

**THE DEVELOPMENT OF A NUTRITION SUPPORT
PROTOCOL FOR CHILDREN WITH ACUTE
LYMPHOBLASTIC LEUKEMIA (ALL): TWENTY CASE
STUDIES FROM SHEIKH KHALIFA MEDICAL CITY, ABU
DHABI, UAE**



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A mini-thesis submitted in partial fulfillment of the requirements for the award of the Degree of Master of Science in Nutrition Management at the Faculty of Community and Health Science, University of Western Cape

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ABSTRACT

Acute lymphocytic leukemia (ALL) is the most common type of childhood cancer accounting for approximately 25% of cancers diagnosed in children less than 20 years of age. It originates in the bone marrow and prevents the normal manufacture of red blood cells, white blood cells and platelets. A poor nutritional status is frequently observed in children with ALL at the time of diagnosis and during treatment which may result in protein energy malnutrition if nutrition intervention is delayed. This retrospective study aims to assess the nutritional status of children newly diagnosed with Acute Lymphoblastic Leukemia (ALL) using 20 case studies between 1 January 2013 and 31 December 2014 from Sheikh Khalifa Medical City (Abu Dhabi, UAE), in order to develop an appropriate nutritional support protocol for pediatric ALL patients treated at this institution.

Study Design

A retrospective descriptive case study design was used. The study population consisted of 20 electronic medical records of patients aged between 1-14 years who were newly diagnosed with Acute Lymphoblastic Leukemia (ALL) and admitted to Sheikh Khalifa Medical City for treatment during the period 1 January 2012 and 31 Dec 2014.

Data Collection

Identification of suitable participants began through a review of each potential study participant's electronic medical record. Data was collected and recorded on a data collection form (Appendix III) from the electronic medical record for each suitable participant for the following at admission and during the full duration of all phases of cancer treatment namely induction, consolidation, interim maintenance, delayed intensification and maintenance. The data collected comprised of the following: age, gender, date of diagnosis, symptoms on diagnosis, the cancer diagnosis (type and subtype), anthropometric measurements (weight, length/ height, head circumference), biochemical values (visceral proteins, blood glucose levels, hemoglobin, hematocrit, lymphocyte count), clinical assessment (stomatitis, anemia, mucositis), diet history (home feeding regimes; consumption of daily requirements; food preferences – types, textures; food allergies, food intolerances; food aversions; use of oral nutritional supplements; treatment-related side-effects; systemic related side-effects (nausea; vomiting; diarrhea; anorexia; appetite changes; taste changes; physical activity level; depression), dietary requirements (age and gender

related nutritional requirements for energy, protein, fat and fluids) and indications for nutritional support (oral feeding; enteral feeding; parenteral feeding).

Analysis of Results

The weights and length/ heights of participants recorded in the electronic medical records were converted to z-scores on the World Health Organization growth charts. The diet prescription of nutritional intervention was interpreted in comparison to the biochemical indices, anthropometric status and dietary intake of each participant. All the data involving changes in anthropometrics, biochemistry, diet history and nutritional interventions from each case study (from diagnosis and through all stages of treatment) was screened and compared with reference values in the context of the age and sex of the child. Evidence based nutritional guidelines were used to document the outcomes of the medical nutrition treatment provided in order to develop a nutrition support protocol for children with Acute Lymphoblastic Leukemia at Sheikh Khalifa Medical City.

Results

The results showed that weight loss expressed as a percentage of body weight provided a more accurate estimate of the true significance of weight loss in subjects undergoing cancer treatment (chemotherapy) for ALL. A weight loss of greater than 5% of body weight over a period of one month is considered a sign of nutritional deprivation even if the subject is not classified as undernourished by anthropometric parameters. Subjects experienced the highest weight loss during the consolidation phase and interim maintenance phases of treatment.

Conclusion

It can therefore be concluded that pediatric subjects on cancer treatment for ALL at SKMC and receiving nutritional support underwent changes in nutritional status as manifest by a reduction in more than 5% of their body weight during three phases of treatment namely induction, consolidation and interim maintenance. An appropriate nutrition support protocol was developed based on the results and experience obtained from this study for pediatric ALL patients treated at SKMC.

DECLARATION

I declare that the work contained within this mini thesis is original. I have solely been responsible for the organization of the study herein, as well as all aspects of data collection and the analysis of results, unless otherwise stated.

L. Pillay

Looventhree Pillay



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KEYWORDS:

Acute Lymphocytic Leukemia (ALL)

Acute Myelogenous Leukemia (AML)

Nutritional status

Malnutrition

Undernutrition

Over nutrition

Chemotherapy

Radiation therapy

Nutritional support



DEFINITION OF ABBREVIATIONS

ALL: Acute Lymphocytic Leukemia

AML: Acute Myelogenous Leukemia

BMI: Body mass index

H: Height

HAMLET: Human alpha-lactalbumin made lethal to tumor cells

MUAC: Mid upper arm circumference

PSGA: The Pediatric Subjective Global Assessment

PYMS: Pediatric Yorkhill Malnutrition Score

TSF: Triceps skinfold thickness

SCAN: The Nutrition Screening Tool for Childhood Cancer

SKMC: Sheikh Khalifa Medical City

STAMP: Screening Tool for Assessment of Malnutrition in Pediatrics

UAE: United Arab Emirates

URTI: Upper respiratory tract infection

WBC: White blood cell

WHO: The World Health Organization



CHAPTER 1



INTRODUCTION

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1.1. INTRODUCTION

Acute lymphocytic leukemia (ALL) is the most common type of childhood cancer accounting for approximately 25% of cancers diagnosed in children less than 20 years of age (Al-Mulla *et al*, 2014; Zhanga *et al*, 2014; Owens *et al*, 2013). It originates in the bone marrow and is characterized by the continuous multiplication of malignant white blood cells which results in an excess of lymphoblasts in the bone marrow and the peripheral blood. This prevents the normal manufacture of red blood cells, white blood cells and platelets (Children's Oncology Group, 2015; Owens *et al*, 2013) and this deviation from the normal hematopoietic processes leads to bicytopenia and leukocytosis and/or pancytopenia and aplastic anemia in patients at initial diagnosis for ALL (Children's Oncology Group, 2015). A poor nutritional status is frequently observed in children with ALL at the time of diagnosis and during treatment which may result in protein energy malnutrition if nutritional intervention is delayed.

1.2. RATIONALE OF THE STUDY

In the Middle East, leukemia is reported to be one of the ten most common malignancies and is the major form of pediatric cancer which accounts for 39.4% of pediatric cancer diagnosis. Leukemia in Middle Eastern countries was found to occur in 36% of subjects in the 0-10 year age group; 16 % in subjects in the 10-20 year age group and in 19% of subjects in the 20-30 year age groups (Tadmouri *et al*, 2010). In the United Arab Emirates the geographic distribution of leukemia cases was reported as follows: 25 % were from Abu Dhabi; 20.8 % from Al Ain and 17.7 % from Sharjah (Tadmouri *et al*, 2010). Pediatric ALL is said to be the most common malignancy in the Middle East, with a peak age range of 3-6 years which is similar to the age range reported in western countries (Al-Mulla *et al*, 2014). The incidence of ALL in males was found to be slightly higher than females with a gender ratio of males: females being 1.4: 1.

1.3. PROBLEM STATEMENT

In the United Arab Emirates (UAE), the incidence of cancer is the third leading cause of death in the total population, following cardiovascular disease and accidents (Badrinath *et al*, 2004). Leukemia is the third most common cancer especially amongst females and is the most common form of pediatric cancer, accounting for 39.4%. Aggressive treatment modalities like chemotherapy and radiation therapy impact negatively on the nutritional status of a child with Acute Lymphoblastic Leukemia (ALL) resulting in a poor nutritional status which is frequently observed at the time of diagnosis and during treatment. Adequate nutrition is therefore an

important concern in children with ALL as a good nutritional status helps them cope better with the side-effects of anticancer therapy which has a negative impact on their nutritional intake

1.4. AIM OF THE STUDY

This retrospective study aims to assess the nutritional status of children newly diagnosed with Acute Lymphoblastic Leukemia (ALL) using 20 case studies between 1 January 2013 and 31 December 2014 from Sheikh Khalifa Medical City (Abu Dhabi, UAE), in order to develop an appropriate nutritional support protocol for pediatric ALL patients treated at this institution.

1.5. SPECIFIC OBJECTIVES

1.5.1. To assess the nutritional status of children newly diagnosed with ALL by using anthropometric measurements (weight, length/height, head circumference and BMI), biochemical data (visceral proteins, blood glucose levels, hemoglobin, hematocrit, lymphocyte count) and diet history records (home feeding regimes, food preferences – types, textures, feeding environment food allergies, food intolerances) at diagnosis.

1.5.2. To assess the nutritional status of children newly diagnosed with ALL by using anthropometric measurements (weight, length/height, head circumference and BMI), biochemical data (visceral proteins, blood glucose levels, hemoglobin, hematocrit, lymphocyte count) and diet history records (home feeding regimes, food preferences – types, textures, feeding environment food allergies, food intolerances) at the start and end of induction chemotherapy.

1.5.3. To assess the nutritional status of children newly diagnosed with ALL by using anthropometric measurements (weight, length/height, head circumference and BMI), biochemical data (visceral proteins, blood glucose levels, hemoglobin, hematocrit, lymphocyte count) and diet history records (home feeding regimes, food preferences – types, textures, feeding environment food allergies, food intolerances) at the start and end of consolidation chemotherapy.

1.5.4. To assess the nutritional status of children newly diagnosed with ALL by using anthropometric measurements (weight, length/height, head circumference and BMI), biochemical data (visceral proteins, blood glucose levels, hemoglobin, hematocrit, lymphocyte count) and diet history records (home feeding regimes, food preferences – types, textures, feeding environment food allergies, food intolerances) at the start and end of interim maintenance chemotherapy.

1.5.5. To assess the nutritional status of children newly diagnosed with ALL by using anthropometric measurements (weight, length/height, head circumference and BMI), biochemical data (visceral proteins, blood glucose levels, hemoglobin, hematocrit, lymphocyte count) and diet history records (home feeding regimes, food preferences – types, textures, feeding environment food allergies, food intolerances) at the start and end of delayed intensification chemotherapy.

1.5.6. To assess the nutritional status of children newly diagnosed with ALL by using anthropometric measurements (weight, length/height, head circumference and BMI), biochemical data (visceral proteins, blood glucose levels, hemoglobin, hematocrit, lymphocyte count) and diet history records (home feeding regimes, food preferences – types, textures, feeding environment food allergies, food intolerances) at the start and end of maintenance chemotherapy.

1.5.7. To develop an appropriate nutrition support protocol for pediatric patients newly diagnosed with ALL at Sheikh Khalifa Medical City (Abu Dhabi, UAE) by screening all the data involving changes in anthropometrics, biochemistry, diet history and nutritional interventions, from each case study, from diagnosis and through all stages of treatment (induction, consolidation, interim maintenance, delayed intensification and maintenance) and comparing this data with reference values in the context of the age and sex of the child as well as evidence based nutritional guidelines. This was done to determine whether the nutrition interventions provided during each treatment phase had an impact on the nutritional status of each case study. These results were then used to develop a nutrition support protocol for children with Acute Lymphoblastic Leukemia at SKMC. This protocol will serve to standardize the feeding practice of children with ALL in order for them to achieve their nutritional goals during treatment.

1.6. LAYOUT

The layout of this write up is as follows:

Chapter 2: Literature Review

Chapter 3: Methodology

Chapter 4: Results

Chapter 5: Discussion

Chapter 6: The development of a nutrition support protocol

Chapter 7: Conclusion and Recommendations

Chapter 8: Limitations of the Study



CHAPTER 2

LITERATURE REVIEW



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2.1. Introduction

Acute lymphocytic leukemia (ALL) is the most common type of childhood cancer accounting for approximately 25% of cancers diagnosed in children less than 20 years of age (Al-Mulla *et al*, 2014; Zhanga *et al*, 2014; Owens *et al*, 2013). It originates in the bone marrow and is characterized by the continuous multiplication of malignant white blood cells which results in an excess of lymphoblasts in the bone marrow and the peripheral blood. This prevents the normal manufacturing of red blood cells, white blood cells and platelets (Children's Oncology Group, 2015; Owens *et al*, 2013). This deviation from the normal hematopoietic processes leads to bicytopenia and leukocytosis and or pancytopenia and aplastic anemia in patients at initial diagnosis for ALL (Children's Oncology Group, 2015).

The most common symptoms of childhood ALL include lethargy, fatigue, bone pain and a loss in appetite (Salim *et al*, 2014). Bone pain which is a common symptom of childhood ALL occurs as a result of leukemic infiltration in the periosteum resulting in osteopenia (Children's Oncology Group, 2015).

2.2. Incidence of Acute Lymphoblastic Leukemia

In the Middle East, leukemia is reported to be one of the ten most common malignancies and is the major form of pediatric cancer which accounts for 39.4% of pediatric cancer diagnosis. Leukemia in Middle Eastern countries was found to occur in 36% of subjects in the 0-10 year age group; 16 % in subjects in the 10-20 year age group and in 19% of subjects in the 20-30 year age group (Tadmouri *et al*, 2010). In the United Arab Emirates, the geographic distribution of leukemia cases was reported as follows: 25 % were from Abu Dhabi; 20.8 % from Al Ain and 17.7 % from Sharjah (Tadmouri *et al*, 2010). Pediatric ALL is said to be the most common malignancy in the Middle East, with a peak age range of between 3-6 years of age which is similar to the age range reported in western countries (Al-Mulla *et al*, 2014). The incidence of ALL in males was found to be slightly higher than females with a gender ratio of males: females being 1.4: 1.

In their study on 1150 ALL patients in the Middle East, Al-Mulla *et al* (2014) found the most common symptom at diagnosis to be pallor, followed by fever. Bone pain was reported in 39.6% of the patients. Testicular involvement was clinically suspected in 26.7% but was confirmed in only 2.4% of the male patients. On presentation lymphadenopathy was confirmed in 62.6%; splenomegaly in 60.8% and hepatomegaly in 59.5% of the patients (Al-Mulla *et al*, 2014). Some

studies have suggested that the high rate of consanguinity in the Arab population could account for the increased incidence of leukemia in children however the results of other studies have been inconsistent (Tadmouri *et al*, 2010).

2.3. The classification of childhood ALL

In children, the type and subtype of leukemia is determined by testing samples of blood and bone marrow which plays a major role in determining the treatment options and predicts the prognosis of the disease (American Cancer Association, 2015). Leukemic cells often spread to other organs of the body such as the liver, spleen, lymph nodes, testes or central nervous system and if this should happen, the treatment has to be more intense in order to destroy the malignant cells (American Cancer Association, 2015).

ALL is classified according to the type of lymphocyte (B cell or T cell) the leukemic cells are found in and the degree of maturity of the cells. The subtypes of ALL are named as follows: (American Cancer Association, 2015)

2.3.1 B-cell ALL

B cell ALL starts in B cells and is found in 80-85% of children with ALL.

2.3.1.1. Early pre-B ALL is found in about 10% of cases.

2.3.1.2. Common ALL is found in about 50% of cases

2.3.1.3. Pre-B ALL is found in about 10% of cases.

2.3.1.4. Mature B-cell ALL which is also known as Burkitt leukemia is rare accounting for only 2-3% of cases and is treated differently from most leukemias.

2.3.2. T-cell ALL

T-cell ALL occurs in 15-20% of children with ALL and is more common in boys than girls. It mainly affects older children than B-cell ALL and sometimes causes breathing problems by affecting the thymus gland and may spread to the cerebrospinal fluid.

2.3.2.1. Pre-T ALL is found in about 10% of cases.

2.3.2.2. Mature T-cell ALL is found in about 15-20% of cases,

Research done on 1150 Middle Eastern ALL patients by Al-Mulla *et al* (2014) found that 84.2% were classified as having B-cell involvement; 14.8% was classified as having T -cell

involvement and 11% showed mature B-cell involvement. In addition most of the patients did not have CNS involvement (Al-Mulla *et al*, 2014).

2.4. The etiology and risk factors for ALL in children

The etiologic factors contributing to the development of acute lymphoblastic leukemia (ALL) has not been completely established however it has been linked to a few strong risk factors such as birthweight (Tower and Spector, 2007); the mode of feeding (breastfeeding and formula feeding) (Schraw *et al*, 2014); gender (Gholami *et al*, 2013); maternal diet (Petridou *et al*, 2005); being an identical twin (Cancer Association, 2015); radiation exposure (Amitay and Keinan-Boker, 2015) and Trisomy 21 (Downs syndrome) (Inaba *et al*, 2013; Whitlock *et al*, 2005).

2.4.1. Birthweight: several studies have found a positive association between high birth weights (usually defined as > 4 kg) and the risk of developing childhood leukemia (Tower and Spector, 2007). A study conducted by Hjalgrim *et al* (2003) on 10 282 cases found that children who weighed more than 4 kg at birth had a 26% higher risk of developing ALL and this trend risk for developing ALL increased by 14% for every 1 kg rise in birthweight (Tower and Spector, 2007 citing Hjalgrim *et al*, 2003). Several consequent studies have firmly established the association between accelerated intrauterine growth and ALL (Schraw *et al*, 2014). A proposed mechanism for this is the action of insulin-like growth factor 1 (IGF-1) which is a peptide produced in the liver and which also functions to promote growth in many cellular processes within the human body. High levels of IGF-1 have been associated with a high birth weight in infants. An increased birthweight has been found to produce an increased number of stem cells which can undergo malignant transformation therefore predisposing an infant to a higher risk of developing childhood leukemia (Tower and Spector, 2007). It has also been postulated that IGF-1 might stimulate the growth of cells that already have preleukemic genetic abnormalities.

