Nutrition in the Pediatric Oncology Patient

Cape Town Metropole Pediatric Interest Group

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Red Cross Children's Hospital

Paediatric Working Group Guidelines: Developers Summary

Scope and Purpose

The Guidelines for Pediatric oncology and haematology have been developed by the Western Cape Paediatric Nutrition Working Group in response to the need for evidence-based guidelines with respect to the nutrition management of children with oncological diseases.

The aim of this Guideline is to provide an evidence based nutrition management resource tool, which may be used by health professionals involved in the prescription and supply of nutrition support to infants or children with oncological diseases.

This Guideline uses an "A, B, C, D" approach e.g. Anthropometry, Biochemistry, Clinical and Dietary, to provide a step by step reference as to how to approach nutrition support.

These guidelines outline nutrition support in children with malignancies from the ages of 0 – 18 years of age. They are not meant to be prescriptive and there may be individual case variations.

Stakeholder Involvement

Members of the Paediatric Working Group are outlined in table 1:

Table 1: Paediatric Working Group Members and Reviewers

	Principal Author	Affiliations
Full Time Members		
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Rigour of Development

A Pubmed search was completed using key words such as "_pediatric oncology and nutrition". Table 1 was used to define the type of articles desired. Thirty articles were identified using the key words. The search was narrowed to include papers graded as being 1+++ to 2+ levels of evidence. [If this was not available change to which ones were included and rationale – e.g. consensus papers etc.]

Grading of levels of evidence (LOE) according to the Scottish Intercollegiate Guideline Network (SIGN) 2000

Grading	Level of evidence
1+++	High quality meta analyses, systematic reviews of RCT's or RCT's with very low risk of bias
1+	Well conducted meta analyses, systematic review of RCT's or RCT's with low risk of bias
1-	Meta analyses, systematic reviews of RCT's or RCT's with a high risk of bias
2++	High quality systematic reviews of case controlled or cohort studies
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies e.g. case reports, case series. Evidence from non analytical studies e.g. case reports, case series
4	Evidence from expert opinion

The principle author was responsible for compiling the guideline, which was circulated amongst members of the working group in addition some of the ad hoc members.

All guidelines went through a process of first to third drafts. The recommendations within the guidelines were drafted following a review of the literature and discussions within the group.

All benefits and potential harm of the nutrition recommendations within the guidelines have been discussed and reviewed by the panel at length. The recommendations provided within the text and summary tables are referenced and evidence based.

This guideline has been reviewed by the department of paediatric oncology and haematology at Red Cross Children's Hospital who are considered to be experts in their field. Comments received have been incorporated into the clinical guidelines.

This guideline will be reviewed in 2008 and updated accordingly.

Clarity and Presentation

The format of this clinical guideline aims to direct the health professional through a logical Nutrition Care Plan approach using A, B, C, D e.g. Anthropometry, Biochemistry, Clinical and Dietary using a series of summary tables, which can be used as a quick reference abridged version for the key recommendations. In addition to these tables the full text may be consulted as required.

A variety of management options have been present targeting clients within the Public and Private Health Care sector. The guideline provides a stratified management approach and identifies current nutrition support systems through which they could be implemented.

Applicability

The working group did not perceive any potential barriers as all nutrition support strategies are currently available within Public and Private Health Care centres and are available on national tenders. All cost implications have been considered and the most cost effective nutrition management strategies have been recommended.

Within the Nutrition Care Plan Summary Tables appropriate review processes have been identified. In addition all tools are presented with an audit process.

Editorial Independence

The principal author, working group and or reviewers did not receive any funding to complete these guidelines and no conflicts of interest are recorded by the team.

Contents Page

Glossary

WBC	White Blood Cell
AMC	Arm muscle circumference
MUAC	Mid upper arm circumference
AMA	Arm muscle area
BMT	Bone marrow transplant
RTHC	Road to health chart
PN	Parenteral nutrition
RDA	Recommended daily allowance
GIT	Gastrointestinal tract
BMR	Basal metabolic rate
REE	Resting energy expenditure
mg	Milligram
dL	Deciliter
μL	Microliter
ml	Milliliter
g	Gram
kg	Kilogram
m^2	Square meter
min	Minutes
IV	Intravenous
MTX	Methotrexate
Kcal	Kilocalories
EPA	Eicosapentanoic acid
PEM	Protein energy malnutrition
IBW	Ideal body weight
% EWH	Percentage estimated weight for height
% EWA	Percentage estimated weight for age
% EHA	Percentage estimated height for age
IgA	Immunoglobulin A
INR	International numeration ratio
NGT	Nasogastric tube
ALL	Acute Lymphoblastic leukemia
CLL	Chronic Lymphocytic Leukemia
AML	Acute Myeloid Leukemia
CML	Chronic Myeloid leukemia
GVHD	Graft versus host disease
WHO	World Health Organisation

Summary of recommendations for the nutrition management of pediatric oncology and hematology

Overview
• Malnutrition can adversely affect tolerance to therapy, increase the risk of co-morbidities and influence the overall survival • Goals of nutritional support: o Prevent or reverse nutritional deficits o Promote normal growth and development o Minimise morbidity and mortality o Maximise quality of life
Cancers associated with high nutritional risk
• Advanced disease during initial intense treatment • Locally advanced or metastatic Wilm's tumor and neuroblastoma • Soft tissue sarcomas • Infants diagnosed < 12months • Some Non-Hodgkin's lymphoma and advanced Hodgkin's disease • Multiple relapsing leukemia • Acute myeloid leukemia • Brain tumours, especially those with decreased level of consciousness
Risk factors associated with the development of PEM
• Irradiation to the gastrointestinal tract • Intense frequent course of chemotherapy (< 3 weeks) • Major abdominal surgery • Advanced disease • Lack of family or health care support system • Alterations in taste, anorexia, mucositis, emesis, diarrhoea
Entry Criteria for nutrition support during hospitalisation
▪ Total weight loss of > 5% relative to pre-illness BW. ▪ Weight for height < 90%. ▪ Decrease in current percentile for weight (or height) of two percentiles ▪ Adipose energy reserves as determined by triceps skinfold thickness < 5th percentile for age and gender. ▪ Voluntary food intake is < 70% of estimated requirements for 5 days for well-nourished patients. ▪ Anticipated gut dysfunction due to treatment for more than 5 days for well-nourished patients. ▪ High nutritional risk patients based on tumour type and oncology treatment regimes. ▪ Bone marrow transplant as a treatment for any tumour.
Anthropometry

