIC NORMAL DIET	200	10	13%	12.5%
14/10/24	NETUROPENIC NORMAL DIET	302	18	18%	22.5%
15/10/14	NETUROPENIC NORMAL DIET	360	23	22%	28%
16/10/24	NETUROPENIC NORMAL DIET + RTF @100 ML 3RD HRLY	933	45	58%	56%
17/10/24 BMT D#1	RTF 100ML 3RD HRLY	1457	57	92%	71%

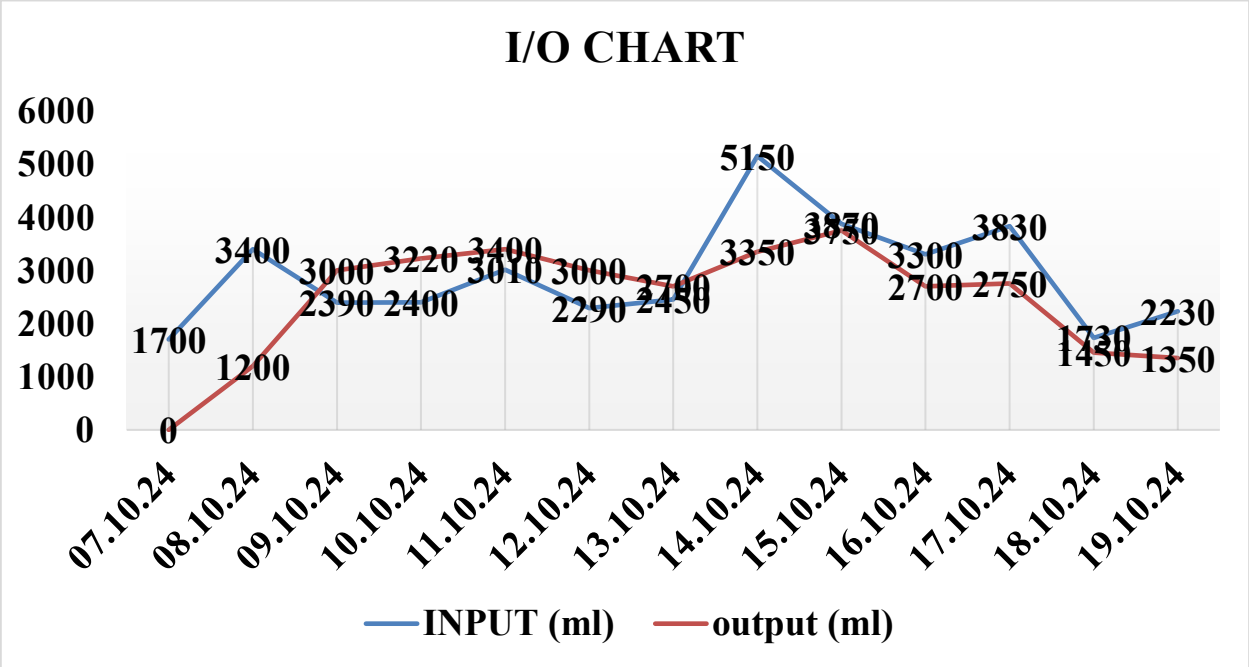
DATE	DIET PROGESSION	CALORIE	PROTEIN	Calorie meet%	Protein meet %
07/11/24 #22	NETUROPENIC NORMAL DIET	1119	53	70%	66%
08/11/24 #23	NETUROPENIC NORMAL DIET	1136	52	71%	65%
09/11/24 #24	NETUROPENIC NORMAL DIET	1130	58	71%	78%
10/11/24 #25	NETUROPENIC NORMAL DIET	1604	80	100%	100%
11/11/24 #26	NETUROPENIC NORMAL DIET	1604	80	100%	100%