2.4.2. Breastfeeding: The World Health Organization (Schraw *et al*, 2014) and The American Academy of Pediatrics (Academy of Nutrition and Dietetics, 2015) recommend exclusive breastfeeding for the first 6 months of an infant's life in order to achieve optimal growth, development and health. There have been several published studies to examine a possible relationship between being breastfed and childhood leukemia. The most recent meta-analysis published on this topic in 2007 found that breastfeeding for more than 6 months of age lowered the risk of a child developing ALL in childhood by 20% (Amitay and Keinan-Boker, 2015 citing Ip *et al*, 2007). Breastfed infants were also found to have a greater number of natural killer cells and the acid pH of the stomach of breastfed infants was found to promote the formation of

human alpha-lactalbumin made lethal to tumor cells (HAMLET) which is a protein-lipid complex that induces apoptosis-like death in tumor cells and leaves fully differentiated cells unaffected (Amitay and Keinan-Boker, 2015).

2.4.3. Formula feeding: Cow's milk and cow's milk based formula feeds have been shown to elevate insulin-like growth factor 1 (IGF-1) levels which could impact on leukemogenesis (the development of leukemia). High IGF-1 exposure has been directly associated with the increased risk of ALL (Schraw *et al*, 2014). Research by Schraw *et al* (2014) on 142 cases of ALL (between the ages of 1 and < 14 years old) found the duration of formula feeding and introduction of solids with each additional month of age increased the odds of developing ALL. A limitation to this study was the absence of data on IGF-1 levels to accompany the infant feeding data.

2.4.4. Gender: ALL is slightly more common in males than females though the reason for this is unknown (Gholami *et al*, 2013).

2.4.5. Maternal Diet: Research by Petridou *et al* (2005) reported a lower risk for ALL in children (12- 59 months) whose mothers consumed a healthy and traditionally Mediterranean diet (a high intake of vegetables, legumes, fruit, fish, cereals, olive oil and a low intake of saturated fat, meat and meat products, sugars and syrups) during pregnancy. This study also positively associated maternal age at birth with ALL risk in infants. The risk of childhood ALL has been shown to be significantly higher in children who are born to parents that are older.

2.4.6. Identical twins: an individual who has an identical twin who develops ALL before the age of six years of age has an increased risk of developing ALL. If an identical twin develops ALL within the first few months of life, the other twin is almost always found to develop the same type of leukemia (Cancer Association, 2015).

2.4.7. Radiation exposure: being exposed to high levels of radiation is a risk factor for ALL. Treating cancer with radiation therapy also increases the risk of leukemia and the risk is said to be higher for both radiation and chemotherapy which are both used in the treatment of cancer (Amitay and Keinan-Boker, 2015).

2.4.8. Trisomy 21 or Downs syndrome: children with Downs syndrome have a 10 to 20 fold increased risk in developing ALL between the ages of 1-4 years old (Inaba *et al*, 2013; Whitlock *et al*, 2005) with ALL occurring in 1 in 300 children with Downs syndrome versus 1 in 3500 children without Downs syndrome (Maloney, 2011 citing Robertson, 1992 and Lange, 2000). In

a large cohort study conducted by Whitlock *et al* (2005) children with ALL and Down's syndrome were also found to have lower platelet count coupled with a lower incidence of splenomegaly and lymphadenopathy and a higher hemoglobin level at diagnosis than children with ALL without Down's Syndrome. A review by Maloney (2011) found a greater incidence in remission induction failure in Down's syndrome ALL patients than non- Down's syndrome ALL patients. In the United Kingdom ALL trials found increased mortality in Down's syndrome ALL patients during induction; post remission consolidation; delayed intensification and during the third year of maintenance treatment in boys (Maloney, 2011).

2.5. The treatment of pediatric ALL

At diagnosis, risk groups are used to classify ALL instead of stages. The risk classification of childhood ALL is described as follows (Children's Oncology Group, 2015):

Standard risk ALL: includes children with a white blood cell count of less than 50 000/microliter at diagnosis.

High risk ALL: includes children with a white blood cell count equal to or greater than 50 000/microliter at diagnosis.

Treatment is based on the risk group and could span around 2-3 years. The treatment regimens currently in use to treat childhood ALL is aimed at disrupting and destroying the growth and division of cancer cells. The treatment is systemic which causes damage to healthy cells in the skin, hair follicles, mucus membranes, reproductive system and the gastrointestinal tract resulting in hair loss (alopecia) which includes loss of body hair, eyebrows and eyelashes; malabsorption; mucositis and a loss in taste (Chan, 2007). Patients receive high doses of chemotherapy without much break between cycles in order to induce remission (Owens *et al*, 2013).

Chemotherapy treatment protocols are based on the following factors (Children's Oncology Group, 2015):

- The age of the patient at diagnosis.
- The white blood cell (WBC) count at diagnosis: children with WBC count greater than 50 000 require more aggressive treatment.
- Subtype of leukemia: `B-cell precursor` is the most common type and `T-cell` is a less common type.

- Central nervous system leukemia: children with leukemia cells in the spinal fluid at diagnosis require more aggressive treatment.
- Testicular leukemia: this is common in 1-2% of boys with leukemia.
- Chromosomal alterations in the leukemia cell: these abnormalities affect the type of treatment.
- Response to therapy: the efficacy of the treatment is measured by counting the percentage of leukemia cells in the bone marrow at various intervals during the first month of therapy. Children who show poor response to treatment may require more aggressive treatment.

ALL treatment protocols are divided into 4 phases namely: (Children`s Oncology Group, 2015)

Induction: during this phase which usually lasts 4 weeks, children receive a combination of 3 or 4 drugs either by mouth, intravenously or into the spinal fluid in order to destroy leukemia cells and allow normal blood cells to develop. Almost 98% of children with ALL enter remission after the induction phase.

Consolidation: the duration of this phase is between 12-16 weeks and drugs different to those used during the induction phase are administered to patients either orally or intravenously.

Delayed intensification: this cycle lasts 8 weeks and is aimed at preventing the leukemia from returning.

Maintenance: this final stage of treatment lasts between 2-3 years and is less aggressive than the previous phases in that it mostly consists of oral medications given at home.

Over the past decade the use of advanced multimodality treatments in children with ALL has produced an estimated 70% cure rate (Lughetti *et al*, 2012) and an 85% (5 year event free) survival rate (Chan, 2007). Cancer treatment toxicity is a major limitation causing frequent dose limitations and interruptions in treatment schedules (Chan, 2007).

2.6. Nutrition screening of children with ALL

Malnutrition is a serious concern for children with cancer. Nutrition screening and assessment is therefore vital to detect and manage cancer related nutritional problems. Nutrition screening is a simple, cost effective process carried out by health care staff at first contact with the patient in order to identify and assess patients at risk for malnutrition or who are malnourished to ensure

quick referral to a dietitian or nutrition support team for further nutritional assessment (McCarthy *et al*, 2012).

There is several nutrition screening tools in use for a pediatric setting, with the most commonly used screening tools being The Pediatric Subjective Global Assessment (PSGA); The STAMP Tool and The Pediatric Yorkhill Malnutrition Screening (PYMS) and The Nutrition Screening Tool for Childhood Cancer (SCAN) (Murphy *et al*, 2015).

2.6.1. The Pediatric Subjective Global Assessment (PSGA)

The pediatric subjective global assessment is a comprehensive questionnaire comprised of information on a child`s physical examination; recent anthropometric measures; weight history; dietary intake (type, volume, frequency, rating of appetite changes in feeding or eating problems and dietary restrictions); frequency and duration of gastrointestinal symptoms (loss of appetite, vomiting, diarrhea, constipation, stomach pain and nausea) and laboratory tests (for nutritional proteins) (Secker and Jeejeebhoy, 2007). This tool when applied along with the Pediatric Yorkhill Malnutrition Screening on 247 subjects in the United Kingdom was found to have a high specificity and positive predictive value however its sensitivity was low (Moeeni and Day, 2012 citing Gerasimidis *et al*, 2010). However it was also found to be lengthy, time-consuming, expensive and difficult to apply to all patients, this resulted in this tool being considered `more of an assessment tool, able to identify children with established malnutrition rather than a screening tool` (Moeeni and Day, 2012).

2.6.2. The STAMP Tool

The STAMP tool makes use of 5 simple steps which considers 3 elements namely clinical diagnosis; nutritional intake and anthropometric measurements of hospitalized pediatric patients between the ages of 2-16 years. Each element is assigned a score and the total score is supposed to indicate a low or moderate or high risk of malnutrition (McCarthy *et al*, 2008). Patients with a high risk score are referred to the dietitian and / or nutrition support team for nutrition intervention; patients with a medium risk score are monitored and reassessed after 3 days and those with a low risk are reassesses weekly. This tool has been validated in one study which included 89 subjects, of which 20% were classified as being at nutritional risk. More studies are however needed to further validate this tool within a clinical setting (Moeeni and Day, 2012). Literature by Selwood *et al* (2010) found the STAMP tool to score all children receiving cancer treatment as being `high risk` due to the scoring system used.

2.6.3. The Pediatric Yorkhill Malnutrition Screening (PYMS)

The Pediatric Yorkhill Malnutrition Screening (PYMS) has been described by Gerasimidis *et al* (2010) as `an inexpensive and simple tool effective in identifying pediatric patients at risk for malnutrition and nutritionally related complications`. It assesses BMI, history of recent weight loss, changes in the nutritional intake of a child and the effect of the present medical diagnosis on the nutritional status of the child and it requires an accurate weight to be taken on the day on which the patient is screened (Gerasimidis *et al*, 2010). `The accuracy of the tool was assessed by two research dietitians who compared the nursing screening results with a full dietetic assessment, anthropometry and body composition measurements however the tool failed to include a specific question regarding previous underlying disease or chronic conditions` (Moeeni and Day, 2012).

2.6.4. The nutrition screening tool for childhood cancer (SCAN)

The nutrition screening tool for childhood cancer (SCAN), is a simple, practical, quick and valid screening tool which can be utilized to identify the need for nutritional intervention in children with cancer (up to the age of 18 years old) (Murphy *et al*, 2015). The tool consists of 6 questions with each question assigned a score of 1-2. The score allocated to each question determines the nutritional risk of the patient (Murphy *et al*, 2015). SCAN was evaluated against the pediatric subjective global assessment tool and a score of greater than or equal to 3 had 100% sensitivity and 39% specificity for detecting chronically malnourished children with cancer. `The SCAN cutoff of greater than or equal to 3 was determined to be the ideal cut-off as no child with malnutrition will go undetected` (Murphy *et al*, 2015). It also utilizes information that is readily available and simple to use which makes it easy and quick to administer, reliable and consistent with low false positive or false negative findings. However the limitation of the SCAN tool is its inability to detect patients at risk for obesity during cancer treatment (Murphy *et al*, 2015).

The selection criteria for a screening tool include the following:

- (a) Quick and efficient.
- (b) Simple to use and user –friendly to patients and healthcare staff (Gerasimidis *et al*, 2010).
- (c) Validity – the tools ability to differentiate between those `who are malnourished`, `at risk for malnutrition` and those `not at risk for malnutrition` (Moeeni and Day, 2012).
- (d) Reliability – which patient groups it is appropriate for? ; does it produce a consistent result if different people use it? (Moeeni and Day, 2012).

- (e) Inexpensive – easy to implement. Equipment needed for implementation is available
- (f) Has an acceptable level of sensitivity and specificity and positive and negative predictive values.

At Sheikh Khalifa Medical City (SKMC) the nutrition screening tool currently incorporated into the electronic pediatric patient chart is composed of 7 questions requiring a yes or no answer. The questions are as follows: unintentional weight loss within the past 3 months; reduced dietary intake in the last week; is the patient severely ill (confined to bed due to severe illness / scheduled for major surgery); does the patient look underweight? ; impaired nutritional status based on the oral intake of the patient in the past 3 or 2 or 1 month; severity of disease (hip fracture, COPD, chronic hemodialysis, diabetes, oncology, major abdominal surgery, pneumonia, head injury, bone marrow transplant, ICU patient with assisted ventilation and inotropic drugs). If the score is more than 2 a dietitian consult is generated by the system. If the score is between 0-1 the patient is rescreened in 7 days. This tool has not been validated for use in the pediatric population which means that a number of pediatric patients at `risk for malnutrition` are not effectively identified and/or referred for further nutritional intervention. This therefore impacts on the treatment of malnutrition which lengthens hospital stay; decreases wound healing and can possibly increase mortality in patients.

2.7. Nutritional assessment of children with ALL

Adequate nutrition is an important concern in children with ALL as a good nutritional status helps them cope better with the side-effects of cancer therapy by decreasing their risk of developing infections which can have a negative impact on their quality of life and survival.

Nutritional status is defined as the extent to which nutrients are available and utilized by the body to meet metabolic demands to maintain health and promote growth (Shaw and Lawson, 2007). An inadequate intake of nutrients at any time during childhood may impact on the growth and development of a child (Ladas *et al*, 2005). Current methods of assessing the nutritional status of children involve a combination of objective anthropometry, biochemical and immunologic measurements, clinical assessment and diet history (Nieuwoudt, 2011; Mosby *et al*, 2009). The A; B; C; and D of the nutritional assessment process includes the following:

2.7.1. Anthropometric measurements

Anthropometric measurements are rapid, inexpensive and non-invasive to obtain. In infants and children the most sensitive measurements of growth are weight, length/height, head circumference and body mass index (BMI). These measurements are commonly plotted on growth curves (against established reference data and adjusted for age) to monitor growth, detect growth abnormalities and accurately assess the nutritional status of infants and children (Collins *et al*, 2010).

2.7.1.1. Weight: it is an indicator of current health and nutritional status and can be influenced by a patient's body composition, fluid status, medication, organ enlargement or tumor mass. When plotted on a growth chart, the weight-for-age of a child is indicative of a child's weight compared with other children of the same age and gender. It is also useful for tracking weight gain in infants and children, as well as, to explain changes in weight for length or BMI for age. Weight-for-age cannot be used to classify a child as 'underweight or overweight'. It is more appropriate to use weight for length (in infants and children under the age of two years old) or weight for height (in children above the age of two years old) to identify underweight, overweight or within normal limits. (Pediatric Nutrition Reference Guide, 2013). Weight gain in children is often described in terms of the amount of weight a child has gained over a given period of time, also known as velocity of weight gain. Unintentional weight loss in children is often indicative of health and /or nutritional problems (Pediatric Nutrition Reference Guide, 2013).

$$\% \text{ Weight Change} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

In children, growth depends on a sustained increase in fat and lean body mass and an increased demand due to a disease-state competes with the specific energy needs for growth (Bauer *et al*, 2011). In the pediatric population objective anthropometric parameters such as history of weight loss and a greater than 5% weight loss in one month is considered abnormal in children (Bunting *et al*, 2013 and Bauer *et al*, 2011).

2.7.1.2. Length / Height: recumbent length is measured for infants and toddlers up to 24 months of age and after 24 months of age standing height or stature is measured. Length or height is an indicator of a child's linear growth relative to age and is used to define the shortness or tallness of a child. When plotted on a growth chart, the length or height-for-age of a child indicates the child's length/height in comparison to other children of the same age and gender and reflects the long-term nutritional status; as length/height is affected more slowly than weight when a child experiences undernutrition or overnutrition. Undernutrition may cause poor linear growth or stunting which results in the child's height being less than his/her genetic potential and over nutrition may result in early maturation and accelerated linear growth, resulting in a child being tall for age. A gain in height/ stature is said to occur more slowly than a gain in weight and may therefore require an extended period of nutritional rehabilitation to achieve. In children 1-3 years old, the Waterlow criteria can be used to assess the extent of chronic malnutrition resulting in stunting (Pediatric Nutrition Reference Guide, 2013).

2.7.1.3. Head circumference: Head circumference is an indicator of brain growth and may be affected by chronic undernutrition during the critical period of brain development which occurs from birth to 36 months of age (Bauer *et al*, 2011). There is a poor relationship between head circumference and nutrition after the age of 36 months. Head size is also affected by genetics and in clinical practice a head circumference for age less than the 5th percentile on the head circumference for age growth chart is often described as microcephaly and similarly, a head circumference- for-age greater than the 95th percentile is described as macrocephaly.

2.7.1.4. Body mass index in children (BMI): is a screening tool which is age and gender specific and is used to identify children who are under or overweight (Pediatric Nutrition Reference Guide, 2013). BMI is calculated by using the following equations:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height}^2 (\text{m}^2)}$$

The BMI is also described in the literature as the simplest, most non-invasive and acceptable tool that is used to indirectly measure body fatness which can be related to adiposity and health risks in children in later life (Bauer *et al*, 2011).