Measure *Daily:* ▪ Weight *Weekly* ▪ Height ▪ MUAC ▪ Triceps, biceps, sub-scapular skinfold measurements **Calculate** *On each assessment:* • % EWA • % EWH • % EHA • *(see anthro guideline)*	***Comments:*** ▪ Weight is inaccurate when child has oedema, large tumour masses and organs extensively infiltrated with tumour, effusions or organ congestion, excess fluid administration. ▪ Redo weight post surgical resection of solid tumours ▪ Skinfold measurements are inaccurate if the patient has oedema
Classifications of malnutrition: Requiring Nutrition intervention: • Nutrition support should be commenced in all patients classified as having moderate malnutrition unless they are at risk of tumorlysis syndrome during induction chemotherapy. • In those with mild malnutrition their status should be reviewed the following month, if there is no improvement with respect to weight or height/ length, nutrition support should be commenced immediately.	**Classification of malnutrition using height for age, weight for height or nutrition risk score.** **Height for age: Chronic malnutrition; stunting** • Mild 90 – 95% • Moderate 85 –90% • Severe <85% **Weight for Height: Acute Malnutrition; wasting** • Normal 90 – 110% • Mild 80 – 90% • Moderate 70 – 80% • Severe < 70% **Weight for age: acute malnutrition; wasting** • Obese >120% • Normal > 90% • Mild malnutrition 76 – 90% • Moderate malnutrition 61 – 75% • Severe malnutrition < 60% **Nutrition Risk Screening Tool score:** • 1 – 3 no current nutrition risk • 4 – 5 some nutrition risk • > 6 malnourished

<table>
<tr><th colspan="2">Biochemistry</th></tr>
<tr><td>Monitor the following
• Urea, creatinine, sodium, potassium during chemotherapy
• Glucose if receiving corticosteroids
• FBC: Haemoglobin, platelets, WCC, Neutrophils
• Liver function tests when receiving TPN (refer to PN protocol)</td><td>Comments
• Limit the use of sugar in isolation if patient presents with glycosuria

• Monitor potassium, phosphate, urea and creatinine during tumorlysis syndrome.</td></tr>
<tr><th colspan="2">Clinical</th></tr>
<tr><td>• Determine from Medical History :
➢ Type and stage of tumour,
➢ Intensity of planned treatment,
➢ Presence or absence of remission</td><td>• Determine from Diet History:
➢ Appetite and recall of actual food intake
➢ Acquired food aversions and food intolerances
➢ Use of nutritional supplements
➢ Treatment and related complications
➢ Recent weight changes
➢ Treatment schedules and other medication affecting GIT
➢ Developmental status
➢ Family and social history</td></tr>
<tr><th colspan="2">Dietary Requirements</th></tr>
<tr><td>• Energy
• < 1 year : 120-150kcals/kg
• > 1 year : Schofield x 1.5-1.8 combined activity and stress factor</td><td>Comments
• Decrease energy requirements post surgical resection and during maintenance chemotherapy</td></tr>
<tr><td>• Protein
• < 1 year : 2-4g/kg
• > 1 year : RDA for age</td><td>• Restrict protein to RDA during tumour lysis syndrome

• Supplement glutamine at 0.57g/kg, before and during selected intensive chemotherapy regimes ,to decrease duration of mucositis
• Dissolve glutamine powder in at least 100mls cold clear liquid and administer as a swish and swallow solution</td></tr>
<tr><td>• Fat
• < 2 year : 30-50% NPE
• > 2 year : 30% of NPE</td><td>• Restrict fat to 2g/kg if patient is neutropenic or if INR is prolonged</td></tr>
<tr><td>• Fluid
• Infants : 120-150mls/kg
• 1-6 years : 80-95mls/kg
• 7-18 years : 50-75mls/kg</td><td>• Fluid restriction may be indicated during cardiac failure or tumour lysis syndrome.</td></tr>
<tr><th colspan="2">Nutritional Support Route</th></tr>
<tr><th colspan="2">Oral feeding</th></tr>
<tr><td colspan="2">• Indicated in:
➢ patients with low nutritional risk,
➢ less advanced disease or
➢ disease in remission on maintenance chemotherapy.</td></tr>
</table>

Enteral feeding	
Entry criteria for the administration of enteral feeding ▪ Present state of malnutrition at diagnosis that failed to or is not expected to improve within 1 week. ▪ No improvement in nutritional status with food based supplements or supplementary drinks alone. ▪ Weight loss after diagnosis > 5% from the weight at diagnosis. ▪ Voluntary food intake is < 70% of estimated requirements for 5 days with no improvement after prescription of dietary supplementary drinks ▪ Anticipated gut dysfunction due to treatment for more than 5 days for well-nourished patients.	**Comments** • Use soft fine bore polyurethane NGT (French 8 or 10.) • Platelet cover may be needed before NGT insertion in patients that have low platelet counts. • Consider overnight feeding where indicated. • Polymeric energy enriched formula is the first feed of choice. • Progress to semi-elemental formula if gut function is compromised.
TPN	
Entry criteria for TPN • Unable to meet dietary requirements via enteral route • Severe GI intolerance due to : o Mucositis o GVHD of the GIT o Typhilitis	• Refer to PN protocol for complete requirements
Follow up / Discharge	
• Provide referral letter for continuing nutrition support at referral hospital. • Provide NSP referral to obtain dietary supplementation if indicated. • Monitor MUAC, weight and height at monthly outpatient visits. Calculate % EWA, EHA,EWH and classify according to Waterlow and WHO criteria. • High risk for the development of obesity in patients on chemotherapy regimens that include steroids, especially in AML and ALL. • Healthy eating guidelines should be provided with the emphasis on weight maintenance to prevent growth stunting in these cases.	

1. Introduction

The types of cancer seen in children are divided in haematologic malignancies and solid tumors. Leukemias account for 30%, lymphomas 10-15% and solid tumors 55-60% of malignancies.[19] The most common solid tumors are brain tumors, nephroblastomas (Wilm's tumor), neuroblastoma, rhabdomyosarcoma, osteosarcoma and Ewings 'sarcoma.[11]

Childhood cancers are commonly amenable to a combination of treatment modalities. Most tumors are responsive to chemotherapy, which is the principal treatment for leukemia, but solid tumors also require local control in the form of surgery and /or radiotherapy. [11]

1.1 Malnutrition

The occurrence of malnutrition in children with childhood tumors is multifactorial. Malnutrition develops during therapy for cancer in 40-80% of children.[25]The prevalence of malnutrition is related to the type of tumor and the extent of the disease. It is more commonly seen in patients with advanced neuroblastoma, Wilms tumor, Ewing sarcoma and advanced lymphomas. [24] Malnutrition is usually more severe with aggressive tumors in the later stages of malignancy. The more intensive treatment regimens, necessitated by advanced malignancy and by relapse after initial therapy, frequently exacerbate malnutrition.[29] Between 25-40% of children undergoing abdominal irradiation with chemotherapy can be expected to develop malnutrition. [19]

A malignant tumor leads to changes in a child's metabolism, which includes an increased Cori-cycle, failure to down regulate energy expenditure in the presence of a reduced energy intake and an increased lipolysis. All of these factors lead to an ineffective use of nutrients and contributes to the development of malnutrition. [2]

Malnutrition is usually progressive through the course of treatment, which can be attributed to cachexia, chemotherapy, radiotherapy, hospitalization and inadequate nutrition intake. This often leads to further weight loss and stunts the growth of the child.[12]

Malnutrition seen in this population group has been described as being mainly iatrogenic in nature resulting from hypermetabolism generated by the disease itself along with gastrointestinal problems associated with tumor bulk resulting in early satiety, other mechanical and absorptive problems and surgery. [12]