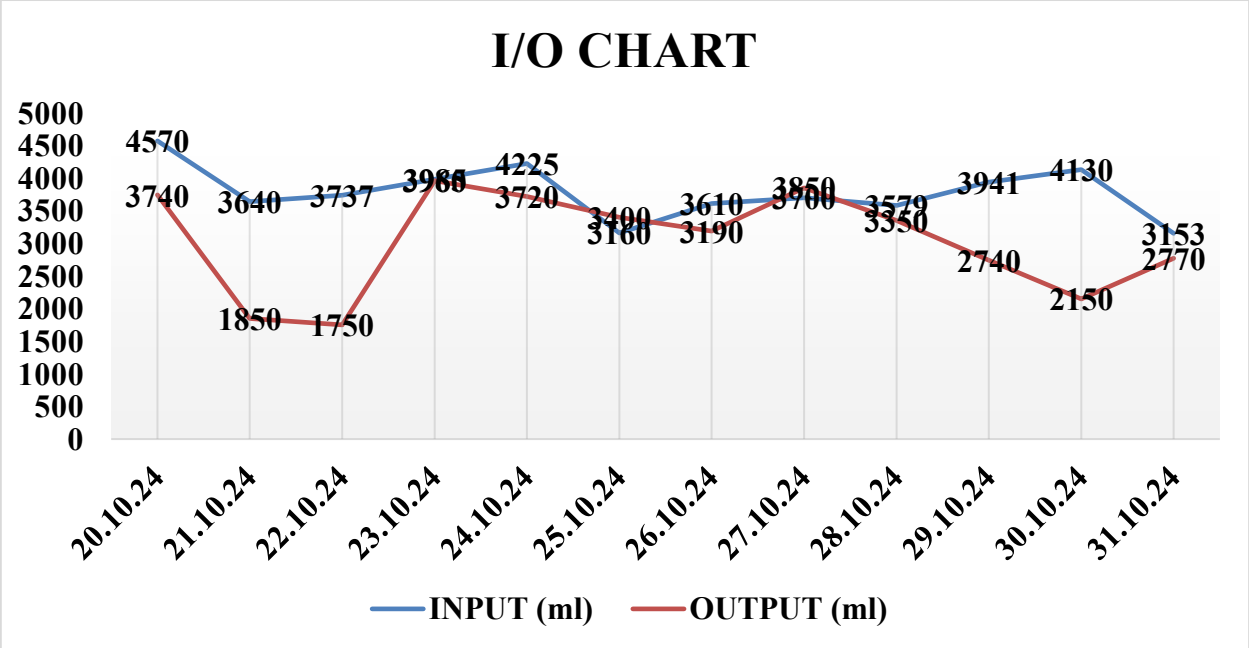
MACRO NUTRITENT GRAPHICAL VIEW

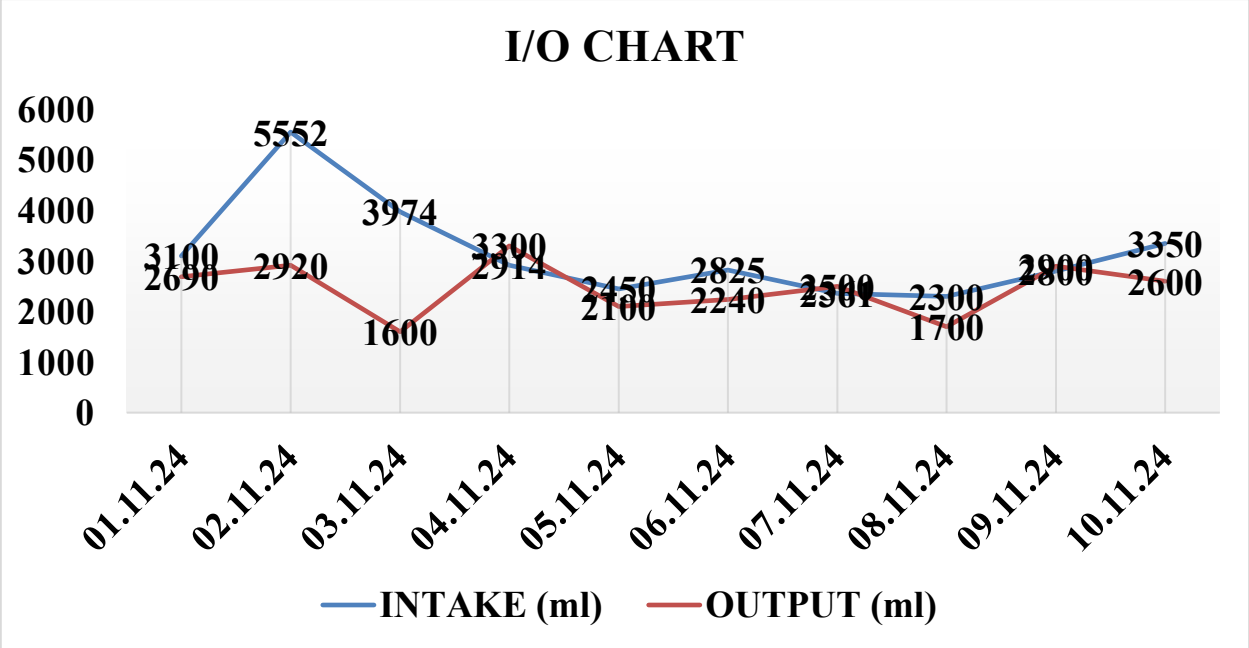




FLUID MAINTANCES :