2.7.1.5. Growth charts

Growth charts are tools consisting of a series of percentile and z-score curves, used to evaluate the growth of children by recording a series of anthropometric measurements based on the age and gender of the child. Percentiles and z-scores are described as a numeric summary of each child's placement relative to an appropriate reference population on a growth chart, to provide the most accurate measure of protein energy malnutrition (Collins *et al*, 2010). The most common growth charts in use today are:

2.7.1.5.1. The growth charts published by the Centers of Disease Control and Prevention (CDC)

These growth charts are based on pooled data from five National Health and Nutrition Examination surveys.

2.7.1.5.2. The World Health Organization growth charts

These growth charts are based exclusively on healthy children living under optimal conditions for achieving their full growth potential as all the children were breastfed in many different countries (Brazil, Ghana, India, Norway, Oman and the United States) and none of the mothers used tobacco/cigarettes (WHO, 2010).

Weight-for-age when plotted on an appropriate growth chart is an indicator of a child's weight compared with other children of the same age and sex and is the most useful tool to track weight gain in children. However it is not used to classify a child as underweight or overweight (Pediatric Nutrition Reference Guide, 2013).

Length/height-for-age when plotted on an appropriate growth chart is an indicator of a child's length/height weight compared with other children of the same age and sex and is a useful tool to measure the linear growth of a child. It also represents the long term nutritional status of a child and is affected more slowly than weight when a child experiences under or over nutrition. Undernutrition usually causes poor linear growth or stunting (Pediatric Nutrition Reference Guide, 2013).


Weight- for-length/height is used as an indicator for normal weight or underweight and overweight as the body weight is dependent on a child's stature. A weight-for-length/height value below the 5th percentile is indicative of undernutrition and a weight for length/height value above the 95th percentile is indicative of over nutrition.

BMI- for-age is the most reliable method of predicting a visual assessment of underweight or over weight in a child. However children that are athletic may have a BMI value indicative of overweight though they lack adiposity. A BMI-for-age less than the 5th percentile are indicative of underweight.

Percentiles and z-scores are used to assess the anthropometric measurements of infants and children in order to evaluate their growth and nutritional status (WHO, 2008). Z-scores are said to have a number of advantages compared to percentiles in that they are calculated based on the distribution of the reference population; reflect the reference distribution and are compared across ages, sexes and anthropometric measurements (WHO, 2008). Z-scores can also be analyzed as a continuous variable in studies and can therefore be used to quantify the extreme growth status at both ends of a distribution (WHO, 2008).

Table 1 below summarizes recommendations for defining malnutrition based on z-scores.

Table 1: Recommendations for defining malnutrition based on z-scores (Academy of Nutrition and Dietetics, 2015)



Primary Indicator	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Weight-for-length z- score	-1 to -1.9 z-score	-2 to -2.9 z-score	-3 or greater z-score
Length z- score	no data	no data	-3 or greater z-score
Deceleration in weight-for-length z-score	decline of 1 z-score	decline of 2 z-scores	decline of 3 z-scores

2.7.2. Biochemical and hematology data:

Laboratory measurements that are most frequently used to assess the nutritional status of children include visceral proteins (prealbumin, transferrin and retinol binding protein); blood glucose levels; hemoglobin; hematocrit; lymphocyte count; lipid profiles (Madrono *et al*, 2011).

2.7.2.1. Albumin

Albumin has been widely used as a marker of nutritional status however due to its long half-life of 21 days and its ability to be affected by certain medications such as corticosteroids, insulin and thyroid hormones; dehydration and certain disease states such as severe liver and renal disease, intravascular volume overload, malabsorption syndromes, chemotherapy and zinc deficiency, limits its use as a marker for malnutrition (Madrono *et al*, 2011). Studies have shown hypoalbuminemia to be a marker for both malnutrition and severe inflammation. During trauma inflammatory mediators' decrease albumin concentrations thereby facilitating the need for C-reactive protein levels to be monitored in order to differentiate between the nutritional and inflammatory causes of low serum albumin levels (Nieuwoudt, 2011).

2.7.2.2. Prealbumin

Prealbumin has a shorter half-life than albumin. Literature by Mosby *et al* (2009) identifies serum prealbumin and retinol binding protein as better indicators of current protein intake and nutritional status in children (Mosby *et al*, 2009).

2.7.2.3. Blood glucose levels

In malnourished patients with cancer, glucose intolerance and insulin resistance is common occurrence as the result of an increase in glucose production during the fasting state (Dare *et al*, 2013).

2.7.2.4. Hemoglobin

Hemoglobin carries oxygen and gives blood cells their red color. Hemoglobin levels therefore measure the blood's ability to carry oxygen. Low serum hemoglobin and hematocrit levels are common in children receiving chemotherapy and can also be falsely high in patients who are dehydrated (Madrono *et al*, 2011).

2.7.2.5. Hematocrit

This test measures the amount of space (volume) red cells occupy in the blood. The value is usually expressed as a percentage for example a hematocrit level of 25 means that 25% of the blood's volume is made up of red blood cells (Madrono *et al*, 2011).

2.7.2.6. White blood cell count

Children with ALL are found to have an abundance of immature white blood cells and a small number of red blood cells and platelets. The white blood cell count may be found to be normal, low or high however more often than not patients with ALL are found to present with neutropenia. The severity and prevalence of infections are inversely correlated with the absolute neutrophil count. Infections commonly occur when the neutrophil counts are low (Madrono *et al*, 2011).

2.7.2.7. Total lymphocyte count

Total lymphocyte count is a useful indicator for nutritional status and is appropriate for all age groups. Under nutrition causes immunologic changes such as a low total lymphocyte count which can increase the frequency and severity of an infection (Madrono *et al*, 2011).

2.7.2.8. Platelets (thrombocyte)

Platelets are the smallest type of blood cell and are important in blood clotting. During injury, platelets clump together to stop the bleeding at the site of injury (Madrono *et al*, 2011).

2.7.3. Clinical assessment

Clinical assessment involves the clinical examination of a patient in order to find signs and symptoms of nutrient deficiencies or excesses which include the absence or presence of oedema, cachexia, obesity, skin changes, dry mucous membranes, petechiae or ecchymoses, healing of wounds, glossitis, stomatitis and cheilosis and the evaluation of body composition- including fat and muscle stores (Mosby *et al*, 2009). Other signs of malnutrition are liver enlargement, changes in skin, hair, eyes, face, lymph glands, mouth, gums and teeth.

Table 2 below describes the signs and possible causes of a nutrition –based clinical assessment in children.

Table 2: Nutrition- focused clinical assessment in children (Pediatric Nutrition Reference Guide, 2013).

Signs	Possible nutrition related causes
Cachexia	Insufficient protein and energy
Cheilosis	Insufficient riboflavin
Delayed wound healing	Insufficient vitamin C and zinc.
Dry mucus membranes	Inadequate nutrition.
Poor fat and muscle stores	Prolonged effect of insufficient energy
Glossitis	Insufficient vitamin B12
Oedema	Insufficient protein.
Pallor	Insufficient iron, vitamin B12, vitamin C, folic acid pyridoxine.
Petechiae or ecchymoses	Insufficient vitamin C.
Stomatitis	Insufficient vitamin C.
Skin changes -Hyperpigmentation	Insufficient vitamin B12, folic acid and niacin.

2.7.4. Diet history

Diet history plays an important role in the pediatric nutrition assessment of a child as it evaluates the usual intake of the child in order to assess the nutritional adequacy of the child`s diet, eating and feeding behaviors and food consumption patterns. Information included in the diet history should include the following (Mosby *et al*, 2009):

- a. Home feeding regimes
- b. Food preferences – types, textures
- c. Food allergies and food intolerances
- d. Feeding environment
- e. Problems when chewing or swallowing
- f. Religious and cultural food habits
- g. The use of vitamin and mineral supplements
- h. Feeding skills of the child based on the child`s age

- i. Stooling habits
- j. Developmental level and sleep patterns

There are several methods in practice today for obtaining the diet history of a child and the most frequently used methods are the 24 hour recall; 3-Day food record; food frequency and calorie count. Regardless of the method used, the diet history should provide all the necessary information required to estimate the macronutrient and micronutrient content of the child's diet (Mosby *et al*, 2009).

Malnutrition is a condition that encompasses both states of a deficiency (undernutrition) and / or an excess in energy, protein and other nutrients (over-nutrition/ obesity) (Joosten *et al*, 2011). Primary undernutrition which occurs as a result of an inadequate food intake is common in children from lower socioeconomic countries and is often present at the time of ALL diagnosis (Mosby *et al*, 2009). Secondary undernutrition, on the other hand, occurs as a result of the disease state and is frequently observed in children undergoing cancer therapy which occurs as a result of treatment-related complications such as a mucositis, anorexia, nausea, vomiting and malabsorption (Mosby *et al*, 2009).

In developing countries, socioeconomic and nutritional factors play a role in the prognostic evaluation of children with ALL (Khan *et al*, 2006). Malnutrition is also more visible at diagnosis as a result of low energy intakes versus an increased energy demand whereas in developed countries children with ALL were found to show a lower prevalence of malnutrition at diagnosis. Clinical trials have also shown that undernutrition is an adverse prognostic factor in children with ALL as it decreases bone marrow reserves, leading to frequent relapses and a shortened remission phase (Khan *et al*, 2006). A study by Khan *et al* (2006) conducted on 163 pediatric patients diagnosed with ALL, of whom 102 were undernourished and 61 well nourished, reported that underweight children were less likely to complete their treatment and were therefore at a higher risk for relapses and mortality than children who were of normal weight at diagnosis.

Malnutrition and cancer cachexia are frequent consequences of pediatric cancer and its treatment. Cachexia also known as wasting syndrome is said to alter the body's compensatory mechanisms to conserve protein and decrease energy expenditure (Ladas *et al*, 2005). Cancer cachexia, though not fully understood, is characterized by wasting of lean muscle tissue, muscle atrophy, fatigue and weight loss due to early satiety (Ladas *et al*, 2005). Studies have shown that

cytokines are involved in the alteration of protein, carbohydrate and lipid metabolism which results in loss of lean muscle tissue and muscle atrophy (Nieuwoudt, 2011; Ladas *et al*, 2005).

2.8. Side-effects of cancer treatment

Pediatric cancer survivors are reported to be twice as likely to be diagnosed with hypertension, dyslipidemia, and type 2 diabetes and up to seven times more likely to experience cardiac conditions than their siblings in later life` (Rosen *et al*, 2013).

2.8.1. Overweight and obesity

Glucocorticoid therapy which forms part of the treatment protocol for ALL in children has a side effect of causing excessive weight gain which can lead to obesity. This is a common feature in children during and after treatment (Murphy *et al*, 2006). Steroids are known to initiate negative anabolic effects like an increased appetite causing an increased energy intake, accompanied by altered substrate oxidation and fat accumulation around the areas of the neck, face, waistline and arm circumference (Tan *et al*, 2013). Dexamethasone and prednisolone are two glucocorticoids that are used to treat ALL. Several studies claim dexamethasone to be more beneficial in the treatment of ALL in children; however it was also found to be more toxic than prednisolone, causing greater fat mass and weight gain in patients (Murphy *et al*, 2006). `Dexamethasone is reported to be 18 times as potent as prednisolone in suppressing short term growth and in increasing body weight` (Murphy *et al*, 2006 citing Ahmed *et al*, 2002) and `patients on dexamethasone were reported to gain significantly more weight than patients treated with an equivalent dose of prednisolone` (Murphy *et al*, 2006 citing Groot-Loonen *et al*, 1996). A study by Collins *et al* (2010) found children on ALL treatments with dexamethasone to have a greater prevalence of overweight/ obesity post induction remission. It was also observed that the most weight gain occurred during the delayed intensification phase; when glucocorticoids were used for a longer period of time as compared with other treatment phases (Tan *et al*, 2013 and Lughetti *et al*, 2012). In the national health survey study conducted in Italy by Lughetti *et al* (2012) which included 414 ALL survivors, body weight was found to significantly increase during the first year post treatment and was found to continue for 4 years post follow up in ALL survivors. Underweight and overweight are considered undesirable for children diagnosed with leukemia as it is an indicator of poor prognosis (Tan *et al*, 2013).

A study by Baillargeon *et al* (2005) reported the weight gain pattern in Hispanic children with ALL who had normal BMI at diagnosis to have a significant increase in BMI between the start of

treatment and 12 months after treatment; a moderate increase in BMI was seen between 12 to 24 months after treatment initiation and slight decrease in BMI was observed 30 months after initiation of treatment. In the same study children who were found to be overweight at diagnosis, over time showed no significant increase or decrease in BMI and girls were found to become obese between diagnosis and at the end of treatment whereas boys were found to have a gradual increase in BMI until adolescence (Baillargeon *et al*, 2005).

Past studies have suggested that the increased adiposity observed in children on ALL treatment could be linked to a decrease in growth hormone and resistance to leptin. Leptin is an adipocyte-derived hormone which normally regulates appetite and energy expenditure, however when fat mass increases (as in the case of an increased caloric intake) leptin levels were found to increase as well, resulting in leptin resistance which gives rise to obesity (Tan *et al*, 2013). Research by Arguelles and colleagues cited by Lughetti *et al* (2012) found a positive correlation between weights, BMI and skinfold measurements and serum leptin levels in children 36 months post ALL diagnosis. `Serum leptin levels were reported to be elevated 6 months post ALL diagnosis and one year after chemotherapy withdrawal` (Lughetti *et al*, 2012). Obesity and overweight are also implicated in the development of other co-morbid conditions such as type 2 diabetes, metabolic syndrome, lipid abnormalities, hypertension, cardiovascular disease and secondary cancers (Hunger *et al*, 2015). Recent research by Zhang *et al* (2014) conducted on 1742 pediatric ALL survivors found the BMI z-score for these subjects to be considerably higher than that of the standard reference population with the strongest risk for obesity occurring in pediatric ALL survivors who were off treatment for less than 5 years.

The Middle Eastern study by Al-Mulla *et al* (2014) on 1150 ALL subjects found 87.4 % of the subjects to have a normal nutritional status based on the weight for age of subjects at diagnosis and only 3.1% of subjects were found to be obese.

2.8.2. Lifestyle changes

Hospitalization to start chemotherapy; combined with impaired motor function and reduced physical activity has been linked to the high incidence of overweight and obesity in children receiving treatment for ALL (Zalina *et al*, 2009). Glucocorticoid treatment was found to reduce muscle mass and cause motor neuropathies that could persist for up to 2 years after treatment (Rosen *et al*, 2013).

2.8.3. Changes in taste

Cancer treatments such as chemotherapy and bone marrow transplantation is said to cause changes in taste perception (increased sourness and bitterness or a metallic taste) in children on treatment, this can negatively impact on the nutritional status of child therefore the assessment of energy intake is a key part of the nutritional assessment. Growth in children is said to occur as a result of a sustained increase in lean body mass and fat combined with an inadequate intake of nutrients during childhood years (Ladas *et al*, 2005).

2.8.4. Vomiting and nausea

The prolonged effects of chemotherapy often induces vomiting which has a damaging effect on the gastrointestinal tract, causing lesions and inflammation to the epithelial lining of the gut. This in turn decreases food intake and absorption. Chemotherapy -induced nausea, diarrhea and taste changes further decrease food intake especially during the induction and consolidation phase of treatment (Skolin *et al*, 2006).

2.8.5. Other gastrointestinal complications of cancer therapy

These include diarrhea, constipation, and mucositis and reduced gastrointestinal motility. Diarrhea was found to influence a child's dietary intake and absorption of nutrients which may lead to dehydration and electrolyte imbalances if untreated (Ladas *et al*, 2005). Constipation has been frequently observed in children with cancer receiving vincristine containing regimens (Ladas *et al*, 2005). A significant number of children on cancer treatment develop mucositis which results in lesions (increased risk for systemic infections), pain and oral hemorrhage which reduces their oral intake and increases their risk for under-nutrition (Owens *et al*, 2011). Most studies have found ALL patients with Down's syndrome to have more reports of mucositis during treatment than non-Down's syndrome patients (Maloney, 2011). Chemotherapy and the use of broad spectrum antibiotics in ALL patients has been reported to directly impact on the structure of the microbiota in the gut which directly affects nutrient availability and absorption and indirectly affects carbohydrate digestion and fermentation resulting in increased calorie absorption, obesity and insulin resistance (Rosen *et al*, 2013).

2.8.6. Hyperglycemia

Hyperglycemia has been identified as a complication during induction therapy in children. The use of high dose steroids, L-asparaginase, intravenous fluids and diet has been suggested to contribute to the prevalence of hyperglycemia during induction phase chemotherapy (Dane *et al*,

2013). Glucocorticoids can increase blood glucose by blocking the effects of insulin by increasing liver gluconeogenesis; L-asparaginase on the other hand decreases insulin levels. Literature by Dane *et al* (2013) has also suggested that `increased exposure to dexamethasone independently increases glucose and immune paresis with a resultant increase in infection rates`. Patients with Downs syndrome were found to have a higher incidence of treatment-related hyperglycemia during induction chemotherapy; although the reason is unclear it has been suggested that an increased tendency to islet cell autoimmunity or the reduced functioning of pancreatic reserve may be a possible cause (Dare *et al*, 2013). Chemotherapeutic agents such as methotrexate and doxorubicin have been found to alter the gut barrier which triggers the release of lipopolysaccharides produced by the gram negative bacteria in the intestine and this in turn causes metabolic endotoxemia which induces insulin resistance (Rosen *et al*, 2013).