Additional factors that can contribute to nutritional deterioration include: [3]

a) Anorexia ; which may be directly related to the nausea and vomiting caused by chemotherapy and radiotherapy or be psychological in nature
b) Infection ; as a clear relationship exists between malnutrition and infection together with chemotherapy and radiotherapy acting as immune depressants
c) Stomatitis/ Mucositis ; which leads to a decrease in adequate oral intake contributing to malnutrition
d) Diarrhoea ; which is a common complication of childhood malignancy and therapy
e) Nausea and vomiting
f) Malabsorption
g) Blood Loss leading to iron deficiency
h) Renal damage and nutrient loss
i) Mechanical gut problems due to direct or functional intestinal obstruction

j) Dysgeusia and xerostomia
k) Psychological factors e.g. learned food aversion

1.2 Risk factors for the development of malnutrition in childhood cancers

- Advanced disease at time of referral or during hospitalization
- Lack of tumor response
- Abdominal and pelvic irradiation
- Intensive chemotherapy resulting in nausea and vomiting, gastro- intestinal or hepatic toxicity in the absence of appetite stimulants
- Surgery to the abdomen
- Psychological depression,
- Absence of supportive health care team and
- Lack of attention to enteral nutrition

1.3.1 Cancers associated with high nutritional risk based on intensive multimodal therapy[19]

- Advanced disease during early treatment
- Locally advanced and metastatic Wilm's tumours and Neuroblastoma
- Soft tissue sarcomas (Ewings and Rhabdomysarcoma)
- Some non-Hodgkin's lymphoma and advanced Hodgkin's disease
- Multiple relapsing leukemia
- AML
- Poor prognosis ALL
  - High Risk
    - Infants < 12 months
    - Certain chromosomal abnormalities
    - Failure to go into remission by 28 days
  - Relapsed
  - Brain tumors, especially those involving the diencephalan or those resulting in decreased level of consciousness.

1.3.2 Low nutrition risk based on less intensive chemotherapy protocols

- Good prognosis ALL
- Non-metastatic solid tumors
- Advanced diseases in remission during maintenance treatment

2. Anthropometry

2.1 Nutritional Status

Nutritional status affects outcome, with weight loss having an independent effect on prognosis. Those children who have a poor nutritional status have lower survival rates compared to those with a good nutritional status. In one study comparing 18 children with newly diagnosed stage IV neuroblastoma, those who were malnourished were more likely *(p=0.08)* to relapse and or die 1 year into the treatment. The median survival for the group who was malnourished was 5 months versus 12 months for the well-nourished group.

Children with cancer, especially solid tumors, have reduced body protein stores due to whole body protein breakdown. This may occur as a result of the disease itself, treatment or complications of the disease. Catabolism of lean body mass is a common effect of the disease, making the assessment of body composition a vital part of the nutritional assessment. [21]

A study done by Garofolo et al demonstrated that the z-scores, AMC, MUAC were statistically more depleted among children with solid tumors than those with hematological diseases. Hematological malignancies consist of cells that proliferate rapidly which enables earlier diagnosis and greater response to chemotherapy. Patients receiving corticosteroids may also present with nutritional side effects related to therapy of which the most relevant are increases in fat mass and loss of muscle mass. [21]

An impaired nutritional status before bone marrow transplant (BMT) is also seen as a negative prognostic factor for outcome after BMT with the better nourished patient having a shorter time to engraftment. [15]

Negative implications of a poor nutritional status includes [4,11]

- Delayed growth and development
- Impaired immune response
- Decreased tolerance to therapy leading to dose adjustments in chemotherapy
- Increased infection rate
- Decreased sense of wellbeing
- Decreased survival/poorer outcome

2.2 Assessment of nutritional status

Malnutrition at the time of diagnosis may be more common than previously estimated due to nutritional assessment previously being based on weight and height. Many of the solid tumors have large masses masking the child's real weight, distorting weight to height ratios, making these insensitive malnutrition indexes.[2] Weight may also be inaccurate when the child has edema, organs extensively infiltrated with tumor effusions or organ congestion and when the patient has had amputations, as in osteosarcomas.[22] Height is also a poor index of malnutrition as stunting only occurs following chronic malnutrition, which in an acute illness is unlikely to be reflective [2]

The upper limbs e.g. arms are not directly influenced by tumor mass or edema and can be used as an additional method to provide a more accurate and complete characterization of body composition. The results were confirmed by Brennan et al who demonstrated that weight and height overestimated nutritional status while anthropometry of the arm was shown to be independent of tumor size. [21]

Biceps and triceps skinfold measurements provide an estimate of the body's fat reserves whereas arm muscle area can serve as an estimate of muscle protein reserves.[4] Arm circumference and triceps measurements are practical if compared to other available methods used for assessment of body composition, which can not be practical or cost effective when performed at the bedside or in the field. [21]

Mid-upper arm circumference is a simple, low-cost objective method of assessing nutritional status and may be a useful screening tool for children 1- 5 years. MUAC reflects bone, fat and muscle mass and is not influenced by total body water when comparing with weight for height score.[13]

MUAC is a useful measurement in children 1-5years as it increases fairly rapidly with the increases more likely to comprise muscle and less likely to be affected by edema. In order to fully differentiate between lean and fat mass, triceps skinfold measurements are necessary.[11] It is recommended that the RTHC is used to determine pre-tumor weight trends in children <1year.

Table1: MUAC reference ranges for moderate – severe malnutrition

MUAC Reference Ranges for Moderate to Severe Malnutrition 6 months - 14 years old		
Infants 6mo-12mo	• Is MUAC less than 110mm?	Severe Malnutrition
	• Is MUAC less than 115mm?	Moderate Malnutrition
Children 1yr-5yrs	• Is MUAC less than 110mm?	Severe Malnutrition
	• Is MUAC less than 135mm?	Moderate Malnutrition
Children 6yrs-9yrs	• Is MUAC less than 135mm?	Severe Malnutrition
	• Is MUAC less than 155mm?	Moderate Malnutrition
Children 10yrs-14yrs	• Is MUAC less than 160mm?	Severe Malnutrition
	• Is MUAC less than 185mm?	Moderate Malnutrition

Diagnostic criteria should be used together when classifying a patient as being malnourished e.g. estimated weight loss in association with clinical judgment. One variable alone should not be considered sufficient for classifying malnutrition.

It is therefore recommended that MUAC and upper arm skinfold measurement, in combination with weight and height, be completed in all patients with solid tumors on admission and weekly during course of treatment to provide a more accurate reflection of their nutritional status.