I/O CHART
6000
5000
4000
3000
2000
1000
0
5552
3974
3300
2825
2500
2300
2900
3350
3100
2690
2920
1600
2914
2450
2100
2240
2301
1700
2800
2600
01.11.24
02.11.24
03.11.24
04.11.24
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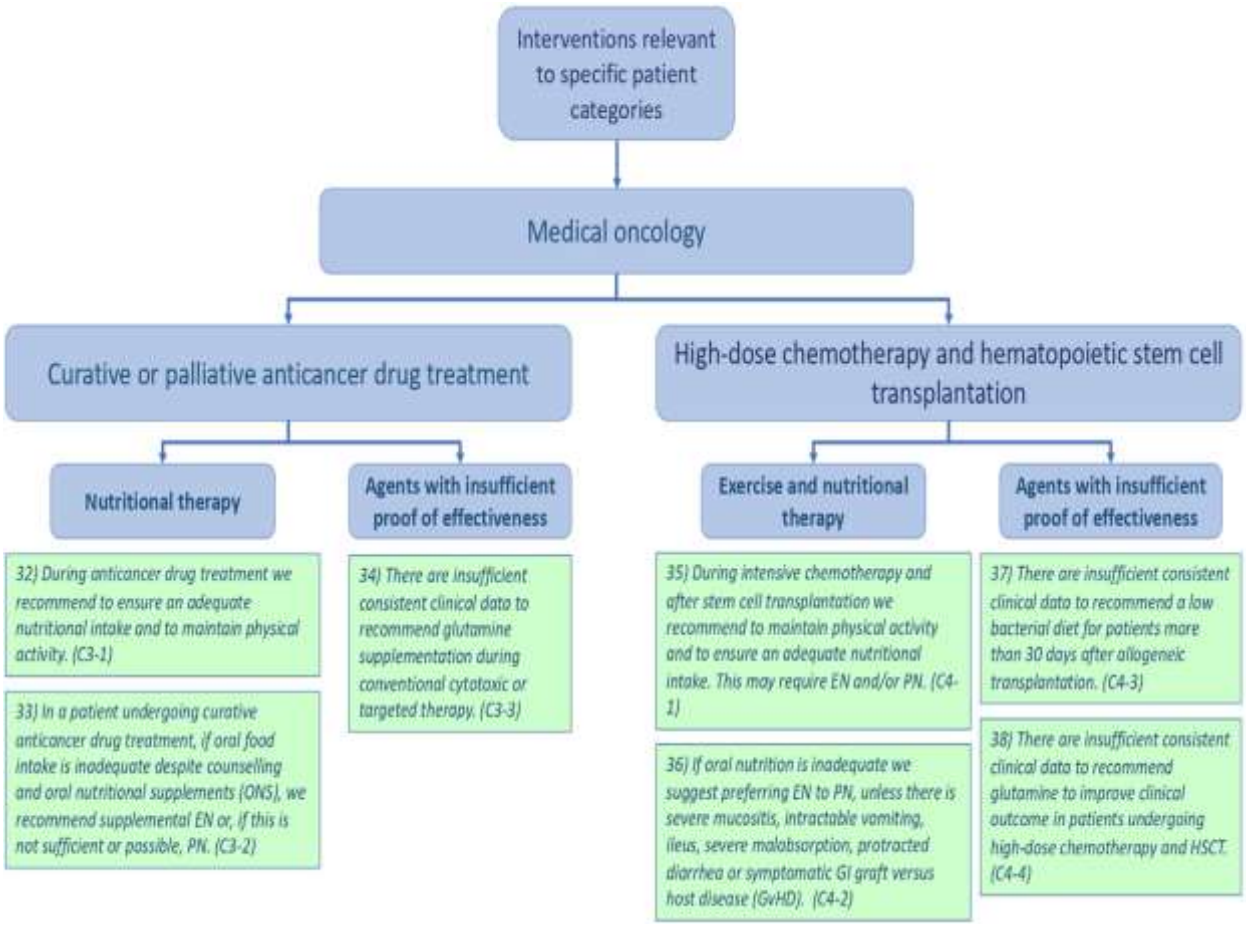
06.11.24
07.11.24
08.11.24
09.11.24
10.11.24
INTAKE (ml)
OUTPUT (ml)