2.8.7. Osteoporosis

Bone mass is often reduced at diagnosis of ALL and falls dramatically during the first 6 months of chemotherapy (Salim *et al*, 2013). The long term use of corticosteroids and antiemetics reduce the synthesis of collagen causing easy bruising, decreased absorption and bone loss giving rise to osteomalacia, osteoporosis and skeletal anomalies in children receiving treatment for ALL (Rosen *et al*, 2013). Literature by Salim *et al* (2014) noted that osteopenia and osteoporosis was observed during all phases of ALL treatment and throughout the post treatment period for up to 20 years. In total 39% of children with ALL had fractures by completion of their treatment. The fracture rate in children with ALL was found to be 6 times more than in healthy children up to 12 months following chemotherapy (Salim *et al*, 2014 citing Rogalsky *et al*, 1986).

2.9. Nutrition support in pediatric cancer

Studies report approximately 46 % of children with cancer experience malnutrition as a result of the disease and of complications that may arise as a result of chemotherapy such as xerostomia; mucositis; food aversion resulting from vomiting; and nephrotoxicity which causes increased nutrient losses (Bauer *et al*, 2011; Owen *et al*, 2013). Steroids induce hyperglycemia, fluid retention, weight gain, altered body composition, electrolyte and imbalances and increase the long term requirements for calcium, zinc, vitamin C and vitamin D in children on ALL treatment (Owens *et al*, 2013).

Early identification of undernourished patients from diagnosis and throughout the lengthy treatment process is essential to ensure patients receive their recommended caloric intake based

on their current condition and age, in spite of the negative effects of intense cycles of chemotherapy (Bauer *et al*, 2011). Nutritional support in childhood cancer is therefore aimed at preventing or reversing the effects of protein energy malnutrition to sustain and promote normal growth; enhancing therapy; decreasing the complications of cancer treatment; improving the immune status of the child; treating nutritional deficiencies and promoting normal eating behavior in order to improve the quality of life (Selwood *et al*, 2010; Gonzalez *et al*, 2004). Table 3 below describes the short term and long term consequences of malnutrition on pediatric cancer patients (Bauer *et al*, 2011).

Table 3: Short term and long term consequences of malnutrition on pediatric cancer patients (Bauer *et al*, 2011).

SHORT TERM CONSEQUENCES	LONG TERM CONSEQUENCES
<ul style="list-style-type: none"> • Wasting of muscle and fat mass. • Decreased tolerance of chemotherapy. • Unfavorable response to chemotherapy. • Treatment delays. • Fatigue. • Biochemical disturbances (anemia, hypoalbuminemia). • Delayed recovery of normal bone marrow. • Changes in body composition. • Drug dose alterations • Decreased quality of life. • Greater levels of psychological distress. • Higher susceptibility to infections. 	<ul style="list-style-type: none"> • Growth impairment resulting in reduced final height. • Impact on motor, cognitive and neurodevelopmental impairment. • Risk for metabolic syndrome. • Risk for secondary cancers. • Risk for aging. • Increased mortality rate. • Retardation of skeletal maturation. • Abnormal bone mineral density. • Decreased quality of life.

Currently there is a lack of internationally specific nutrition guidelines for pediatric cancer patients. This makes nutritional support a challenge as cancer treatments affect a child`s appetite, tolerance to food and fluids and utilization of food to promote and maintain normal growth. Several tools have been identified to estimate the energy and nutrient needs of a child with

cancer which includes age-appropriate Dietary Reference Intakes (DRI) and The World Health Organization's equations for basal metabolic rate. Literature by Nieuwoudt (2011) quotes The Children's Oncology Committee recommendation to increase the calorie needs for a child undergoing cancer treatment by approximately 20% above their normal requirements and to increase their protein needs by 50% above their normal requirements.

Nutrition support guidelines by Bauer *et al* (2011) to treat undernutrition recommends the following:

2.9.1. Oral feeding

Oral feeding is recommended as the first route of feeding, especially for children with low nutrition risk who are able to consume sufficient nutrients. Dietary counselling with the input of a registered dietitian is important to enhance the oral intake of the child and an individualized approach with family participation is vital to enable families to overcome the side-effects of cancer treatment (a loss of appetite, nausea, vomiting, mucositis and stomatitis) which negatively impact a child's oral intake. The majority of children was found to require a balanced age-appropriate diet with food fortification to make foods and snacks more energy dense with or without the addition of high calorie oral nutritional supplements and nutrition education on eating problems related to the side-effects of treatment. In a hospital setting procedure and treatment timings were found to interfere with mealtimes. Patients were also admitted for long periods of time which made meals repetitive and boring. One study addressed this problem by providing a cook to order service with individualized age-appropriate portion sizes, child-friendly cutlery and crockery and the provision of snacks throughout the day for children who cannot tolerate full meals (Bauer *et al*, 2011).

Children undergoing chemotherapy often experience taste and smell changes. These chemosensory changes can affect the perceived flavor of oral nutritional supplements frequently prescribed. Research regarding the palatability of oral nutritional supplements in pediatric cancer patients undergoing chemotherapy is lacking. A study by Ijpma *et al* (2016) conducted on 60 adult patients with gastric cancer found the palatability of milk-based vanilla oral nutritional supplement to decrease over time, namely before, during and after chemotherapy; however the palatability of a milk based strawberry oral nutritional supplement was preferred before, during and after chemotherapy. It was therefore the recommendation of this study to offer a variety of types and flavors to malnourished cancer patients throughout the treatment period.

2.9.2. Enteral feeding

Enteral nutrition by means of a nasogastric tube feed (NGT) or percutaneous endoscopic gastrostomy (PEG) or jejunostomy has been shown to be successful in reversing malnutrition and maintaining an adequate nutritional status in children with a `high risk for malnutrition` and a poor oral intake and who are unable to meet their nutritional needs via the oral route (Nieuwoudt, 2011). Enteral nutrition as a sole source of nutrition or as an overnight enteral feed has been found to be safe and effective in the home environment for pediatric cancer patients who are unable to consume an adequate oral diet. It has a lower risk for infection, preserves gut integrity and reduces bacterial translocation and is thus recommended since it is more practical and safer than parenteral nutrition (Bauer *et al*, 2011 citing Rickard *et al*, 1986).

Multiple studies have reported success in improving the nutritional status of children by means of nasogastric tube feeds, during intensive cancer treatments including bone marrow transplantation with minimal complications (Selwood *et al*, 2011 citing De Swarte-Wallace *et al*, 2001; Pietsch *et al*, 2000; den Broeder *et al*, 1998). Enteral formulas containing intact protein were found to be well tolerated during chemotherapy cycles however following chemotherapy protein hydrolysate and amino acid based formulas were found to be better tolerated as children may display reduced gastrointestinal motility with a risk for malabsorption (Selwood *et al*, 2011 citing Ward, 2003).

The recommended criteria for starting enteral feeding according to Bauer *et al* (2011) are:

- Weight two centiles below height centile.
- Percentage weight for height < 90% of the ideal.
- Decrease in current percentiles for weight or height of two centiles.
- Total weight loss > 5% since diagnosis.
- Reduced oral intake of < 70% of estimated average requirement for > 5 days.

Nasogastric and nasoduodenal feeding is recommended for short duration feeding as these feeding devices cause nasal discomfort, recurrent pulmonary aspiration and easy tube dislodgment (El- Matary, 2008). For long duration feeding gastrostomy (a tube is inserted directly into the stomach through an opening in the anterior abdominal wall) or jejunostomy (a tube is inserted directly into the small intestine) feeding tubes are recommended. Enteral nutrition is however discouraged in cancer patients with mucositis and enteral tube insertion is not recommended in children with neutropenia or thrombocytopenia as these children have an

increased risk of bleeding during feeding tube insertion (El- Matary, 2008). A study conducted by Barbosa *et al* (2012) found malnourished children with cancer to show improved growth parameters, in terms of z-scores for weight-for-age and BMI, during the administration of enteral nutrition. The side-effects of cancer treatments such as nausea, vomiting and diarrhea pose limitations to the use of enteral nutrition support in cancer patients. The addition of prokinetic agents and post pyloric feeding has been found to minimize vomiting (Barbosa *et al*, 2012). A multidisciplinary team is important to ensure adequate nutritional support for children and adults with cancer.

2.9.3. Total parenteral nutrition

Total parenteral nutrition (TPN) is recommended for patients whose enteral feeding regimes are unable to provide adequate nutrients. Parenteral nutrition is used primarily for nutrition support when the gastrointestinal tract cannot be used. The general consensus from a number of studies conclude that parenteral nutrition should be reserved for children who are unable to tolerate enteral feeding as a result of an abnormal gastrointestinal function either related to the treatment or the tumor. In pediatric cancer patients it is mainly used for those with severe mucositis or neutropenic colitis (Nieuwoudt, 2011; Ladas *et al*, 2005).

The choice of central versus peripheral parenteral nutrition depends on the length of therapy. Peripheral parenteral nutrition is recommended for short term therapy which usually lasts between 7 to 10 days. Parenteral nutrition therapy requires more monitoring than enteral nutrition and carries the highest incidence of septic complications (Nieuwoudt, 2011). Most studies aiming to assess the effectiveness of TPN in pediatric cancer patients have found a positive effect on reversing malnutrition during the initial phase of treatment (Andrassy *et al*, 1998; Rickard *et al*, 1986; Donaldson *et al*, 1982). TPN is associated with liver disease which remains a dreaded complication of parenteral nutrition in children. The risk of refeeding syndrome remains a serious complication in aggressive nutritional rehabilitation (by enteral and / or parenteral route) in severely malnourished children with cancer (Nieuwoudt, 2011). Literature by Nieuwoudt (2011) report that `a recent Cochrane Review (to determine the effects of enteral and parenteral support in children with cancer undergoing chemotherapy) found limited evidence to suggest that parenteral nutrition is more effective than enteral nutrition in well-nourished children and young people with cancer undergoing chemotherapy`. Clinical studies reported by Andrassy *et al* (1998) found well-nourished children receiving `abdominal radiation and

intensive chemotherapy to demonstrate improved maintenance of body weight, fat and muscle reserves when administered TPN in contrast to those on oral diets`.

2.9.4. Vitamin and mineral supplements

Some authors suggest that vitamin and mineral supplements are needed to compensate for the reduction in antioxidants which occurs as a result of chemotherapy. It has been suggested that the use of antioxidants during chemotherapy could interfere with the action of chemotherapeutic drugs on the tumor and thereby reduce the efficacy of the treatment (Rickard *et al*, 1986). Therefore the use of antioxidants in cancer treatment regimens remains controversial as studies so far have been inadequate and inconsistent to guide clinical practice (Nieuwoudt, 2011).

The use of multivitamin and mineral supplement is recommended in the case of poor oral intake in children with cancer, however children who are eating a variety of foods in their diet will not benefit from such a supplement. Vitamins when given in excess cause toxicity therefore administration of mega doses of a single vitamin are not encouraged. Children receiving nutritionally complete sip feeds and those on a enteral feeding regimes will not require additional vitamins as their requirements will be met by the sip feed / formula (Nieuwoudt, 2011).

2.9.5. Glutamine supplementation

`Glutamine supplementation has been recommended in the relief of severe mucositis however more research in this area is needed` (Nieuwoudt, 2011). There has also been inconsistent or unconfirmed evidence regarding the use of pre and probiotics in the nutritional management of pediatric cancer patients and the American Academy of Pediatrics has recommend that the use of pre and probiotics be avoided in seriously or chronically ill children until the safety of administration has been established (Nieuwoudt, 2011).

2.10. Summary

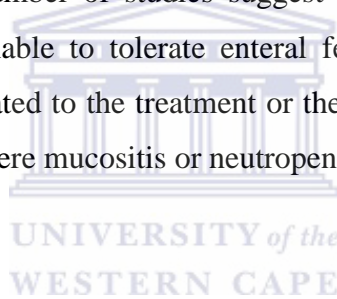
The literature suggests that approximately 46 % of children with cancer experience malnutrition as a result of the disease and the complications that may arise as a result of chemotherapy such as xerostomia; mucositis; food aversion resulting from vomiting; and nephrotoxicity which causes increased nutrient losses. Therefore early identification of undernourished patients from diagnosis and throughout the lengthy treatment process is essential to ensure patients receive their recommended caloric intake based on their current condition and age, in spite of the negative effects of intense cycles of chemotherapy. Currently there is a lack to internationally specific nutrition guidelines for pediatric cancer patients. This makes nutritional support a

challenge as cancer treatments affect a child's appetite, tolerance to food and fluids and utilization of food to promote and maintain normal growth.

Oral feeding is recommended as the first route of feeding, especially for children with low nutrition risk who are able to consume sufficient nutrients. Dietary counselling with the input of a registered dietitian is important to enhance the oral intake of the child and an individualized approach with family participation is vital to enable families to overcome the side-effects of cancer treatment (a loss of appetite, nausea, vomiting, mucositis and stomatitis) which negatively impact a child's oral intake.

Enteral nutrition by means of a nasogastric tube feed (NGT), percutaneous endoscopic gastrostomy (PEG), jejunostomy has been shown to be successful in reversing malnutrition and maintaining an adequate nutritional status in children with a 'high risk for malnutrition', poor oral intake and who are unable to meet their nutritional needs via the oral route

The general consensus from a number of studies suggest that parenteral nutrition should be reserved for children who are unable to tolerate enteral feeding as a result of an abnormal gastrointestinal function either related to the treatment or the tumor. In pediatric cancer patients it is mainly used for those with severe mucositis or neutropenic colitis.



CHAPTER 3

METHODOLOGY



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METHODOLOGY

The study design, study sample, methods used to collate and analyze the data to achieve the aims and objectives of the study is presented in this chapter.

3.1. Study design

A retrospective descriptive case study design was used.

3.2. Study population and study sample

The study population consisted of electronic medical records of patients aged between 1-14 years who was newly diagnosed with Acute Lymphoblastic Leukemia (ALL) and admitted to Sheikh Khalifa Medical City for treatment during the period 1 January 2012 and 31 Dec 2014. The study sample consisted of 20 electronic medical records of patients who were admitted and completed all phases of treatment (induction, consolidation, delayed intensification and maintenance) at Sheikh Khalifa Medical City during this time frame (1 January 2012 and 31 Dec 2014).

Inclusion criteria:

All pediatric patients between the ages of 1-14 years old newly diagnosed with acute lymphoblastic leukemia (ALL) and received all phases of chemotherapy treatment at Sheikh Khalifa Medical City, between 1 January 2012 to 31 December 2014.

Exclusion Criteria:

All pediatric patients below the age of 1 year old or above the age of 14 years old newly diagnosed with acute lymphoblastic leukemia (ALL) and received treatment at Sheikh Khalifa Medical City, between 1 January 2012 to 31 December 2014.

All pediatric patients between the ages of 1-14 years old newly diagnosed with acute lymphoblastic leukemia (ALL) and who failed to complete all stages of treatment at Sheikh Khalifa Medical City, between 1 January 2012 to 31 December 2014.

3.3. Data collection method

Identification of suitable participants began through a review of each potential study participant's electronic medical record.

Data was collected and recorded on a data collection form (Appendix III) from the electronic medical record for each suitable participant for the following at admission and during the full

duration of all phases of cancer treatment namely induction, consolidation, interim maintenance, delayed intensification and maintenance:

- Age
- Gender
- Date of diagnosis (dd/mm/yyyy)
- Symptoms on diagnosis
- Cancer diagnosis (type, subtype, new diagnosis).
- Anthropometric measurements (weight, length/ height, head circumference).
- Biochemical values (visceral proteins, blood glucose levels, hemoglobin, hematocrit, lymphocyte count).
- Clinical assessment (stomatitis, anemia, mucositis).
- Diet history (home feeding regimes; consumption of daily requirements; food preferences – types, textures; food allergies, food intolerances; food aversions; use of oral nutritional supplements; treatment-related side-effects).
- Systemic related side-effects (nausea; vomiting; diarrhea; anorexia; appetite changes; taste changes; physical activity level; depression).
- Dietary requirements (age and gender related nutritional requirements for energy, protein, fat and fluids).
- Indications for nutritional support (oral feeding; enteral feeding; parenteral feeding).

Anthropometry:

Patient`s weight and length/height measurements were recorded at diagnosis and at the start and end of each treatment phase from the patient`s electronic medical record. Patient weights were recorded in kilograms (kg) with a precision of 0.1kg using a SECA digital scale. The weighing scales on the hospital wards are calibrated monthly as per hospital policy. Young children below the age of 24 months old were weighed unclothed and older children above the age of 24 months old were weighed with clothes (no shoes) and weight was thereafter adjusted for clothes. The length/ height was measured in centimeters; young children (below 24 months old) were measured in the recumbent position and older children (24 months and older) were measured standing up. The head circumference of children (12 – 36 months old) was measured in centimeters, using a tape measure around the largest part of the head. The body mass index (BMI) was calculated with the most current weight and height measurements using the following formula:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height}^2 (\text{m}^2)}$$

The anthropometric measurements which were included in the electronic medical record of each patient included in the study were electronically plotted on the World Health Organization growth charts according to the age and gender of each patient.