3. Biochemistry

Biochemical data commonly used for nutritional assessment may be influenced by the disease or treatment. Hemoglobin and hematocrit values will reflect the disease state rather than the nutritional status in children with leukemia, lymphoma and Hodgkin's disease. Serum albumin does not clearly reflect weight for height percentiles, calorie intake or dietary protein intake in pediatric patients.[22] Pre-albumin has the best validity when evaluating nutritional status.[21]

Visceral protein status indicators, renal and hepatic function, serum lipids, glucose and electrolytes should also be reviewed for detection of nutrition deficiencies.[22]

Table 2: Monitoring schedule for patients with cancer [20]

Parameter	Hospitalised patients on PN	Hospitalised patients on oral or enteral feeds	Outpatients on oral or enteral feeds
Electrolytes, glucose	Daily	Weekly	Monthly
Urea, Creatinine	Weekly	Weekly	Monthly
Calcium, phosphorous, magnesium	Daily to weekly	Weekly	Monthly
Triglyceride	Weekly	Monthly	As indicated
LFT's	Weekly	Weekly	Monthly
Trace elements	Monthly	As indicated	As indicated
Carnitine	Monthly	As indicated	As indicated
Vitamin levels	Monthly	As indicated	As indicated

3.1 Tumorlysis syndrome

Tumor lysis occurs before therapy or 1-5 days after the start of therapy for tumors that have a high cell turnover and that are very sensitive to chemotherapy. It is most commonly seen in Burkitt's lymphoma and T-cell leukemia. It is a direct result of the breakdown of the malignant cells and may be aggravated by malignant infiltration of the kidneys. [19]

Abnormalities seen are Hyperuricemia, hyperphosphatemia and hyperkalemia. Prevention of renal failure, caused by uric acid crystals blocking the renal tubules, entails hydration, alkalinization and allopurinol. For most patients this regimen is sufficient to prevent clinically significant tumorlysis and renal failure. If hyperkalemia and renal failure can not be controlled, dialysis is indicated with the preference to hemodialysis as it removes uric acid better. [19]

During acute renal failure nutrition support should be maximized within the prescribed fluid allowance. Protein intake should be restricted to the RDA.[12]

4. Clinical Assessment

A detailed medical history is essential to the nutritional evaluation of the patient. The most important aspects are:

- Type and stage of tumor
- Intensity of planned anti-tumor therapy
- Presence or absence of remission [20]

Important information when assessing a dietary history in children with cancer[20]

- Appetite or recall of actual food intake
- Presence of a limited or monotonous diet
- Acquired food aversions and specific food intolerances
- Use of nutritional supplements
- Recent changes in weight and energy or activity levels
- Treatment and related complications
- Treatment schedules and sleeping periods that interfere with meal hours
- Other medication that affects appetite or GIT
- Prolonged periods of neutropenia
- Developmental status, feeding status milestones and swallowing function
- Family history, parental heights, sibling growth patterns
- Social history

5. Nutritional Support

Nutrition support for the patient with cancer is an important part of the overall treatment regimen. Nutrition treatment is an adjunctive to anti-neoplastic therapies and is not the primary therapy for tumor treatment.[11]

The predictive identification of patients who are becoming nutritionally depleted will provide the opportunity for earlier nutritional intervention and potentially avoid the need for longer intervals of aggressive nutritional support. Nutritional assessment should start at diagnosis and continue throughout treatment.[22, 20]

The main aims of nutritional support are to reverse malnutrition seen at diagnosis, prevent malnutrition associated with treatment and to promote weight gain and growth rather than weight maintenance.[11] Any nutritional support should ensure an

energy intake resulting in a positive energy balance, enabling the child to grow and develop despite the presence of the malignancy.[2]

Good nutritional status may also improve the efficacy of chemotherapy. Research done by Dewy et al found that the chemotherapy response was lower in patients who had experienced weight loss. The median survival was also shorter in the patients who had experienced weight loss, when compared with the controls. Donaldson also showed that the lower a patients nutritional status at the time of referral, the greater the risk was of disease recurrence. A study of 17 patients with stage 4 neuroblastoma showed that patients with a favorable nutritional course had significantly fewer treatment delays and fewer drug dose reductions throughout their treatment course. [24, 26]

The question is always raised whether the nutrients given to replete the host may stimulate further growth of the tumor mass. Clinical studies of children with malignancy have however failed to demonstrate an increase in tumor growth or decreased survival despite improved host nutritional status [11]

5.1 Entry Criteria for nutrition support [11]

- Total weight loss of > 5% relative to pre-illness body weight
- Weight for height < 90%
- A decrease of two percentiles in current percentile for weight or height
- Adipose energy reserves as determined by triceps skinfold thickness < 5th percentile for age and gender
- Voluntary food intake <70% of estimated requirements for 5 days for well nourished patients
- Anticipated gut dysfunction for >5 days due to treatment, in well-nourished patients
- High nutritional risk based on tumor type and oncology treatment regimens
- Bone marrow transplant as a treatment for any tumor

5.2 Calculating Dietary Requirements

5.2.1 Energy requirements

Study results of children (8-15.8 years) with solid tumors showed that they had a higher basal metabolic rate (BMR) at the time of diagnosis, when compared to reference values. BMR is defined as the minimum amount of energy required to maintain all essential bodily functions. The increase in BMR indicates that the tumor is more than an inert mass requiring removal. It consists of metabolically active tissue initially increasing basal energy requirements, which should be accounted for when determining requirements for nutritional support.[2]

During medical treatment, however the difference between measured and referenced BMR decreases returning to normal values found in healthy children. The decrease in BMR per kg in this study was associated with treatment efficacy. Data from this study suggest that at least four courses, 2 courses in some patients, of chemotherapy is needed to decrease the BMR of all patients with a solid tumor to reference levels. Individual patient response to therapy and the tumor type also need to be considered.[2]

This study suggests that BMR is corrected with a stress factor of 1- 1.2 to adjust for solid tumor-induced increase in BMR and that adjustments only continue until after the second course of chemotherapy.[2] Other sources suggest that BMR should be multiplied by a combined stress and activity factor of 1.6-1.8 for very young or

malnourished children to allow for growth, stress and light activity.[22] Increased metabolic rates have also been seen at diagnosis in children with acute lymphoblastic leukemia in those children with a high tumor burden. This increased metabolic rate decreased within 14 days in response to treatment [15]

The Schofield weight height equation should be used to calculate REE as it is well correlated with indirect calorimetry.[16] This should then be adjusted by using a combined stress and activity factor of 1.5-1.9 on diagnosis and admission which should be decreased during maintenance chemotherapy or post surgical resection of the tumor.

5.2.2 Protein requirements

RDA for age should be used for those patients who are normal weight for height (>90%). [12]

Table 3. RDA for Proteins [12]

	Age(years)	Proteins (g/kg)
Infants	0-0.5	2.2
	0.5-1	1.6
Children	1-3	1.2
	4-6	1.1
	7-10	1.0
Males	11-14	1.0
	15-18	0.9
Females	11-14	1.0
	15-18	0.8

For patients with greater requirements (refer to high- risk patients identified in section 1) adjust protein to 1.5-2.0 times the RDA. [12]

5.2.3 Fat requirements

Fat supplies 40% to 50% of the energy consumed in infancy and about 40% of the energy consumed after infancy by individuals in developed countries. For healthy children over 2 years of age it is recommended that < 30% total calories from fat and < 10% total calories from saturated fatty acids.[12]

Fat is protein-sparing, because its availability reduces the body's need to use protein as an energy source. Fats are sources of and facilitate the absorption of the fat-soluble vitamins A, D, E,K. [12]

5.2.3.1 Role of omega three fatty acids

Preliminary trials have suggested that eicosapentanoic acid might be useful in the treatment and/or prevention of loss of appetite and loss of weight that occurs in the majority of oncology patients whose cancer has become refractory to anti-neoplastic therapy. Studies that have been done with weight losing pancreatic cancer patients have shown weight gain and an improvement in appetite and performance status.[5,6]

The potential therapeutic role that EPA plays in cancer associated wasting has been identified as: [5,6]

- Suppressing mediators of cancer associated wasting including interleukin-6
- Suppressing proteolysis inducing factor
- Inhibition of the ubiquitin-proteasome system which is the pathway believed to be responsible for the bulk of muscle wasting.