Interventions relevant to specific patient categories
Medical oncology
Curative or palliative anticancer drug treatment
High-dose chemotherapy and hematopoietic stem cell transplantation
Nutritional therapy
Agents with insufficient proof of effectiveness
Exercise and nutritional therapy
Agents with insufficient proof of effectiveness
32) During anticancer drug treatment we recommend to ensure an adequate nutritional intake and to maintain physical activity. (C3-1)
33) In a patient undergoing curative anticancer drug treatment, if oral food intake is inadequate despite counselling and oral nutritional supplements (ONS), we recommend supplemental EN or, if this is not sufficient or possible, PN. (C3-2)
34) There are insufficient consistent clinical data to recommend glutamine supplementation during conventional cytotoxic or targeted therapy. (C3-3)
35) During intensive chemotherapy and after stem cell transplantation we recommend to maintain physical activity and to ensure an adequate nutritional intake. This may require EN and/or PN. (C4-1)
36) If oral nutrition is inadequate we suggest preferring EN to PN, unless there is severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhea or symptomatic GI graft versus host disease (GvHD). (C4-2)
37) There are insufficient consistent clinical data to recommend a low bacterial diet for patients more than 30 days after allogeneic transplantation. (C4-3)
38) There are insufficient consistent clinical data to recommend glutamine to improve clinical outcome in patients undergoing high-dose chemotherapy and HSCT. (C4-4)

Discussion

This integrative review highlights what is currently known about nutritional support for children undergoing BMT. Practice approaches to the initiation of EN versus PN varied greatly among studies, with no consensus reached, and the impact on patient outcomes is unclear. From the literature, it is evident that EN use, including prophylactic placement of G-tubes, is feasible and not inferior to the utilization of PN or NG-tubes. However, there was no consensus regarding the appropriate timeline of placing these tubes. Although inconclusive from this review, there are some data to suggest that supplemental EN use may contribute to reduced infection rates, as well as a decreased incidence and severity of GVHD [36,40,44].

ASPEN has advocated for the use of supplemental EN as the first line for nutritional support for all children with malnutrition [28], and this is echoed by the European Society for Parenteral and Enteral Nutrition (ESPEN) [45], as well as the European Society for Blood and Marrow Transplantation (EBMT) [46,47]. Unfortunately, the implementation of this approach is not being executed uniformly in the pediatric BMT population, despite some evidence of its benefits, including decreased length of stay and lower costs [22,48]. In a multicenter, randomized, controlled trial comparing EN versus PN use in critically-ill adults, minimal differences in outcomes were seen between groups, except for higher costs with PN [49]. By contrast, EN use in combination with PN contributed to improved patient outcomes in other studies, highlighting the potential benefits of continuing EN at any volume possible to maintain a diverse gut microbiota [22,50,51]. NG tube placement is usually performed by day + 1 [43,52]; however, in centers using post-transplant cyclophosphamide, this may be pushed to day + 5 [53]. Some studies turned to prophylactic surgical G-tube placement to help increase the utilization of EN [38,41,43], while others only administered PN during the nighttime, resulting in increased EN intake during the daytime [54]. Barriers to the routine use of EN are multi-factorial and include patient-related, institutional, and pragmatic issues, such as the presence of mucositis or GI distress, provider and/or family perceptions and biases, lack of institutional or national clinical guidelines, and a paucity of randomized-controlled trials, contributing to a lack of high-quality evidence to support practice changes [22].

Malnutrition in children with cancer and those undergoing BMT has been found to be correlated with decreased survival [44,54]. Loeffen et al. evaluated malnourished pediatric oncology patients receiving initial chemotherapy and found significantly decreased survival rates among children who were malnourished at diagnosis and 3 months after diagnosed, compared to adequately nourished children [55]. GVHD is a significant cause of non-relapse-related mortality in BMT patients; therefore, examining ways to decrease the incidence of GVHD is of utmost importance. Kerby et al. [51] found that a diagnosis of malnutrition in the previous 30-day period was associated with a three-to-fourfold increased risk of developing severe aGVHD, and this was hypothesized to be related to the pro-inflammatory nature of malnutrition [54]. The gut microbiome is also understood to play a role in patient outcomes; lack of a stimulated and diverse microbiome, such as that observed with the exclusive use of PN, could contribute to increased rates of GVHD and infections [22,44,50]. Vitamin D is also thought to play a role in immunoregulation and gut inflammation, with several adult and pediatric studies showing increased rates of acute and chronic GVHD in patients with documented vitamin D deficiency [56,57].