Biochemical indices of nutritional status

Biochemical/ laboratory values namely visceral proteins - total protein (g/L), albumin (g/L); blood glucose levels (millimole/L); hemoglobin (g/L); hematocrit (L/L);, lymphocyte count (%); white blood cell count was measured at various stages of treatment as per the existing treatment protocols for ALL.

Diet history and Nutritional interventions

Information on the diet history of patients namely 24 hour dietary recall; food frequency lists; home feeding regimes; food preferences to include food likes and dislikes, food textures, feeding environment, food allergies, food intolerances, food consumption patterns, dietary requirements, treatment-related side-effects and nutritional support interventions were collected from the dietitian notes in the patients file.

3.4. Analysis and interpretation of the data

The data collected on the data collection form (Appendix IV) was entered into Microsoft Excel 2010 spreadsheet (Addendum V).

The weights and length/ heights of participant recorded in the electronic medical records was plotted on the World Health Organization growth charts and then converted to z-scores. Z-scores are a numerical summary of each child's placement relative to an appropriate reference population (Collins et al, 2010). A significant growth abnormality was evident if a participant's z-score for weight-for-age and/or length/height-for-age and/or weight-for length/height and/or BMI-for-age was more than 2 standard deviations greater than or less than the appropriate mean (Bauer et al, 2011) or if a participant experienced a weight loss of greater than 5% of body weight over a period of one month even though participant was not classified as undernourished by anthropometric parameters (Bauer et al, 2011; Jeejeebhoy and Keith, 2005).

The biochemical indices of nutritional status were captured from each participant's electronic medical record and compared and interpreted with reference values in context of the age and sex of each participant.

The prescriptions of nutritional interventions were captured from each participant's electronic medical record and compared and interpreted in comparison to the biochemical indices, anthropometric status and dietary intake of each participant.

All the data involving changes in anthropometrics, biochemistry, diet history and nutritional interventions, from each case study, from diagnosis and through all stages of treatment (induction, consolidation, interim maintenance, delayed intensification and maintenance) was screened and compared with reference values in the context of the age and sex of participants and evidence based nutritional guidelines; in order to document the outcomes of the medical nutrition treatment provided. This was done to determine whether the nutrition interventions provided during each treatment phase had an impact on the nutritional status of each case study. These results were then used to develop a nutrition support protocol for children with Acute Lymphoblastic Leukemia at SKMC in order to reduce the risk of nutrition related problems. This protocol will serve to standardize the feeding practices and achieve the nutritional goals of children on ALL treatment.

3.5. Validity and reliability

It is recognized that the validity and reliability of the data depends on the completeness, correctness and accuracy of the recording in the electronic patient medical records. The data recording form was piloted using the electronic patient files of children with Acute Myeloid Leukemia (AML). The researcher was the only person entering the data into Excel and double entry was done to ensure reliability.

3.6. LIMITATIONS OF THE STUDY

The study is limited by the detail, completeness, quality and accuracy of information from electronic patient medical files.

3.7. ETHICAL CONSIDERATIONS

Ethics approval was obtained from the Sheikh Khalifa Medical City Research Ethics Committee in order to assess the patient's electronic medical files (Appendix I), as well as the University of Western Cape Ethics Committee (Appendix II). There was no personal interaction with patients

as data was obtained from each patient's electronic medical record. No separate individual patient consent was needed to conduct this research, but all data was treated as confidential and code numbers were used instead of patients' names, also no identifiable data was used in the collection of data or in the publication of this study.



CHAPTER 4

RESULTS



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Results

The results of the 20 newly diagnosed ALL subjects admitted between 1 January 2012 and 31 December 2014 to Sheikh Khalifa Medical City (Abu Dhabi, UAE) obtained from the subject's electronic medical record are presented in this chapter.

4.1. Clinical characteristics at diagnosis

The most common clinical characteristics reported at diagnosis were fever, purpuric bruises, flu-like symptoms, anemia, weight loss, bone pain and epistaxis.

4.2. Demographic profile and type of ALL of the study sample

The table below describes the demographics of the 20 subjects who participated in this study by sex, age group and type of ALL at diagnosis.

Table 4: The demographics of 20 newly diagnosed ALL subjects by sex, age group and type of ALL at diagnosis

Age in years	No. of males	No. of females	No. of subjects with Pre B Cell ALL	No. of subjects with B-cell ALL	No. of subjects with T-cell ALL
1-2	7	1	2	6	0
3-4	5	2	2	5	0
5-6	0	1	1	0	0
7-8	1	0	0	0	1
9-10	0	1	0	1	0
11-12	2	0	1	0	1

No: number

There was a male predominance amongst subjects diagnosed with ALL with 15 subjects being male (75%) and 5 subjects being female (25%).

ALL is classified according to the type of lymphocyte (B cell or T cell) the leukemic cells are found in and the degree of maturity of the cells (American Cancer Association, 2015). Eighteen subjects were diagnosed with B and Pre B cell ALL (90%) and 2 subjects were diagnosed with T-cell ALL (10%).

At diagnosis, risk groups are used to classify ALL instead of stages. In this study 16 subjects were diagnosed with standard risk ALL (80%) [Initial white blood cell count less than 50 000] and 4 subjects were diagnosed with high risk ALL (20%) [Initial white blood cell count was greater than 50 000]. Four subjects (20%) were diagnosed with high risk ALL (all males) with

two subjects belonging to the 11-12 year age group and 2 subjects belonging to the 3-4 year age group. One subject with high risk ALL had testicular involvement.

4.3. Anthropometric z-scores and prevalence of malnutrition

Anthropometric measurements for all subjects at diagnosis and at the start and end of each treatment phase were recorded as z-scores for weight-for-age, length/height-for-age and BMI-for-age on the World Health Organization (WHO) growth charts. A growth abnormality was deemed significant if a subject's z-score for any of the above mentioned anthropometric measurements, was found to be more than 2 standard deviations greater than or less than the appropriate mean. Table 4 and table 5 below shows the prevalence of malnutrition at diagnosis and at the start and end of each treatment phase.

Table 5: The prevalence of malnutrition in subjects based on anthropometry (expressed as percentage of subjects) newly diagnosed with ALL at diagnosis and at the start of each treatment phase

Indicators	D	I	C	IM	DI	M
Weight-for-age z-score < -2SD (Underweight)	0	0	0	0	0	5
Weight-for-age z-score > 2SD (Overweight)	0	0	5	0	0	0
Weight for height z-score < -2SD (Wasting)	0	0	0	0	5	0
Weight for height z-score > 2SD (Overweight)	0	0	10	0	0	5
Height-for-age z-score < -2SD (Stunting)	5	5	10	10	5	5
Height-for-age z-score > 2SD	0	0	0	5	5	0
BMI-for-age z-score < -2SD (Underweight)	5	5	0	5	5	0
BMI-for-age z-score > 2SD (Overweight)	5	10	5	0	0	5

D: Diagnosis, I: Induction treatment, C: Consolidation treatment, IM: Interim Maintenance treatment, DI: Delayed Intensification treatment, M: Maintenance treatment, SD: standard deviation.

Table 6: The prevalence of malnutrition in subjects based on anthropometry (expressed as `percentage of subjects`) newly diagnosed with ALL at the end of each treatment phase

Indicators	I	C	IM	DI	M
Weight-for-age z-score < -2SD (Underweight)	0	0	5	0	0
Weight-for-age z-score > 2SD (Overweight)	5	0	0	0	0
Weight for height z-score < -2SD (Wasting)	0	0	5	0	0
Weight for height z-score > 2SD (Overweight)	10	0	0	0	15
Height-for-age z-score < -2SD (Stunting)	5	10	10	5	5
Height-for-age z-score > 2SD	0	0	5	5	10
BMI-for-age z-score < -2SD (Underweight)	0	0	5	5	0
BMI-for-age z-score > 2SD (Overweight)	10	0	0	0	10

I: Induction treatment, C: Consolidation treatment, IM: Interim Maintenance treatment, DI: Delayed Intensification treatment, M: Maintenance treatment, SD: standard deviation.

4.3.1. Weight-for-age z-scores

At diagnosis: All subjects (100 %) were found to have normal weight-for-age z-scores.

Induction treatment: at the start and end of induction treatment all subjects (100%) were found to be of normal weight-for-age.

Consolidation treatment: at the start of consolidation treatment one subject (5%) was found to be overweight (this subject was male from the 7-8 year age group and diagnosed with standard risk T-cell ALL). At the end of treatment all subjects (100%) including the subject that was overweight at the start of treatment were found to be of normal weight-for-age.

Interim maintenance treatment: at the start of interim maintenance treatment all subjects (100%) were found to be of a normal weight-for-age. At the end of treatment one subject (5%) with a normal weight at the start of treatment was found to be underweight (this subject was a male from the 1-2 year age group and diagnosed with standard risk Pre B cell ALL).

Delayed intensification treatment: at the start and end of delayed intensification treatment all subjects (100%) were found to be of a normal weight-for-age. The subject that was found to be underweight at the end of the last treatment phase was able to gain weight as a result of a treatment delay (for a low neutrophil count) between treatment phases which lasted 10 days.

Maintenance treatment: at the start of maintenance treatment one subject (5%) was found to be underweight (this subject was a male from the 1-2 year age group and diagnosed with standard risk Pre B cell ALL and was also found to be underweight-for-age on completion of interim maintenance treatment). At the end of treatment all subjects (100%) were found to be of normal weight-for-age.

4.3.2. Weight- for-height z-scores

At diagnosis: at diagnosis all subjects (100%) were found to be of normal weight for height.

Induction treatment: at the start of induction treatment all subjects (100%) were found to be of normal weight for height. At the end of treatment two subjects (10%) were found to be overweight; both subjects grew in weight but not in height during this treatment phase therefore weight for height z-scores values found them to be overweight at the end of treatment. One subject was male from the 3-4 year age group diagnosed with standard risk Pre B cell ALL and the other subject was male from the 2-3 year age group diagnosed with standard risk B cell ALL.

Consolidation treatment: at the start of consolidation treatment two subjects (10%) were found to be overweight however only one of these two subjects was overweight at the end of induction treatment; the other subject failed to grow in height during induction treatment which resulted in him being overweight. At the end of treatment all subjects (100%) were found to be of normal weight for height. The two subjects that were overweight at the start of treatment failed to grow in weight during this treatment phase therefore resulting in normal measurements.

Interim maintenance treatment: at the start of interim maintenance treatment all subjects (100%) were found to be of normal weight for height. At the end of treatment one subject (5%) was found to be wasted; this occurred as a result of the parent insisting that enteral feeds be stopped mid-treatment. Episodes of mucositis and stomatitis prevented the subject from improving his oral intake. This subject was male from the 2-3 year age group diagnosed with standard risk B cell ALL.

Delayed intensification treatment: at the start of delayed intensification treatment one subject (5%) was found to be wasted; this subject was also wasted at the end of the previous treatment

phase. At the end of treatment all subjects (100%) were found to be of normal weight for height. The subject that was stunted at the start of treatment was restarted on enteral feeds as the sole source of nutrition at the start of this treatment phase which improved his growth parameters.

Maintenance treatment: at the start and end of maintenance treatment one subject (5%) was found to be overweight; this subject failed to grow in height due to congenital issues (Downs syndrome). At end of treatment a total of three subjects (15%) were found to be overweight (this includes the subject with Downs syndrome mentioned above and the other two subjects were found to gain between 15.2-20.6 % weight gain during this treatment phase. The subject with Downs syndrome was male from the 3-4 year age group diagnosed with standard risk B cell ALL; with regards to the other 2 subjects: both were male with one from the 3-4 year age group with high risk Pre B cell ALL) and the other was from 2-3 year age group with standard risk B cell ALL.

4.3.3. BMI-for-age z-score

At diagnosis: one subject (5%) was found to be underweight (this subject was male from the 1-2 year age group diagnosed with standard risk B cell ALL) and one subject (5%) was found to be overweight (this subject was male from the 7-8 year age group diagnosed with standard risk T cell ALL).

Induction treatment: at the start of induction treatment one subject (5%) was found to be underweight (this subject was male from the 1-2 year age group diagnosed with standard risk B cell ALL). Two subjects (10%) were found to be overweight at the start of treatment; one subject was male from the 7-8 year age group diagnosed with standard risk T cell ALL and the other subject was male from the 1-2 year age group diagnosed with standard risk Pre B cell ALL). At the end of treatment two subjects (10%) were found to be overweight; both subjects were of normal BMI at the start of treatment and during the course of treatment one followed a standard diet for age diet and the other followed a high calorie high protein diet plus consumed an oral nutritional supplement throughout treatment. The subject that was overweight at diagnosis was of normal weight at the end of treatment due to poor weight gain and treatment-related side-effects during treatment. One subject was male from the 3-4 year age group diagnosed with standard risk Pre B cell ALL and the other subject was male from the 2-3 year age group diagnosed with standard risk B cell ALL.

Consolidation treatment: at the start of consolidation treatment one subject (5%) was found to be overweight; this subject was also found to be overweight at the end of induction treatment; this subject was male from the 2-3 year age group diagnosed with standard risk B cell ALL. At the end of treatment all subjects (100%) were found to have normal BMI-for-age z –scores.

Interim maintenance treatment: at the start of interim maintenance treatment one subject (5%) was found to be underweight due to poor gain in height during consolidation treatment; this subject was male from the 1-2 year age group diagnosed with standard risk B cell ALL. At the end of treatment this subject continued to be underweight in spite of initiating enteral feeds during the consolidation phase of treatment.

Delayed intensification treatment: at the start of delayed intensification treatment one subject (5%) was identified as being underweight; this subject was also identified as underweight during interim maintenance treatment and this subject was also underweight at the end of this treatment phase in spite of initiating enteral feeds during the consolidation phase of treatment. This subject was male from the 1-2 year age group diagnosed with standard risk B cell ALL.

Maintenance treatment: at the start of maintenance treatment one subject (5%) was found to be overweight; this subject was of normal BMI during the previous treatment phases; this subject was male with Down's syndrome from the 3-4 year age group diagnosed with standard risk B cell ALL. At the end of treatment two subjects (10%) were found to be overweight; one of which was overweight at the start of treatment. The other subject who was found to be overweight at the end of maintenance treatment had a normal BMI at the start of treatment but showed a 20.6% gain in weight at the end of treatment; subject was male from the 2-3 year age group diagnosed with standard risk B cell ALL. This subject was also started on a high calorie high protein diet with a high calorie high protein oral nutritional supplement from the consolidation phase of treatment until the end of delayed intensification treatment.

4.3.4. Height-for-age z-scores

At diagnosis: one subject (5%) was found to be stunted. This subject was male from the 1-2 year age group diagnosed with standard risk Pre B cell ALL.

Induction treatment: at the start and end of induction treatment one subject (5%) was found to be stunted. This subject was also stunted at diagnosis.

Consolidation treatment: at the start and end of consolidation treatment two subjects (10%) were found to be stunted. One of the two subjects was stunted from diagnosis (this subject was male

from the 1-2 year age group diagnosed with standard risk Pre B cell ALL). The other subject was a one year old male diagnosed with standard risk B-cell ALL who failed to improve his growth due to treatment-related side-effects (anorexia accompanied by a food aversion). This negatively affected his nutritional intake in spite of commencing enteral feeds during the consolidation phase.

Interim maintenance treatment: during interim maintenance treatment the two subjects (10%) who were found to be stunted at the end of the last treatment phase failed to grow in height during this phase and continued to be stunted. Also at the start and end of this treatment phase one subject (5%) was found to have a height-for-age above the norm (this subject was male from the 2-3 year age group diagnosed with standard risk B cell ALL). This subject was also receiving enteral feeding with a high calorie high protein formula as his sole source of nutrition during this treatment phase.

Delayed intensification treatment: at the start and end of delayed intensification treatment one subject (5%) was found to be stunted; this subject failed to grow in height since diagnosis. At the start and end of treatment one subject (5%) was found to have a height-for-age above the norm; this subject continued to have above normal height-for-age measurements since the last treatment phase and was receiving enteral feeding with a high calorie high protein formula as his sole source of nutrition since interim maintenance treatment.

Maintenance treatment: at the start and end of maintenance treatment one subject (5%) was found to be stunted; this subject failed to grow in height since diagnosis. At the end of treatment two subjects (10%) were found to have an above normal height-for-age; one of the two subjects were found to have an above normal height-for-age measurement since the interim maintenance phase and the other subject experienced a growth spurt during this phase as he was started on an enteral feed during the interim maintenance phase for having a poor oral intake (this subject was also male from the 2-3 year age group diagnosed with standard risk B cell ALL).

In general, the distribution of anthropometric z-scores showed the highest percentage of stunting during the start and the end of the consolidation (10%) and the interim maintenance (10%) phases. A low percentage of subjects were underweight during all phases of treatment. The highest percentage of overweight was at the start (10%) and the end (10%) of induction treatment and at the end of maintenance treatment (10%).

4.4. Weight changes

In this study, weight loss expressed as a percentage of body weight provided a more accurate estimate of the true significance of weight loss in subjects during cancer treatment (chemotherapy). A weight loss of greater than 5% of body weight over a period of one month is considered a sign of nutritional deprivation even when the subject is not classified as undernourished by anthropometric parameters (Bauer et al, 2011; Jeejeebhoy and Keith, 2005).