There is however conflicting data from other studies and most of the studies showing positive effects were done in patients with pancreatic cancer. There are also no clinical trials available to support its use in the pediatric setting.

5.2.4 Fluid requirements

Normal fluid requirements for age should be followed except if the patient is fluid restricted due to medical reasons (i.e. during renal or cardiac failure)

Table 4. Fluid requirements for age [11]

Age	ml/kg
0-3 months	150
4-6 months	130
7-9months	120
10-12 months	110
1-3 years	95
4-6 years	85
7-10 years	75
11-14 years	55
15-18 years	50

5.2.5 Micronutrient and mineral requirements

Results from a study on 103 children (1-18y) with ALL showed that antioxidant intakes are inadequate when compared to the RDA. Nutrients of particular concern were Vitamin C and E.[28]

Other patient groups at risk for the development of micronutrient deficiencies incude patients receiving TPN without using the GIT for extended periods of time, patients who have sustained radiation-induced or surgical damage to the intestine, patients with chronic infections who are taking antibiotics.[19]

Anti-oxidant supplementation during chemotherapy is not recommended, as there are concerns about the potential adverse reactions with chemotherapy .[28]

The nutritional importance of vitamins, minerals and trace elements are recognized but the optimal daily dose that will preserve lean body mass without enhancing tumor growth is not known. The RDA is also based on populations with nonmalignant disease, thus it is questioned whether these levels should be used as reference.[30]

5.3 Method of feeding

5.3.1 Oral feeding

Oral feeding is the method of choice in patients with a low nutritional risk, not complicated by relapse, sepsis or major abdominal procedures.[11] It is recognized that the greatest limitation of nutritional supplements in the pediatric population is patient acceptance. [22]

Oral feeding interventions, defined as a combination of intense nutrition counselling and nutritional supplementation, have been found to be effective in preventing malnutrition in nourished children who have less advanced disease or disease in remission on maintenance therapy and children with ALL with a good prognosis. It has proved ineffective in preventing malnutrition in children undergoing induction.[3]

Nutritional intervention with counselling to encourage nutrient dense meal consumption may begin during hospitalization, but is most effective when the child is between cycles of therapy and is continuing treatment as an outpatient. During this

time there is less interruptions for tests, allowing parents or caretakers to provide favourite foods more easily. [19]

Table 5. Strategies to improve oral intake during cancer treatment [20]

Loss of Appetite	• Small frequent feedings (6-8 meals and snacks per day) • Encourage nutrient dense beverages between meals • Offer favourite nutritious foods during treatment free periods to prevent learned food aversions
Nausea and vomiting	• Feed 3-4 hours before therapy that typically causes nausea and vomiting • Offer small amounts of cool foods and encourage slow eating • Avoid foods with strong odours • Offer liquids between and not with meals
Mouth sores	• Serve soft or pureed bland food and/or liquids • Add butter, gravy, sauce or salad dressing to moisten foods • Avoid highly seasoned, and hard rough foods
Altered taste perception	• Use stronger seasonings and avoid excessively sweet foods • Offer salty foods • Try new flavours of foods

5.3.2 Enteral feeding

Enteral feeding has shown to be effective in maintaining and improving the nutritional status of children with cancer during the intensive phase of treatment. It is considered a safer, simpler, more physiologic and economic intervention method and has been shown to be more acceptable and better tolerated by children. [4] Data has also shown a positive correlation between increases in weight and mid-arm circumference and the duration of enteral feeding. [20]

Previous studies have highlighted the following reasons why energy requirements are often not met in children with malignancies receiving naso-gastric feeds: [4]

- Low infusion rates during initial days of feeding
- Feeding interruptions due to medical procedures
- Gastro-intestinal intolerance
- Suboptimal prescribed energy goals

Concerns have been raised about the safety of placing nasogastric tubes when patients are vomiting, neutropenic or thrombocytopenic. Data shows no tube related infections (sinusitis) or bleeding complications in 17 children (2-19years) who had nasogastric tubes (6 or 8 French non-weighted tips) inserted while undergoing intensive chemotherapy and/or BMT. Platelets were given before tube placement if the platelet count was < 20000uL. None of the children or their parents reported discomfort from the tube. [25]

Entry criteria for the provision of enteral feeding:[1]

- Present state of malnutrition at diagnosis that failed to or is not expected to improve within 1 week.
- No improvement in nutritional status with food based supplements or supplementary drinks alone.
- Weight loss after diagnosis > 5% from the weight at diagnosis.
- Voluntary food intake is < 70% of estimated requirements for 5 days with no improvement after prescription of dietary supplementary drinks
- Anticipated gut dysfunction due to treatment for more than 5 days for well-nourished patients.

5.3.3 Type of feed

Results from studies comparing the effect of a standard and energy enriched formula revealed that an increase in energy density did not lead to an increase in GI side effects. Patients receiving the energy enriched formula after 10 weeks showed repletion of fat stores and an increase in muscle protein mass as shown by a significant increase in MUAC, biceps and triceps skinfold measurement. There was a significant increase in the weight for height scores and patients were able to achieve 112% of their requirements vs 84% in the patients on the standard tube feed. [4]

This study highlighted that the tolerance of an energy enriched formula is not significantly different to a standard formula during the intensive treatment phase. The enriched formula (1.5kcal/ml) is however more effective in improving the nutritional status and meeting the dietary requirements of patients with malignancies. [4]

If the gastrointestinal tract is patent but functionally compromised, a semi-elemental formula may be better tolerated. [11, 29]

5.3.4 TPN *(refer to TPN clinical guideline)*

PN can be used as an adjunct to enteral nutrition or as the sole source of nutrition in those patients who are unable to maintain oral intake or tolerate enteral feeds.[19] Parenteral nutrition is an appropriate choice for patients who receive the most intense treatment associated with high nutritional risk, especially those considered malnourished at diagnosis.[24]

Studies have shown parenteral nutrition to be effective in reversing and or preventing malnutrition in children with advanced solid tumors or relapsed leukemia/lymphoma, advanced neuroblastoma, metastatic disease involving the bone and children with a variety of tumor requiring abdominal irradiation. [3] In a study of 13 patients receiving treatment for Wilm's tumor, parenteral nutrition was superior to enteral nutrition in reversing malnutrition, preventing delays in chemotherapy and radiotherapy due to granulocytopenia.[24]

The expected duration of PN depends on the stage of disease, duration, type and intensity of treatment, response to treatment, adequacy of nutrient mixture and nutritional goals. Studies have shown PN to be effective only when administered on a long-term basis. Twenty-eight days of PN effectively reversed PEM when adequate energy (+- 90% RDA) and protein (2.5-3g/kg) were provided. Patients with advanced tumors or relapsed leukemia/ lymphomas showed normalized weight for height percentiles, sub-scapular skinfold percentiles, albumin and transferring concentrations. Administration of TPN for this long duration may however not be feasible or practical in many centres.[3,29]