Similar findings can be seen in reviews of adult literature regarding malnutrition and nutritional support during BMT [58,59]. In a trial of adults who underwent autologous BMT, a nutrition optimization protocol that featured early initiation of EN and targeted PN was associated with a decreased rate of

infections, as well as shorter LOS [58]. There was no difference in time to platelet engraftment, and overall survival was not measured past day +30 [58]. Hirose et al. [59] found that severe malnutrition in adult patients prior to the start of allogeneic BMT was associated with a higher risk of acute GVHD, increased non-relapse mortality, and decreased OS, illustrating that there is a role for optimization of nutritional status, even before the patient is admitted for BMT. The EBMT has published guidelines for improving nutrition in BMT patients. However, these are largely extrapolated by studies in adults, and the authors note that specific pediatric guidelines are lacking [46]. Key points from these recommendations include malnutrition risk screening prior to and frequently during BMT, EN usage over PN, the elimination of the usage of low-microbial or neutropenic diets, and prophylactic NG-tube placement on day + 1 [46]

Equally important, this review reveals several rather glaring knowledge gaps regarding the topic of nutritional optimization in children during BMT, thus exposing a significant unmet need in the field. The majority of studies reviewed attempted as much EN support as possible, but ultimately many also required PN use, so it remains unclear whether EN or PN is the superior approach for nutritional optimization, and likely some combination of both will always be required for BMT patients. It would be beneficial to further clarify the impact of nutritional optimization on outcomes post-BMT, determine whether these impacts are significant, and if these effects occur in allogeneic BMTs, autologous, or both. Particular outcomes that might be improved or studied, such as GVHD, infection, length of stay, and overall survival, should be analyzed with respect to the malnutrition status and optimization. A meta-analysis comparing EN versus PN support after BMT, performed by Zama et al. in 2021, showed that the primary use of EN reduced high grade GI aGVHD; however, this analysis primarily contained adult data and included studies that were over 20 years old [60]. Malnutrition screening should be assessed early and often for pediatric BMT patients. However, clear guidelines for when supplemental nutrition should be started, whether prophylactic NG- or G-tubes are warranted, and how to determine the duration of need for these tubes, are lacking. Creating standardized pediatric BMT nutritional support guidelines is not possible until further studies are performed.

This review does contain limitations. Firstly, the lack of research from North American centers limits global generalizability. A limited number of articles met the inclusion criteria, and those included contained small sample sizes, limiting applicability. There were no randomized controlled trials available to be included in this review, and most studies utilized cohort sampling, allowing for sampling errors. The majority of studies were retrospective, allowing for recall bias, as well as errors due to loss of documentation or misinterpretation over time. Most of the articles were of good quality (B); however, none of the articles included were of high quality (Quality A). In some cases, outcomes varied between studies utilizing similar measurements, which makes the interpretation of results particularly challenging. EN tolerance was associated with less intense conditioning regimens in some studies, making it difficult to evaluate if the improved outcomes were due to the less severe regimen-related toxicity or the nutrition support itself. In the studies that evaluated GVHD, there was no discussion on the use of GVHD prophylaxis, and varying donor types and stem cell sources were utilized, further confounding the results. Using both autologous and allogeneic BMT platforms, along with variations in the intensity of preparative regimens and stem cell sources, further hinders the ability to apply these findings across the general pediatric BMT population.

5. Conclusions

Unaddressed malnutrition can significantly impact morbidity and mortality for children who are undergoing BMT. Survival rates for childhood cancer and BMT continue to increase, but there is much room for improvement. Complications during BMT, including infections, GVHD, the need for frequent platelet transfusion requirements, and increased healthcare-associated costs due to prolonged hospitalizations, can potentially be decreased via the optimization of EN. Many children are unable to meet caloric needs orally during their BMT admission, and there is no current consensus on how to best address this. Each pediatric BMT center needs to develop practice guidelines to better serve these patients. The paucity of published literature on this topic limits the conclusions that can be drawn from this review and illuminates a critical unmet need in the field. Future research should focus on ways to improve the early initiation of nutritional support, including determining the best timeline for the initiation of supplemental nutrition, as well as increasing enteral feeding tube placement and utilization to optimize EN administration in children who are admitted for BMT. Reaching a consensus on how to best measure the nutritional status of a pediatric BMT patient, as well as what outcomes to measure following nutritional interventions, will be important for providing more conclusive recommendations. Prospective studies will be useful in determining the most effective interventions to support these nutritional goals.

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