Table 7 below represents the number of subjects that experienced weight and height changes at the end of each treatment phase.



Table 7: The number of subjects with weight and height changes at the end of each treatment phase

Weight and height changes	Induction Treatment	Consolidation Treatment	Interim Maintenance Treatment	Delayed Intensification Treatment	Maintenance Treatment
Number of subjects with weight loss	5	16	13	4	3
Number of patients with > 5% weight loss	3	8	5	0	0
Number of patients with weight gain	14	3	6	15	15
Number of subjects with > 5% weight gain	12	1	1	7	8
Number of subjects with weight unchanged	1	1	1	1	2
Number of subjects with gain in height	8	7	17	12	15
Number of subjects with height unchanged	12	13	3	8	5
Number of subjects with gain in weight and height	5	2	6	8	11

Subjects experienced the highest weight loss during the consolidation phase and interim maintenance phases. The highest weight gain in subjects was observed during the induction, delayed intensification and maintenance phases of treatment. Subjects were found to show a gain in height during the interim maintenance, delayed intensification and maintenance phases of treatment.

Induction phase

Weight-loss during induction treatment

At the end of this treatment phase five subjects (25%) experienced a weight loss. One subject was male from the 1-2 year age group on treatment for standard risk ALL and was on a high calorie high protein diet plus an oral nutritional supplement, one subject was male from the 3-4 year age group on treatment for standard risk ALL and received a high calorie high protein diet plus an oral nutritional supplement, one subject was male from the 11-12 year age group on treatment for high risk ALL and was on a high calorie high protein diet plus an oral nutritional supplement and one subject was male from the 11-12 year age group on treatment for high risk ALL and was on a normal calorie normal protein diet plus an oral nutritional supplement. There were multiple reasons for the weight loss which included anorexia, appetite changes, nausea, vomiting, taste changes and diarrhea.

The subject with the highest weight loss percentage (10.9%) was a male belonging to the 1-2 year age group and was on a high calorie high protein diet plus an oral nutritional supplement.

Three subjects lost more than 5% of their body weight at the end of this treatment phase. One subject was male from the 1-2 year age group on treatment for standard risk ALL and was on a high calorie high protein diet plus an oral nutritional supplement, one subject was male from the 3-4 year age group on treatment for standard risk ALL and received a high calorie high protein diet plus an oral nutritional supplement and one subject was male from the 11-12 year age group on treatment for high risk ALL and received a high calorie high protein diet plus an oral nutritional supplement.

Weight gain during induction treatment

Fourteen subjects experienced a weight gain at the end of this treatment phase. Two of the fourteen subjects were on a normal calorie normal protein diet, both subjects were male from the 1-2 year age group on treatment for standard risk ALL. Seven of the fourteen subjects were on a high calorie high protein diet plus an oral nutritional supplement. Four of the seven subjects were from the 1-2 year age group (three were males and one was a female) on treatment for standard risk ALL, two of the seven subjects were from the 3-4 year age group (one was a male and one was a female) on treatment for standard risk ALL and one of the seven subjects was female from the 9-10 year age group on treatment for standard risk ALL. One of the fourteen subject was on a normal calorie normal protein diet plus an oral nutritional supplement from the 5-6 year age group (female) on treatment for standard risk ALL. Four of the fourteen subjects were on a high

calorie high protein diet plus an oral nutritional supplement plus enteral feed. Three subjects were from the 1-2 year age group (all subjects were male) on treatment for standard risk ALL and one subject was a male from the 3-4 year age group on treatment for high-risk ALL.

Five of the fourteen subjects experienced a gain in weight and height at the end of this treatment phase. Three of the five subjects were on a high calorie high protein diet plus an oral nutritional supplement, one subject was a female from the 1-2 year age group and on treatment for standard risk ALL, one subject was a male from the 3-4 year age group and on treatment for standard risk ALL and one subject was a female from the 9-10 year age group and on treatment for standard risk ALL. One of the five subjects was a female on a normal calorie normal protein diet plus an oral nutritional supplement from the 5-6 year age group and on treatment for standard risk ALL. One of the five subjects was male on a high calorie high protein diet plus an oral nutritional supplement plus enteral feed from the 1-2 year age group and on treatment for standard-risk ALL.

Twelve subjects gained more than 5% of their body weight at the end of this treatment phase. Two of the twelve subjects were male from the 3-4 year age group with one on treatment for Down's syndrome ALL (standard risk) and the other on treatment for high risk ALL; both subjects received a normal calorie normal protein diet. One of the twelve subjects was female from the 5-6 year age group on treatment for standard risk ALL and received a normal calorie normal protein diet plus oral nutritional supplements. Five of the twelve subjects received a high calorie high protein diet plus an oral nutritional supplement; three subjects were from the 1-2 year age group and on treatment for standard risk ALL (three were males and 2 were females). Four of the twelve subjects received a high calorie high protein diet plus an oral nutritional supplement plus an enteral feed; three subjects were male from the 1-2 year age group with three subjects on treatment for standard risk ALL and one subject on treatment for high risk ALL.

Consolidation phase

Weight-loss during consolidation treatment

At the end of consolidation treatment a total of sixteen subjects (80%) experienced a weight loss of between 0.6 -10 % of their body weight. Three of the sixteen subjects received a normal calorie normal protein diet. Two of the sixteen subjects received a high calorie high protein diet. Seven of the sixteen subjects received a high calorie high protein diet plus an oral nutritional supplement; four of the seven subjects received this diet since the induction phase. Three of the sixteen subjects received an enteral feed as their sole source of nutrition. There were multiple

reasons for the weight loss which included anorexia, appetite changes, nausea, vomiting, taste changes, constipation, mucositis, stomatitis, pharyngitis, chemo-induced neuropathy (pain) and diarrhea.

The subject with the greatest weight loss (10% of his body weight) was a male from the 7-8 year age group on a normal calorie normal protein diet since the induction phase and on treatment for standard-risk ALL.

Eight subjects lost more than 5% of their body weight at the end of this treatment phase. Four of the eight subjects received a normal calorie normal protein diet; one subject was male from the 1-2 year age group on treatment for standard risk ALL; one subject was male from the 3-4 year age group on treatment for high risk ALL (on the same diet since the induction phase); one subject was male from the 7-8 year age group on treatment for standard risk ALL (on the same diet since the induction phase) and one subject was male from the 11-12 year age group on treatment for high risk ALL. Two of the eight subjects received a high calorie high protein diet plus an oral nutritional supplement; one subject was female from the 5-6 year age group on treatment for standard risk ALL and one subject was male from the 11-12 year age group on treatment for high risk ALL. Both subjects received a normal calorie normal protein diet plus an oral nutritional supplement during the induction phase. One of the eight subjects received a high calorie high protein diet plus an oral nutritional supplement plus enteral feed; this subject was a male from the 3-4 year age group on treatment for standard risk ALL. This subject was on a high calorie high protein diet plus an oral nutritional supplement during the induction phase. One of the eight subjects received an enteral feed as a sole source of nutrition; this subject was a male from the 1-2 year age group on treatment for standard risk ALL. This subject was on a high calorie high protein diet plus an oral nutritional supplement plus enteral feed during the induction phase.

Weight gain during the consolidation treatment

Three subjects gained weight at the end of consolidation treatment. One of the three subjects was female from the 9-10 year age group and on treatment for standard-risk ALL who received a normal calorie normal protein diet during the induction phase. One of the three subjects was male from the 1-2 year age group and on treatment for standard-risk ALL who received a high calorie high protein diet plus an oral nutritional supplement plus enteral feed; this subject was on a high calorie high protein diet plus an oral nutritional supplement during the induction phase. One of the three subjects received an enteral feed as a sole source of nutrition; this subject was a

male from the 1-2 year age group on treatment for standard risk ALL and was on a high calorie high protein diet plus an oral nutritional supplement plus enteral feed during the induction phase. Two of the three subjects experienced a gain in weight and height at the end of this treatment phase.

One subject gained more than 5% of their body weight at the end of this treatment phase; this subject was male from the 1-2 year age group and on treatment for standard-risk ALL who received a high calorie high protein diet plus an oral nutritional supplement plus enteral feed and was on a high calorie high protein diet plus an oral nutritional supplement during the induction phase. This subject also increased in stature.

Interim maintenance treatment

Weight loss during interim maintenance treatment

Thirteen subjects (65%) lost weight at the end of this treatment phase. Five of the thirteen subjects received a normal calorie normal protein diet; three of the five subjects were on the same diet since the induction phase and the remaining two subjects were started on this diet since the consolidation phase. Five of the thirteen subjects received a high calorie high protein diet plus an oral nutritional supplement; three of the five subjects received this diet since the induction phase. Three of the thirteen subjects received an enteral feed as their sole source of nutrition and received this diet since the consolidation phase.

There were multiple reasons for the weight loss which included anorexia, appetite changes, nausea, vomiting, taste changes, constipation, mucositis, stomatitis, pharyngitis, chemo-induced neuropathy (pain) and diarrhea.

The subject with the highest weight loss percentage (13.9%) was a male from the 1-2 year age group and on treatment for standard-risk ALL who received a normal calorie normal protein diet since the consolidation phase.

Five of the thirteen subjects lost more than 5% of their body weight at the end of this treatment phase. Two of the five subjects received a normal calorie normal protein diet; one subject was male from the 1-2 year age group on treatment for standard risk ALL and the other subject was female from the 9-10 year age group on treatment for standard risk ALL. Two of the five subjects received a high calorie high protein diet plus an oral nutritional supplement; one subject was female from the 5-6 year age group on treatment for standard risk ALL (on the same diet since the consolidation phase) and one subject was male from the 3-4 year age group on

treatment for standard risk ALL (on the same diet since the induction phase). One of the five subjects was a male from the 1-2 year age group on treatment for standard risk ALL and receiving enteral feeds as his sole source of nutrition; this subject was on the same diet since the consolidation phase.

Weight gain during the interim maintenance phase

Six subjects gained weight at the end of this treatment phase. Three of the six subjects received a high calorie high protein diet plus an oral nutritional supplement; two of the three subjects were male from the 1-2 year age group on treatment for standard risk ALL and one of the subjects was male from the 11-12 year age group on treatment for high risk ALL. Two of the six subjects received a high calorie high protein diet plus an oral nutritional supplement plus enteral feed; one subject was male from the 1-2 year age group on treatment for standard risk ALL and one subject was male from the 3-4 year age group on treatment for standard risk ALL. One of the six subjects received an enteral feed as their sole source of nutrition; the subject was male from the 1-2 year age group on treatment for standard risk ALL and on this diet since the consolidation phase. All six subjects experienced a gain in weight and height at the end of this treatment phase.

One subject gained more than 5% of his body weight at the end of this treatment phase; the subject was male from the 3-4 year age group on treatment for standard risk ALL and received a high calorie high protein diet plus an oral nutritional supplement plus enteral feed since the consolidation phase.

Delayed intensification phase

Weight loss during delayed intensification treatment

At the end of delayed intensification treatment four subjects (20%) lost weight. One of the four subjects was male from the 7-8 year age group and on treatment for standard risk who received a normal calorie normal protein diet; this subject was on the same diet since the start of treatment. One of the four subjects was male from the 11-12 year age group and on treatment for high risk who received a high calorie high protein diet plus an oral nutritional supplement; this subject was on the same diet since the start of treatment. The remaining two subjects received an enteral feed as their sole source of nutrition subject; one of the two subjects was male from the 1-2 year age group on treatment for standard risk ALL and the other subject was female from the 3-4 year age group on treatment for high risk ALL. Both subjects received an enteral feed as their sole source of nutrition since the consolidation phase.

None of the subjects experienced a weight loss greater than 5% of their body weight at the end of this treatment phase.

Weight gain during delayed intensification treatment

At the end of this phase fifteen subjects (75%) gained weight. Four of the fifteen subjects received a normal calorie normal protein diet. One of the four subjects was a male from the 1-2 year age group on treatment for standard risk ALL. Two of the four subjects were male from the 3-4 year age (one subject was on treatment for Down's syndrome standard risk ALL and the other subject was on treatment for high risk ALL). Nine of the fifteen subjects received a high calorie high protein diet plus an oral nutritional supplement. Four of the nine subjects were from the 1-2 year age group (three males and one female) on treatment for standard risk ALL. Three of the nine subjects were from the 3-4 year age group (two males and one female) on treatment for standard risk ALL. One of the nine subjects was a female from the 5-6 year age group on treatment for standard risk ALL. One of the nine subjects was a female from the 9-10 year age group on treatment for standard risk ALL. One of the fifteen subjects was male from the 1-2 year age group and on treatment for standard risk ALL who received an enteral feed as his sole source of nutrition since the consolidation phase. Eight of the fifteen subjects experienced a gain in weight and height at the end of this treatment phase.

Seven subjects (35%) gained more than 5% of their body weight at the end of this treatment phase. One of the seven subjects received a normal calorie normal protein diet. Five of the seven subjects received a high calorie high protein diet plus an oral nutritional supplement. One of the five subjects received an enteral feed as his sole source of nutrition since the consolidation phase.

Maintenance treatment

Weight loss during maintenance treatment

At the end of maintenance treatment three subjects (15%) experienced a weight loss of between 0.6 – 0.9%. None of these subjects experienced a significant weight loss of greater than 5% of their body weight.

Weight gain during maintenance treatment

At the end of maintenance treatment fifteen subjects (75%) experienced a weight gain of between 0.9-20.6 percent. Nine of the fifteen subjects received a normal calorie normal protein diet. Five of the fifteen subjects received a high calorie high protein diet plus an oral nutritional supplement. One of the fifteen subjects received a high calorie high protein diet plus an oral

nutritional supplement plus an enteral feed. Eleven of the fifteen subjects experienced a gain in weight and height at the end of this treatment phase.

Eight subjects (40%) gained more than 5% of their body weight at the end of this treatment phase. Five of the eight subjects received a normal calorie normal protein diet. Two of the eight subjects received a high calorie high protein diet plus an oral nutritional supplement. One of the eight subjects received a high calorie high protein diet plus an oral nutritional supplement plus an enteral feed.

In summary a significant weight loss of more than 5% of body weight was observed in subjects on the following diets at the end of each treatment phase:

Induction treatment

At the end of the induction phase three out of eleven subjects lost more than 5% of their body weight on a high calorie high protein diet plus an oral nutritional supplement.

Consolidation treatment

At the end of the consolidation phase three out of five subjects lost more than 5% of their body weight on a normal calorie normal high protein diet.

At the end of the consolidation phase three out of seven subjects lost more than 5% of their body weight on a high calorie high protein diet plus an oral nutritional supplement.

At the end of the consolidation phase one out of two subjects lost more than 5% of their body weight on a high calorie high protein diet plus an oral nutritional supplement plus enteral feed.

At the end of the consolidation treatment one out of four subjects lost more than 5% of their body weight on an enteral feed as a sole source of nutrition.

Interim maintenance treatment

At the end of interim maintenance treatment two out of five subjects lost more than 5% of their body weight on a normal calorie normal high protein diet.

At the end of the interim maintenance treatment two out of nine subjects lost more than 5% of their body weight on a high calorie high protein diet plus an oral nutritional supplement.

At the end of the interim maintenance treatment none of the subjects lost more than 5% of their body weight on a high calorie high protein diet plus an oral nutritional supplement plus enteral feed.

At the end of interim maintenance treatment one out of four subjects lost more than 5% of their body weight on an enteral feed as a sole source of nutrition.

Delayed intensification treatment

At the end of delayed intensification treatment none of the patients receiving nutrition support were found to lose more than 5% of their body weight.

Maintenance treatment

At the end of maintenance treatment none of the patients receiving nutrition support were found to lose more than 5% of their body weight.

It can therefore be concluded that pediatric subjects receiving nutritional support during treatment for ALL underwent changes in nutritional status as manifest by a reduction in more than 5% of their body weight during three phases of treatment namely induction, consolidation and interim maintenance.

4.5. Biochemistry

Laboratory measurements that are most frequently used to assess the nutritional status of children in this study included albumin, blood glucose levels and hemoglobin.

Table 8 below shows the incidence of hypoalbuminemia, hyperglycemia and anemia at the end of each treatment phase

Table 8: The incidence of hypoalbuminemia, hyperglycemia and anemia at the end of each treatment phase

Biochemical data at the end of each treatment phase	Induction treatment (% of subjects)	Consolidation Treatment (% of subjects)	Interim Maintenance Treatment (% of subjects)	Delayed Intensification Treatment (% of subjects)	Maintenance Treatment (% of subjects)
Hypoalbuminemia	65	50	35	45	15
Hyperglycemia	10	0	15	0	15
Low hemoglobin	85	95	75	85	70

4.5.1. Hypoalbuminemia

With regards to biochemistry the highest incidence of hypoalbuminemia was found at the end of induction treatment in 13 subjects (65%); 9 subjects were male with the highest occurrence within the 3-4 year age group. Ten subjects (50%) had hypoalbuminemia at the end of

consolidation treatment; 8 subjects were male with the highest occurrence within the 3-4 year age group.