Other studies in well nourished children also demonstrated improved maintenance of body weight, fat and muscle reserves in patients administered TPN in contrast to control patients receiving oral diets during periods of extensive abdominal irradiation and intensive chemotherapy.[3,29]

Inclusion criteria for the administration of TPN [12, 11]

- Unable to meet dietary requirements with enteral feeding alone
- Abnormal functioning of the Gastro-intestinal tract (GIT) due to ;
  - Severe oral mucositis preventing oral or nasogastric feeding
  - Typhlitis
  - GVHD involving the GIT

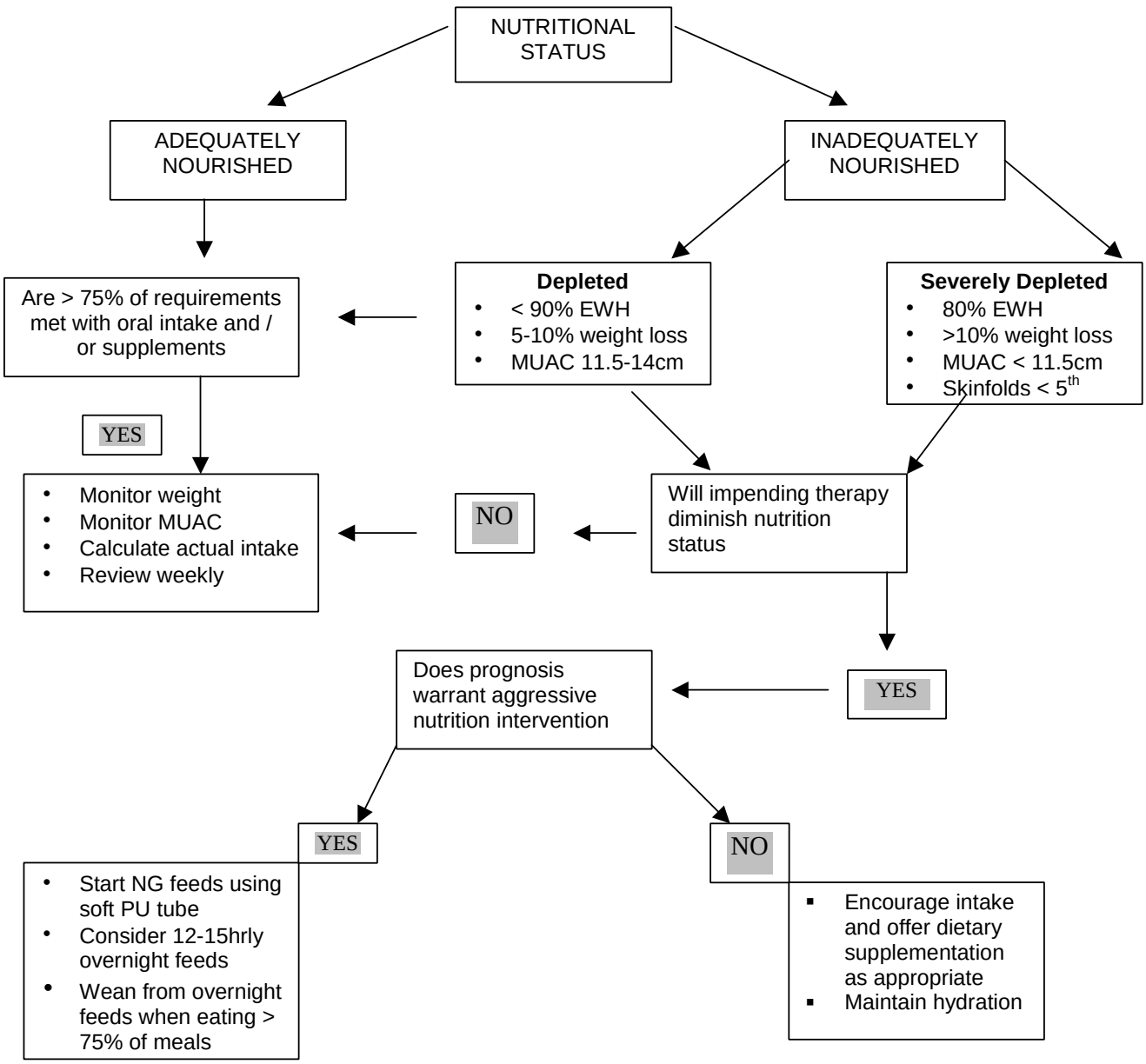
Exit criteria [20]

Aggressive nutritional support should continue until recovery of GI function allows return to enteral feeds to meet dietary requirements.

Goals for nutritional repletion: [19]

- 90% Weight for age or 90% weight for height
- Arm fat area > 5th percentile
- Subscapular skinfold > 10th percentile
- MUAC > 14.5cm

5.3.6 Decision tree for method of nutrition support [12]



6. Mucositis

Chemo- and radiotherapy can adversely affect rapidly dividing cells of the healthy body. The epithelial layer of the alimentary tract can be adversely affected especially the mouth, esophagus and the intestine.[8] Patients undergoing BMT will also invariable develop oro-oesophageal mucositis within 7-10days after chemotherapy or chemoradiotherapy.[15]

Mucositis is characterized by severe inflammation, lesions, ulceration and bleeding. Patients may have intense pain, cramping, nausea and gastro-enteritis. Food and fluid intake may be poor, nutrient absorption decreased and susceptibility to infection increased.[8] Depending on the specific drug, the severity of these effects may force a reduction in dose which could compromise treatment efficacy. [7]

The risk factors for development of mucositis can be grouped into direct and indirect factors:

Direct factors:

- Chemotherapy agent, dose and schedule
- Mucosal damage, microbial flora
- Salivary gland dysfunction
- Patient susceptibility
- Age and gender
- Nutritional status

Indirect factors

- Myelosuppression
- Reduced secretory IgA
- Bacterial, fungal or viral infections

6.1 The role of glutamine

It has been suggested that mucositis may be exacerbated by the lack of adequate amounts of the conditionally essential amino acid glutamine. Under certain clinical conditions endogenous synthesis of glutamine may be inadequate to meet metabolic demands and exogenous supplementation may be required. [17]

Different mechanisms of action of glutamine in the body have been proposed. This includes:

- Improved trophism of enterocytes and colonocytes
- Enhancing the immunological barrier due to its trophic action on the immune system
- Involvement in the acid-base balance
- Substrate for glutathione and thus involved in its anti-oxidant and scavenging actions on free radicals
- Decreased bacterial translocation [18]

Although considered a non-essential amino acid, multiple studies have shown glutamine to be an essential amino acid for enterocytes which becomes depleted during damage to the enteric mucosa.