4.5.2. Hyperglycemia

Two subjects (10%) experienced hyperglycemia at the end of induction treatment; one subject was male from the 11-12 year age group and one subject was female from the 9-10 year age group. Three subjects (15%) experienced hyperglycemia at the end of interim maintenance treatment; all subjects were male with the highest occurrence from the 3-4 year age group. The subject with Down's syndrome ALL experienced hyperglycemia at the end of interim maintenance treatment. Three subjects (15%) experienced hyperglycemia at the end of maintenance treatment; all subjects were male with the highest occurrence within the 1-2 year age group. There were no reports of subjects having hyperglycemia at the end of consolidation treatment and delayed intensification treatment.

4.5.3. Anemia

Low hemoglobin levels were experienced by the majority of subjects at the end of all treatment phases. At the end of consolidation treatment 19 subjects (95%) were anemic; 14 of the 19 subjects were male with the highest occurrence equally divided within the 1-2 year and 3-4 year age groups.

4.6. Treatment delays

Table 9 below shows the most common reasons for treatment delays between the different phases of treatment expressed as a percentage of subjects.

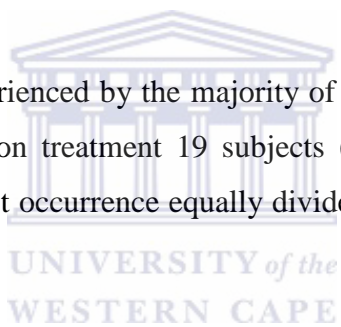


Table 9: Reasons for treatment delays between treatment phases

Reasons for Treatment Delays	Consolidation Treatment (% of subjects)	Interim Maintenance Treatment (% of subjects)	Delayed Intensification Treatment (% of subjects)	Maintenance Treatment (% of subjects)
Low ANC	25	25	5	15
Diarrhea	10	-	-	-
Rash	5	-	-	-
Fever	5	25	-	-
Vomiting	5	-	-	-
Thrombocytopenia	-	5	-	-
URTI	5	-	-	-
High liver enzymes	-	-	-	5

ANC – absolute neutrophil count, URTI – upper respiratory tract infection

Consolidation treatment

At the start of consolidation treatment 4 subjects (25%) experienced treatment delays as a result of neutropenia; all the subjects were male with the highest occurrence in the 1-2 year and 3-4 year age groups. Two subjects (10%) experienced treatment delays as a result of diarrhea; all subjects were male with equal occurrence within the 1-2 year and 11-12 year age groups. Fever, skin rash, vomiting and upper respiratory infection accounted for 5% of the treatment delays experienced by subjects during this treatment phase.

Interim maintenance treatment

At the start of interim maintenance treatment 4 subjects (25%) experienced treatment delays as a result of neutropenia and fever; all the subjects were male with the highest occurrence in the 1-2 year and 3-4 year age groups. One subject (5%) experienced a treatment delay as a result of thrombocytopenia; the subject was a male in the 7-8 year age group.

Delayed intensification treatment

At the start of delayed intensification treatment one subject (5%) experienced a treatment delay due to neutropenia; the subject was male in the 1-2 year age group.

Maintenance treatment

At the start of maintenance treatment 3 subjects (15%) experienced a treatment delay due to neutropenia; the subjects were all male with highest incidence in the 1-2 year and 3-4 year age

groups. One subject (5%) experienced a treatment delay due to elevated liver enzymes; the subject was female in the 1-2 year age group.

In summary treatment delays occurred as a result of neutropenia, diarrhea, skin rash, fever, vomiting, thrombocytopenia, upper respiratory tract infection and elevation in liver enzymes with the most common reasons for treatment delay between treatment phases being neutropenia, diarrhea and fever.

4.7. Treatment-related complications

Table 10 below shows the clinical and systemic complications during the different treatment.



Table 10: The clinical and systemic complications during the different treatment phases

Clinical & systemic complications	Induction treatment (% of subjects)	Consolidation Treatment (% of subjects)	Interim Maintenance Treatment (% of subjects)	Delayed Intensification Treatment (% of subjects)	Maintenance Treatment (% of subjects)
Anorexia	15	15	35	5	-
Appetite changes	70	35	5	15	-
Bone pain	20	-	35	-	-
Chemo-induced neuropathy	-	10	-	5	-
Constipation	5	10	15	5	-
Diarrhea	25	10	5	5	-
Fever	5	20	15	25	-
Hyperglycemia	10	-	-	-	-
Hypertension	5	-	-	-	-
Liver-enzymes elevated	-	5	-	-	-
Mucositis	-	10	15	15	-
Nausea	60	20	15	-	-
Neutropenia	-	25	15	25	5
Pharyngitis	-	5	-	-	-
Peri-orbital swelling	-	5	-	-	-
Perianal ulcer	-	-	-	5	-
Platelets (low)	20	-	-	-	-
Skin reaction	-	-	10	-	-
Stomatitis	-	10	15	15	-
Taste changes	10	5	5	10	-
Tumor-lysis syndrome	10	-	-	-	-
Vomiting	60	45	25	10	-
Zoster infection	-	-	-	5	-

Induction treatment

The most common side-effects experienced during the induction phase were appetite changes in 14 subjects (70%); most subjects were male with the highest occurrence within the 1-2 year and 3-4 year age groups.

Twelve subjects (60%) experienced nausea and vomiting; most subjects were male with the highest occurrence in the 1-2 year and 3-4 year age groups.

Four subjects (20%) experienced diarrhea; most subjects were male with the highest occurrence in the 1-2 year age group. All female subjects that experienced diarrhea were also from the 1-2 year age group.

Four subjects (20%) experienced bone pain during induction treatment; most subjects were male with the highest occurrence 3-4 year age group. Most female subjects that experienced bone pain were also from the 3-4 year age group.

Four subjects (20%) experienced a low platelet count during induction treatment. All of which were males with the highest occurrence in 3-4 year age group.

Two subjects (10%) experienced tumor lysis syndrome during this phase; all subjects were male with equal occurrence in 7-8 year and 11-12 year age groups. The subject in the 11-12 year age group was receiving treatment for high risk ALL.

Consolidation treatment

During the consolidation phase the most common side effect experienced was vomiting in 9 subjects (45%); most subjects were male with the highest occurrence in the 1-2 year and 3-4 year age groups.

Seven subjects (35%) experienced appetite changes; most subjects were male the highest occurrence in the 3-4 year age group.

Four subjects (20%) experienced neutropenia; all subjects were male with the highest occurrence in the 1-2 year age group.

Mucositis and stomatitis was experienced in two subjects (10%); all subjects were male with equal distribution within the 1-2 year and 7-8 year age groups.

Chemotherapy induced neuropathy was experienced by two subjects (10%) during the consolidation phase; all subjects were male with equal distribution within the 1-2 year and 3-4 year age groups.

Interim maintenance treatment

During the interim maintenance phase seven subjects (35%) experienced anorexia; most subjects were male with the highest occurrence in the 1-2 year age group.

Five subjects (25%) experienced bone pain; all subjects were male with the highest occurrence in the 1-2 year age group.

Five subjects (25%) experienced vomiting; all subjects were male with the highest occurrence in the 1-2 year age group.

Three subjects (15%) experienced neutropenia; the subjects were mostly female with the highest occurrence in the 3-4 year age group.

Mucositis and stomatitis was experienced in three subjects (15 %); the subjects were mostly male with equal distribution within the 1-2 year and 11-12 year age groups.

Delayed intensification treatment

During the delayed intensification phase fever was experienced by four subjects (25%); the subjects were mostly male with the highest occurrence in the 1-2 year age group.

Twenty five percent of subjects experienced neutropenia; 80 % of subjects were male with the highest occurrence in the 1-2 year age group.

Three subjects (15%) experienced appetite changes; the subjects were mostly female with the highest occurrence in the 1-2 year age group.

Chemotherapy induced neuropathy was experienced by one subject (5%); the subject was male and belonged to the 1-2 year age group (this subject also experienced chemotherapy induced neuropathy during consolidation treatment).

Mucositis and stomatitis was experienced in 3 subjects (15 %); all subjects were male with highest occurrence in the 1-2 year age group.

Maintenance treatment

The only treatment-related side effect reported during the maintenance phase was neutropenia in one subject (5%); the subject was male and from the 3-4 year age group.

In summary subjects experienced the greatest number of treatment-related complications during the induction, consolidation, interim maintenance, delayed intensification phases of treatment and the lowest number during the maintenance phase. During the induction phase the most

common nutritionally related complications were appetite changes, nausea, vomiting, diarrhea, anorexia, hyperglycemia, taste changes, tumor lysis syndrome and constipation. During the consolidation phase the most common nutritionally related complications were appetite changes, nausea, vomiting, diarrhea, anorexia, taste changes, constipation, mucositis, stomatitis and pharyngitis. During the interim maintenance phase the most common nutritionally related complications were appetite changes, nausea, vomiting, diarrhea, anorexia, taste changes, constipation, mucositis and stomatitis. During the delayed intensification phase the most common nutritionally related complications were appetite changes, vomiting, diarrhea, anorexia, taste changes, constipation, mucositis and stomatitis. During the maintenance phase there was an absence of nutritionally related complications.

4.8. Diet order and nutritional support

At the start of treatment all subjects were prescribed an age-appropriate diet with two snacks as all subjects were found to be of normal weight and height-for-age. Table 7 below reports the diet prescription of subjects during the different treatment phases.



Table 11: The diet prescription of subjects during the different treatment phases

Diet prescription during the different treatment phases	Induction treatment (No. of subjects)	Consolidation Treatment (No. of subjects)	Interim Maintenance Treatment (No. of subjects)	Delayed Intensification Treatment (No. of subjects)	Maintenance Treatment (No. of subjects)
Subjects receiving normal calorie and protein diet only	3	5	5	6	13
Subjects receiving a high calorie and high protein diet only	0	2	0	0	0
Subjects receiving normal calorie and protein diet + oral nutritional supplement	2	0	0	0	0
Subjects receiving a high calorie and high protein diet + oral nutritional supplement	11	7	9	11	5
Subjects receiving a high calorie and high protein diet + oral nutritional supplement + transitioned to an enteral feed	4	2	2	0	2
Enteral feeds only	0	4	4	3	0

Induction treatment

Normal calorie normal protein diet

During the induction phase three subjects (15%) received a normal calorie normal protein diet. All subjects were male with two subjects from the 3- 4 year age group (one subject was on treatment for high risk ALL and the other subject was on treatment for Downs syndrome standard risk ALL) and one subject was from the 7-8 year age group on treatment for standard risk ALL.

The remaining seventeen subjects were transitioned on to energy dense diets with or without oral nutritional supplement and /or an enteral feed due to weight loss which resulted from treatment-related side-effects outlined in Table 6.

Normal calorie normal protein diet plus an oral nutritional supplement

Two subjects (10%) were prescribed a normal calorie normal protein diet plus an oral nutritional supplement due to poor weight gain. One subject was male from the 11-12 year age group on treatment for high risk ALL and the other subject was female from the 5-6 year age group on treatment for standard risk

High calorie high protein diet plus an oral nutritional supplement

Eleven subjects (55%) were prescribed a high calorie high protein diet plus an oral nutritional supplement. Four subjects were from the 1-2 year age group on treatment for standard risk (3 males and 1 female), four subjects were from the 3-4 year age group on treatment for standard risk (2 males and 2 female), one subject was from the 9-10 year age group on treatment for standard risk ALL and one subject was from the 11-12 year age group on treatment for high risk ALL.

High calorie high protein diet plus an oral nutritional supplement plus an enteral feed

Four subjects (20%) were prescribed a high calorie high protein diet plus an oral nutritional supplement plus an enteral feed. Three subjects were from the 1-2 year age group on treatment for standard risk (all male) and one subject was male from 3-4 year age group on treatment for high risk ALL.

Consolidation treatment

Normal calorie normal protein diet

During the consolidation phase five subjects (25%) received a normal calorie normal protein diet. One subject was male from the 1-2 year age group on treatment for standard risk, two subjects were male from the 3-4 year age group on treatment for standard risk, one subject was male from the 7-8 year age group on treatment for standard risk ALL and one subject was male from the 9-10 year age group on treatment for high risk ALL.

Three of the five subjects (15%) who received a normal calorie normal protein diet during the induction phase continued on this diet prescription during the consolidation phase, as they were

able to maintain normal anthropometric measurements however all three patients failed to grow in weight and height during this phase.

The remaining two subjects (10%), one male from the 1-2 year age group on treatment for standard risk ALL with significant weight gain during the induction phase (8% of body weight) and one female from the 9-10 year age group on treatment for standard risk ALL also with significant weight gain during the induction phase (3.7% of body weight) were transitioned from a high calorie high protein diet with supplements to a normal calorie normal protein diet with no supplements.

High calorie high protein diet without an oral nutritional supplement

Two subjects (10%) received a high calorie high protein diet without oral nutritional supplements. One subject was male from the 1-2 year age group on treatment for standard risk ALL and one subject was female from the 3-4 year age group on treatment for standard risk ALL. Both subjects were transitioned from a high calorie high protein diet with supplements during the induction phase to a high calorie high protein diet without oral nutritional supplements during the consolidation phase due to a positive weight gain percentages of 12% and 18% respectively.

High calorie high protein diet with an oral nutritional supplement

Seven subjects (35%) were prescribed a high calorie high protein diet in addition to an oral nutritional supplement. Two subjects were from the 1-2 year age group on treatment for standard risk (one male and one female), two subjects were from the 3-4 year age group on treatment for standard risk (one male and one female), one subject was female from the 5-6 year age group on treatment for standard risk ALL and two subjects were males from the 11-12 year age group on treatment for high risk ALL.

Five of the six subjects remained on this diet prescription since the induction phase; two subjects were from the 1-2 year age group on treatment for standard risk (one male and one female), two subjects were from the 3-4 year age group on treatment for standard risk (one male and one female) and one subject was male from the 11-12 year age group on treatment for high risk ALL.

High calorie high protein diet plus an oral nutritional supplement plus an enteral feed

Two subjects (10%) were prescribed a high calorie high protein diet plus an oral nutritional supplement plus an enteral feed during this phase. One subject was male from the 1-2 year age group on treatment for standard risk ALL and one subject was male from the 3-4 year age group

on treatment for standard risk ALL. Both subjects were previously on a high calorie high protein diet plus an oral nutritional supplement during the induction phase; enteral feeds were started as a result of a poor oral intake resulting in a weight loss of 10.9-12 % of their body weight.

Enteral feed only

Four subjects (20%) received an enteral feed as a sole source of nutrition during this phase. All subjects in this group were on a high calorie normal high protein diet in addition to an oral nutritional supplement plus an enteral feed during the induction phase. As a result of vomiting, mucositis and stomatitis these subjects developed a food aversion and were unable to meet their nutritional needs orally. All subjects were male on treatment for standard risk ALL; three subjects were from the 1-2 year age group and one subject was from the 3-4 year age group.

Interim maintenance treatment

Normal calorie normal protein diet

During the interim maintenance phase five subjects (25%) received a normal calorie normal protein diet. One subject was male from the 1-2 year age group on treatment for standard risk, two subjects were male from the 3-4 year age group on treatment for standard risk, one subject was male from the 7-8 year age group on treatment for standard risk ALL and one subject was male from the 9-10 year age group on treatment for high risk ALL.

All five subjects remained on this diet prescription since the consolidation phase in spite of three of the five subjects having a weight loss percentage greater than 5% of their body weight at the end of the consolidation phase.

High calorie high protein diet plus an oral nutritional supplement

Nine subjects (45%) were prescribed a high calorie high protein diet plus an oral nutritional supplement. Three subjects were from the 1-2 year age group on treatment for standard risk (two males and one female), three subjects were from the 3-4 year age group on treatment for standard risk (one male and two females), one subject was female from the 5-6 year age group on treatment for standard risk ALL and two subjects were males from the 11-12 year age group on treatment for high risk ALL.

Seven of the nine subjects remained on this diet prescription since the consolidation phase due to a poor weight gain during the consolidation phase.

High calorie high protein diet plus an oral nutritional supplement plus an enteral feed

Two subjects (10%) were prescribed a high calorie high protein diet plus an oral nutritional supplement plus an enteral feed during this phase. Both subjects remained on this diet prescription since the consolidation phase due to a poor oral intake as a result of treatment-related side-effects, both subjects were male with one from the 1-2 year age group with standard risk ALL and the other one from the 3-4 year age group also with standard risk ALL.

Enteral feed only

Four subjects (20%) received an enteral feed as a sole source of nutrition during this phase. All four subjects remained on this diet prescription since the consolidation phase due to a food aversion as a result of vomiting, mucositis and stomatitis. Two of the four subjects experienced a weight loss during this phase but gained height while one of the remaining two subjects gained weight and height during this treatment phase.

Delayed intensification treatment

Normal calorie normal protein diet

During the delayed intensification phase six subjects (30%) received a normal calorie normal protein diet. One subject was male from the 1-2 year age group on treatment for standard risk, three subjects were from the 3-4 year age group (two male and one female) with two subjects was on treatment for standard risk ALL and one subject on treatment for high risk ALL; one subject was male from the 7-8 year age group on treatment for standard risk ALL and one subject was male from the 9-10 year age group on treatment for high risk ALL.