It has been hypothesized that oral mucosa may be afforded the same benefit as intestinal epithelium from glutamine supplementation. Providing glutamine systemically does not appear to alter the incidence of clinically apparent mucositis. Topical application of glutamine which increases local content with the oral mucosa

may be beneficial but not for all chemotherapy agents as studies have shown no significant benefit for patients receiving 5 Fluorouracil. [7]

Studies have shown that oral glutamine supplementation is associated with significantly less mouth pain, less difficulty eating, lower maximum grade of mucositis and decreased opiate requirements. Other studies show reduction in days on TPN and morphine use which are objective indicators of a decrease in mucositis severity.[19] These studies have shown that for glutamine to be effective it needs to be administered as a swish and swallow solution to improve contact with the oral and esophageal mucosa.[7] Other studies have proposed that glutamine be prepared in a thick viscous vehicle (syrup like) or thickened type liquid that will allow it to stick to the oral mucosa and allow prolonged exposure. [10]

6.1.1 Dosage

It is believed that the beneficial effects of glutamine are dependant on the dose and duration of administration. The current safe IV dose is 20- 40g /day or 0.285-0.57g/day. Studies have shown beneficial effects using 2g/m2, 0.25g/kg up to 24g/day as oral solutions. Doses of up to 0.57g/kg/day have not been associated with any adverse effects in healthy volunteers or sick patients such as trauma or Bone marrow transplant patients. [19, 10, 4]

All subjects receiving glutamine supplementation started on admission, continued through the chemotherapy or bone marrow regime with an average of 28 days of receiving glutamine supplementation. [9, 17]

6.1.2 Safety

Glutamine is considered to be a very safe supplement in a variety of patient populations.[10]

Measurements used to assess possible toxicity include clinical signs, biochemical parameters, including amino acids concentrations, glucose, glucagon, ammonia, urea and total nitrogen and standard chemistries. [10]

Patient with liver disease may have alterations in urea synthesis and ammonia excretion. Patients with kidney disease might experience decreased elimination of ammonia. It is therefore reasonable to exclude patients with a creatinine clearance < 30ml/min or total bilirubin>10mg/dl from receiving glutamine supplementation. [10]

Other concerns have been the potential of glutamine supplementation to stimulate cancer growth. Investigators have not found any evidence to substantiate this claim. Glutamine may however assist with decreasing drug resistance.[10]

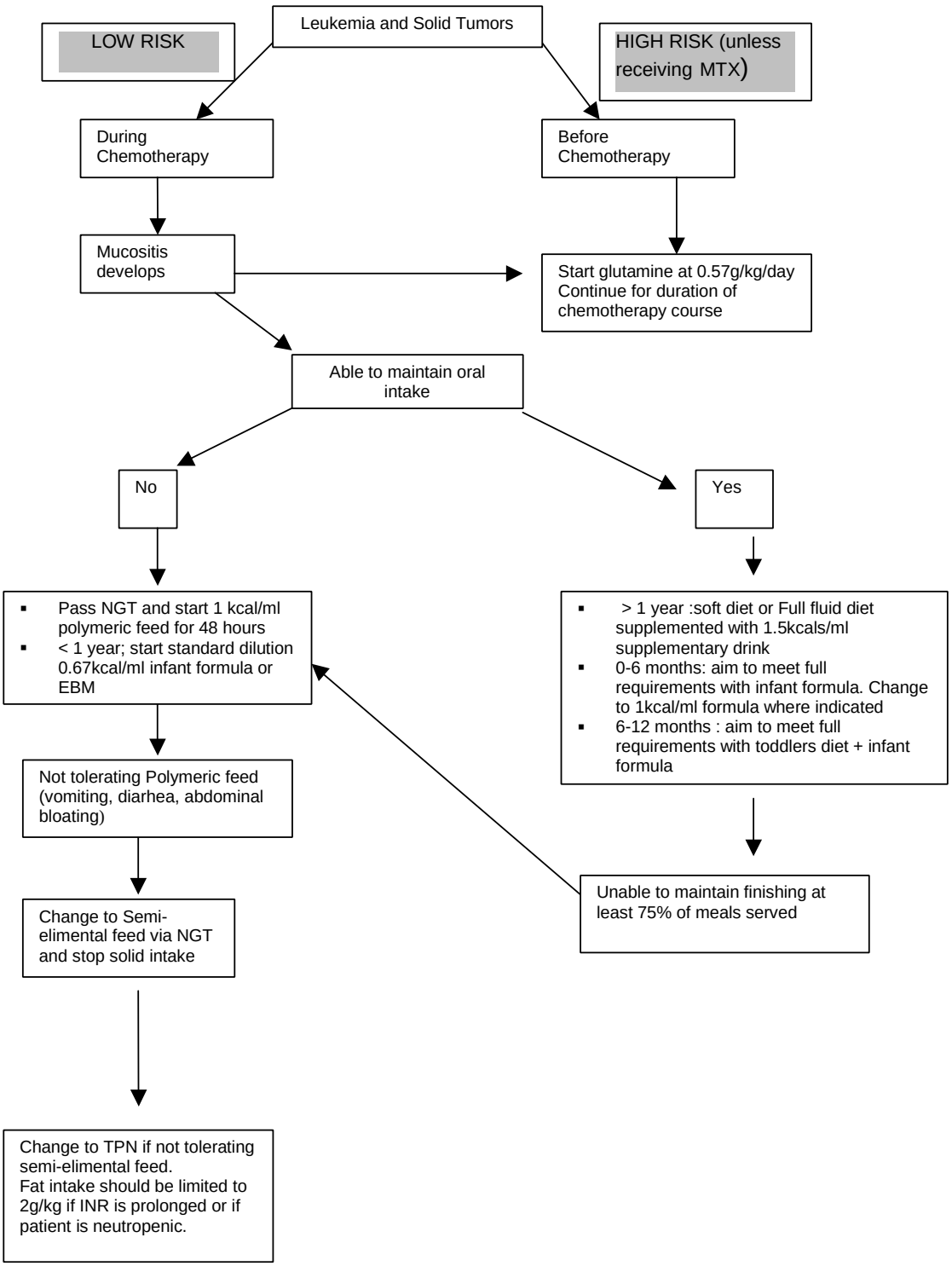
Glutamine can interfere with methotrexate (MTX) cellular efflux and inhibit its renal clearance possibly exposing the host to greater MTX concentrations and increasing mucositis. This information can be used to lower the dose of MTX if patients are receiving glutamine and possibly lowering other adverse effects related to MTX administration. [10]

6.2 Summary recommendations for prevention of mucositis

- Patients with an intensive chemotherapy regimen, such as those with Burkitt's Lymphoma and AML, or those requiring radiotherapy involving the upper GIT(e.g. head and neck rhabdomyosarcoma), have a higher risk and frequency for the development of mucositis .
- Start glutamine supplementation at 0.57g/kg on admission for those patients at risk of moderate to severe mucositis following the completion of leucovorin rescue after multi-agent regimes containing high dose MTX.
- Powdered glutamine is the supplement of choice as it is cost effective, easy to use, well absorbed, well tolerated and tasteless and can be mixed in any beverage or soft moist food. [7]
- Continue supplementation during chemo- and radiotherapy to aid in reducing the duration and severity of mucositis.

Please refer to algorithm on next page.

6.3 Algorithm for Glutamine supplementation and Nutritional Support in Oncology and Hematology



7. Bone Marrow Transplant

7.1 Introduction

Bone marrow transplant is used in the treatment of solid tumors, hematologic diseases and auto-immune disorders. It is a sophisticated therapeutic procedure consisting of the administration of high dose chemotherapy followed by the intravenous infusion of hemopoietic stem cells to re-establish marrow function in patients with damaged or defective marrow.[1]

Table 6 : Diseases treated by bone marrow transplantation [1]

Hematologic malignancies	Solid tumours	Other pathologic conditions
AML	Testicular cancer	Severe aplastic anemia
CML	Ovarian cancer	B-thalassemia
ALL	Glioma	Severe combined immunodeficiency
CLL	Neuroblastoma	Autoimmune disorder
Non- Hodgkin lymphoma		Amyloidosis
Hodgkin's disease		Heriditary metabolic disorders

7.2 Nutritional related complications of BMT [1,22]

- Severe and prolonged mucositis and esophagitis caused by total body irradiation.
- Insults to the GIT by graft versus host disease (GVHD) leading to abdominal pain and severe diarrhea.
- Altered taste, xerostomia, excessive saliva, nausea, vomiting, anorexia, steatorhea and multiple organ dysfunction may occur.
- Malnutrition caused by the use of high dose steroids and anti-virals to manage GVHD.
- The duration and intensity of symptoms as well as the stress of treatment may prevent oral intake for 1-7 weeks post transplantation, making PN the preferred method of nutrition support.

7.2.1 Acute GVHD and the GIT [1,22]

- Major complication occurs from 7-10 days to <3 months after allogenic BMT in 30-60% of patients
- If liver is involved, severe cholestasis occurs as a result of the destruction of small bile ducts which leads to increased serum bilirubin concentrations and impairment of liver functions
- Upper intestinal GVHD symptoms include anorexia, dyspepsia, and the inability to eat.
- Lower gastrointestinal GVHD presents with severe diarrhea which may be associated with bleeding, cramping abdominal pain requiring medication and refractory nausea and vomiting.
- Patients with severe GVHD may require a period of bowel rest with TPN.

7.2.2 Metabolic alterations [1]

- Impaired glucose tolerance due to steroid or cyclosporine administration or septic complications
- Pancreatic B cell function may be negatively affected
- Elevated serum cholesterol and triacylglycerol concentrations in patients maintained on long term cyclosporine therapy for chronic GVHD
- Altered vitamin status as a result of poor intake and malabsorption of water and lipid soluble vitamins

7.3 Role of low microbial diets in Bone Marrow Transplant

Low microbial diets have been used on the premise that it may reduce the risk of bacterial infection in patients with compromised immune systems due to the reduced exposure to potential pathogens in the gastrointestinal tract. These recommendations have been based on theoretical concepts of reducing the risk of contracting infections from pathogens found in food sources rather than on clinical trials. [22, 27]

Immuno-compromised patients are at an increased risk for food borne infection with the CDC identifying E Coli, Salmonella enteritidis, Listeria monocytogenes and Campylobacter jejuni as the 4 bacterial pathogens of greatest concern. Improper holding temperatures and poor personal hygiene of food handlers contribute most to disease incidence and education to parents and caregivers is essential in preventing food-borne infections. Emphasis should be placed on hand washing, high risk foods, proper storage, defrosting, cooking, reheating and cooling temperatures, cross-contamination, and sanitation. [22]

Table 7. Sanitary Food practices for immune compromised patients [20]

• Good hand washing before and after preparing and eating meals
• Do not share food with others
• Avoid foods from street vendors, salad bars, shared bins of foods in grocery stores
• Wash raw foods well prior to eating
• Cook meat until well done
• Avoid raw eggs
• Avoid soft French-style cheeses, pates, uncooked hot dogs, sliced deli meats
• Keep foods <5°C or >60°C to minimize growth of bacteria
• Clean all preparation items thoroughly before and after use to avoid cross-contamination
• Do not keep refrigerated leftovers for more than 3 days

Table 8 outlines foods that are believed to pose a high risk for food-borne infection and is being avoided in selected settings.[11]

Table 8. High Risk Foods [11]

▪ Raw eggs and cooked egg dishes	▪ Reheated chilled meals
▪ Soft and blue veined cheeses	▪ Ready to eat poultry
▪ Pate	▪ Shellfish
▪ Live and bio yoghurts	▪ Soft whip cream
▪ Take away foods	▪ Nuts and dried fruit

It has been argued that due to insufficient research and increased costs associated with providing low microbial diets, there is little need to implement them in an effort to decrease risk of infection. The methods used to prepare foods to ensure low microbial content often alter the food's taste and texture. These changes in food characteristics can affect a patient's food acceptance and intake. [27]

The lack of research currently available highlights that it would be beneficial to expand the body of knowledge regarding the effectiveness of low microbial diets. It is proposed that a pilot study designed to evaluate the effectiveness of low microbial diets at reducing the incidence of infection in immune-compromised patients may establish if dietary sources of bacteria are a real concern for bone marrow transplantation patients. [27]

8. Alternative therapies

The use of alternative nutrition therapies may pose the following problems:

- Unexpected or undesirable interactions between preparations and prescribed medications may affect the action of drugs routinely used during treatment.
- Potential contamination of preparations derived from plants poses the risks of bacterial, fungal or parasitic infections which may cause life threatening infections in immuno-suppressed children
- Alternative nutrition therapy may be chosen as the sole source of treatment. [22]

It is recommended that the dietician and fellow members of the medical team should be sensitive to the family's views and biases and that the family be educated as appropriate.[22]

9. Long-term plan

There is a high risk of obesity in patients who survive pediatric cancers especially ALL and AML. This may be related to the impact of therapy on the patient's height, a reduction in physical activity and a resulting change in body composition. Some chemotherapy regimens, especially those including steroids, may promote excessive weight gain.

Retrospective studies of children in long term remission from ALL indicate that excessive weight gain may start during treatment and persist into remission.[19] Reports have also found a 52% incidence of insulin resistance amongst long term survivors of long-term cancer. It is recommended that healthy diet principles and acceptable activity options for weight maintenance and control be provided in cases where malnutrition is not a concern.[20] Food restrictions during intensive treatment may make treatment more difficult. The goal should be placed on weight maintenance to prevent stunting of overall growth.[19]

Growth hormone deficiency, with decreased growth velocity and delayed onset of puberty, has been observed in children treated with BMT. Other endocrine complications have also been attributed to anti-neoplastic therapies; many that are not apparent until the child matures. Regular evaluations of the endocrine glands are recommended. [22]

10. Summary Recommendations [20, 24, 19]

- Nutritional status must be defined with respect to local norms.
- A complete dietary assessment should be done at diagnosis and continue at regular intervals during treatment.
- Arm anthropometry offers advantage over measures of weight and height and provides useful assessment of nutritional status in those patients whose weight is not reliable.
- The greater the tumor burden and more dose-intense the therapy, the higher the risk of nutritional morbidity.
- Any patient who meets the criteria for nutritional intervention and is receiving treatment expected to prevent adequate nutrient consumption, is a candidate for aggressive nutritional support.
- Dietary supplementation can reverse malnutrition and improve the tolerance to chemotherapy.
- Malnutrition should not be accepted as an unavoidable consequence of cancer and/or its therapy.

- Every effort should also be made to prevent obesity and other chronic disease of adulthood in long term cancer survivors.

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