Three of the six subjects remained on this diet prescription since the interim maintenance phase. The remaining three of the six subjects were on a high calorie high protein diet plus an oral nutritional supplement during the interim maintenance phase. Two the three subjects, one male from the 1-2 year age group on treatment for standard risk ALL and one male from the 11-12 year age group on treatment for high risk ALL, gained weight and height during the interim maintenance phase and was transitioned on to a normal calorie normal protein diet during this phase.

High calorie high protein diet with an oral nutritional supplement

Eleven subjects (55%) were prescribed at high calorie high protein diet plus an oral nutritional supplement during this phase. Four subjects were from the 1-2 year age group on treatment for standard risk ALL (three males and one female), three subjects were from the 3-4 year age group

on treatment for standard risk ALL (two males and one female), one subject was from the 5-6 year age group on treatment for standard risk ALL (female) and one subject was from the 11-12 year age group on treatment for high risk ALL (male).

Six of the eleven subjects remained on this diet prescription since the interim maintenance phase.

Enteral feed only

Three subjects (15%) received an enteral feed as a sole source of nutrition during this phase. All three subjects remained on this diet prescription since the consolidation phase due to a food aversion as a result of vomiting, mucositis and stomatitis and did not gain weight during the interim maintenance phase. Two subjects were male from the 1-2 year age group on treatment for standard risk ALL and one subject was a male from the 3-4 year age group on treatment for high risk ALL.

Maintenance treatment

Normal calorie normal protein diet

During the maintenance phase thirteen subjects (65%) received a normal calorie normal protein diet. Four subjects were male from the 1-2 year age group on treatment for standard risk ALL, six subjects (four males and two females) were from the 3-4 year age group (five subjects were on treatment for standard risk ALL and one subject was on treatment for high risk ALL), one subject was male from the 7-8 year age group on treatment for standard risk ALL, one subject was female from the 9-10 year age group on treatment for standard risk ALL and one subject was male from the 11-12 year age group on treatment for high risk ALL.

Six of the thirteen subjects remained on this diet prescription since the delayed intensification phase. The remaining seven subjects were on a high calorie high protein diet plus an oral nutritional supplement during delayed intensification phase and were transitioned on to a normal calorie normal protein diet during this phase due to a significant gain in weight.

High calorie high protein diet plus an oral nutritional supplement

Five subjects (25%) were prescribed a high calorie normal high protein diet in addition to an oral nutritional supplement. Three subjects were from the 1-2 year age group on treatment for standard risk ALL (two were males and one was a female), one subject was a female from the 5-6 year age group on treatment for standard risk ALL and one subject was male from the 11-12 year age group on treatment for high risk ALL.

Four of the five subjects remained on this diet prescription since the delayed intensification phase and all subjects had a weight gain on this diet plan at the end of maintenance treatment. The remaining subject was transitioned from an enteral feed (as a sole source of nutrition) during the delayed intensification phase to a high calorie high protein diet plus an oral nutritional supplement during this phase as he had gained more than 5% of his body weight. This subject was a male from the 11-12 year age group and also gained weight and height at the end of the maintenance phase.

High calorie high protein diet plus an oral nutritional supplement plus an enteral feed

Two subjects (10%) were transitioned from an enteral feed (as a sole source of nutrition) to high calorie normal high protein diet plus an oral nutritional supplement plus an enteral feed during this phase. Both subjects were male; one was from the 1-2 year age group (on standard risk treatment for ALL) and the other subject was from the 3-4 year age group (on high risk treatment for ALL). The subject from the 1-2 year age group lost weight but gained height at the end of this treatment phase. The subject from the 3-4 year age group (on high risk treatment for ALL) gained weight and height at the end of this treatment phase.

In summary nutrition support in the form of a normal calorie normal protein diet plus an oral nutritional supplement occurred only during the induction phase. Nutrition support in the form of a high calorie high protein diet plus an oral nutritional supplement occurred mostly during the induction, consolidation, interim maintenance, delayed intensification and maintenance phases of treatment. Nutrition support in the form of a high calorie high protein diet plus an oral nutritional supplement plus enteral feed occurred mostly during the induction, consolidation, interim maintenance and maintenance phases of treatment. Nutrition support in the form of enteral feeding as a sole source of nutrition occurred mostly during the consolidation, interim maintenance and delayed intensification phases of treatment.

4.9. Remission

At the end of induction treatment a total of eighteen subjects (90%) were reported to have achieved remission. Two subjects (10%) did not achieve remission, both subjects were male and received treatments for high risk ALL and belonged to the 3-4 year and 11-12 year age groups.

CHAPTER 5

DISCUSSION



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Introduction

All subjects included in this study were diagnosed with the same type of cancer (acute lymphoblastic leukemia) and received the same type of cancer treatment (chemotherapy) under the same treatment protocols and policies. The data gathering for all subjects in this study was therefore the same.

5.1. Symptoms at diagnosis

In this study the most common clinical characteristics at diagnosis was fever without any evidence of infection, purpuric bruises, flu-like symptoms, anemia, weight loss, bone pain as a result of an infiltration of the bone marrow by a large number of leukemic cells and epistaxis. A Middle Eastern study by Al-Mulla *et al* (2014) reported the prevalence of bone pain amongst the signs and symptoms upon presentation of ALL as being higher than in western countries. Another study by Salim *et al* (2014) on pediatric ALL cases reported pallor as the most common symptom of ALL at diagnosis followed by fever, bone pain, lethargy, fatigue and a loss in appetite. The comparison of these results with other studies is limited due to a lack of published studies.

5.2. Characteristics at diagnosis

The peak age of diagnosis in this study was between the ages of 1 to 2 years old. Although there is a lack of published studies in the United Arab Emirates on the incidence of pediatric ALL, the Middle Eastern study conducted by Al-Mulla *et al* (2014) on 1150 pediatric patients with ALL found the peak age range of children at diagnosis to be between 3-6 years of age which was similar to the age range reported in western countries. Another study by Lughetti *et al* (2012) reported the peak age of ALL occurrences in children to be between the ages of 2- 6 years of age.

The most common type of ALL amongst subjects in this study was B-cell ALL which was similar to the findings of Al-Mulla *et al* (2014).

The ratio for males to females in this study was calculated to be 3:1 which was different from the sex-based incidence ratio of 1.4: 1 (males: females) reported by Al-Mulla *et al* (2014). Other studies published by The Cancer Oncology Group (2015) and an earlier study by Gholami *et al* (2013) reported the prevalence of ALL to be slightly more common in males than females though the reason for this was unknown.

In this study, B-cell ALL was found in 60% of subjects and T-cell ALL was found in 10% of subjects. Five percent of subjects with T-cell ALL had testicular involvement. Five percent of the total subjects included in the study was diagnosed with Trisomy 21(Downs syndrome) B-cell ALL. The Cancer Oncology Group (2015) reported similar findings; B-cell ALL was reported to be the most common type ALL in children (80-85% of children with ALL) and T-cell is a less common type (15-20% of children with ALL); and testicular involvement in males was reported to be present in 1-2% of males with leukemia. Due to the small sample size of this study 5% of male subjects were found to have testicular involvement.

The risk classification of ALL in children is important in treatment decisions and therapeutic protocols and is determined by the initial white blood cell count at diagnosis; standard risk ALL includes subjects with an initial white blood cell count less than 50 000/microliter and high risk ALL includes subjects with an initial white blood cell count greater than 50 000/microliter. In this study 80% of subjects were diagnosed with standard risk ALL and 20 % with high risk ALL. All subjects within the high risk group were male. The comparison of these results with other studies is limited due to a lack of published studies.

5.3. Cancer treatment

At Sheikh Khalifa Medical City (SKMC), the ALL treatment protocols used are as per the guideline of The Children's` Oncology Group (USA) and treatment involves 5 treatment phases, namely induction, consolidation, interim maintenance, delayed intensification and maintenance. The goal of induction treatment was to eradicate more than 99% of the initial leukemic cells present in the bone marrow in order to restore normal haemopoiesis. Induction treatment regimens at SKMC included the addition of glucocorticoids (prednisolone or dexamethasone), vincristine and a third drug (asparaginase, anthracycline or both). A three drug induction regime was used to treat most standard risk cases of ALL and children with high risk ALL was treated with four or more drugs during the induction phase.

Literature by The Children's Oncology Group (2015) reported the clinical remission rates in children to be between 96-99% on completion of induction treatment. In this study 90% of subjects achieved remission on completion of induction treatment. This finding was similar to that of Owens *et al* (2011) which reported a cure rate of pediatric ALL approaching 90%. The Middle Eastern study conducted by Al-Mulla *et al* (2014) on 1150 pediatric patients with ALL reported the end of induction remission rate to be 96.6% which was slightly higher than the finding in this study.

Research by Maloney (2011) found a greater incidence in remission induction failure in Down's syndrome ALL patients than non-Down's syndrome ALL patients; in this study the subject with Down's syndrome ALL successfully achieved remission on completion of induction treatment.

5.4. Nutrition screening

The first step in the management of under-nutrition or over-nutrition was the identification of undernourished or over-nourished patients or those at risk for developing malnutrition. Nutrition screening was generally carried out by those members of the nursing team at first contact with the patient. The tool used in screening should be quick, easy to complete and validated for use in a pediatric oncology setting (McCarthy *et al*, 2012). At Sheikh Khalifa Medical City the nutrition screening tool incorporated into the electronic patient record was not a validated tool which makes its use in the pediatric oncology setting unreliable and inconsistent in detecting patients at risk for malnutrition during each treatment session.

5.5. Anthropometric measurements during treatment

In this study anthropometric measurements for all subjects were recorded as z-scores for weight-for-age, length/height-for-age and BMI-for-age on the World Health Organization (WHO) growth charts at diagnosis and at the start and end of each treatment phase. A growth abnormality was deemed significant if a subject's z-score for any of the above mentioned anthropometric measurements, was found to be more than 2 standard deviations greater than or less than the appropriate mean. At diagnosis all subjects were of normal weight-for-age and one subject was found to be stunted, stunting is a measure of linear growth that reflects the cumulative effect of chronic malnutrition (Children's Oncology Group, 2015). Weight fluctuations were evident during the different treatment phases as patients experienced treatment-related side-effects during the different phases of treatment which had a negative impact on their nutrition status.

In general, 5% of subjects were found to be underweight at diagnosis and at the end of interim maintenance phases when BMI-for-age z-scores was used. At the end of other treatment phases, subjects were found to display normal BMI-for-age z-scores. Collins *et al* (2010) citing Reilly *et al* (1999), a study of more than 1000 children in the United Kingdom with standard risk ALL at diagnosis, found that the BMI-for-age z-score provided a good measure for protein energy malnutrition. These investigators reported that approximately 7% of the children in their study were malnourished at diagnosis (BMI-for-age z-score less than -2). Literature published by Maldonado-Alcazar *et al* (2013) reported the prevalence of malnutrition at diagnosis in their

study to be 7% for children living in developed countries and 21-23% for children living in developing countries.

With regards to overweight 5% of subjects were found to be overweight at diagnosis and 10% of subjects were found to be overweight at the end of induction and maintenance treatments. Literature by Tan *et al* (2010) on 53 pediatric patients diagnosed with ALL and undergoing chemotherapy treatment found a large number of patients in his study to be overweight rather than underweight, as shown by the percentile distribution of various anthropometric indices. The study by Tan *et al* (2010) also revealed an early trigger towards childhood obesity during the latter part of ALL treatment especially during the maintenance phase.

Weights for age, height-for-age and BMI-for-age are considered as the most sensitive indices for growth in children (Selwood *et al*, 2010). In this study weight loss expressed as a percentage of body weight lost provided a more accurate estimate of the true significance of weight loss in subjects on cancer treatment (chemotherapy). A weight loss of greater than 5% of body weight over a period of one month was considered a sign of nutritional deprivation even when the patient was not classified as undernourished by anthropometric parameters (Bauer *et al*, 2011; Selwood *et al*, 2010; Jeejeebhoy and Keith, 2005). It was therefore important to consider weight loss percentage in the assessment of obese or overweight patients as they would have to lose a great amount of body weight before they are classified as underweight by anthropometric cut off points, even though they may be in a negative nutritional balance during cancer treatment. The results of this study showed that subjects experienced the greatest weight loss percentage during the consolidation (80%) and interim maintenance (65%) phases of treatment. This was as a result of treatment-related side-effects such as low absolute neutrophil count, thrombocytopenia, anemia, diarrhea, allergic rash from a component of the chemotherapy, vomiting, fever and upper respiratory tract infection which had a profound effect on the subject's nutritional intake leading to a nutritional deprivation. The interim maintenance phase of chemotherapy was found to be the most demanding phase of treatment in this study as subjects experienced the greatest number of treatment-related side-effects and least weight gain. This is in line with published literature from the Oncology Cancer Group (2015).

Other possible reason for weight fluctuations in subjects in this study was explained by the use of steroids which formed part of the treatment; during the first phase of treatment (induction) patients received high daily dose of steroids to induce remission. Past studies have shown antileukaemic drugs such as prednisolone and dexamethasone to induce weight gain and fat

accumulation by increasing the appetite and energy intake in pediatric patients on cancer treatment ultimately leading to overweight and obesity (Tan et al, 2010 citing Murphy *et al*, 2006; Ladas *et al*, 2005; Reilly *et al*, 2001).

After induction treatment steroid treatment became transient and was only administered on alternate weeks during the chemotherapy cycle. The data collection in this study was based on time intervals corresponding to chemotherapy phases and many patients were assessed during the on and off steroid phase. Therefore patients experienced phases of excessive intake when on steroids followed by reduced intake for the rest of the treatment.

In this study subjects on treatment for ALL underwent changes in nutritional status as manifest by a reduction in growth, weight gain and weight loss. Several factors such as diet, treatment-related side-effects of chemotherapy, high doses of steroids received during each treatment phase and a lack of physical activity were possible reasons for the changes in weight observed.

5.6. Biochemistry during treatment

Chemotherapy involves giving high doses of drugs to patients diagnosed with ALL in order to kill the cancer that exists within the bone marrow and also the central nervous system in order to prevent relapse (Oncology Cancer Group, 2015). Bone marrow toxicity was common in all subjects undergoing chemotherapy in this study during all cycles of treatment and presented as leukopenia (a decrease in white blood cells); thrombocytopenia (a decrease in platelets); pancytopenia (a decrease in all blood cells); anemia (a decrease in red blood cells) or neutropenia (a decrease in neutrophils). Most subjects received blood transfusions as per the treatment protocol when hemoglobin levels were below 80-90 g/L to prevent subjects from becoming severely immunocompromised. Hemoglobin levels were found to return to normal once treatment was stopped and normal bone marrow function returned.

The liver function tests showed the damaging effect of treatment on the liver; all subjects displayed high liver enzyme values during the course of treatment as the liver was responsible for metabolizing the chemotherapeutic agents however the hepatotoxicity of these chemotherapeutic drugs was usually temporary and liver function was found to return to normal once the drugs were stopped.

Renal function was also compromised as a result of the toxic effects of the chemotherapeutic drugs and the duration of treatment with short breaks between chemotherapy cycles. A full discussion on the detrimental effect of chemotherapy on the liver and kidneys goes beyond the

purpose of this study; however in order to interpret the results it was essential to take into consideration the functionality of these organs.

In this study, the oncology team made use of serum albumin levels to assess the nutritional status of subjects. Chemotherapy and steroid treatment are also known to affect serum albumin levels and one must also bear in mind that an indirect relationship exists between inflammation and hypoalbuminemia. Inflammation is known to contribute to net protein loss in individuals as a result of catabolism; albumin levels have to therefore be analyzed in relation to C-reactive protein levels in order to ascertain whether the low albumin levels are as a result of a poor nutritional status or as a result of inflammation (Selwood *et al*, 2010). Although albumin was used as an indicator of poor nutritional status in this study, its use to detect a poor nutritional status in subjects was believed to be inappropriate. Serum prealbumin which is a more sensitive marker of nutritional status in children receiving chemotherapy was not tested during the entire course of chemotherapy and could be acknowledged as a limitation of this study.

Blood glucose levels were obtained as part of the routine biochemical panel as transient hyperglycemia was a recognized side effect of corticosteroids and asparaginase use especially during induction treatment. Overweight and risk of overweight were also significant risk factors of transient hyperglycemia (Zhang *et al*, 2014; Robertson *et al*, 2009). Hyperglycemia was evident in 10% of subjects during the induction treatment and in 15% of subjects during the interim maintenance and maintenance treatment phases respectively. In some studies the use of high doses of steroids combined with L-asparaginase and intravenous fluids have been implicated in the prevalence of hyperglycemia during induction treatment (Dare *et al*, 2013). Glucocorticoids have also been positively linked to an increase in blood glucose levels in children on cancer treatment by increasing liver gluconeogenesis. Patient`s with Down syndrome were also found to have a higher incidence of treatment-related hyperglycemia during induction chemotherapy; though the reason for this is unclear. In this study the subject with Down syndrome ALL had one reported episode of hyperglycemia at the end of interim maintenance treatment.

5.7. Clinical findings during treatment

In this study subjects experienced a variety of treatment-related side-effects such as pain, nausea, vomiting, hair-loss, weight gain or weight loss, constipation, diarrhea, neutropenia during the course of treatment. Constipation resulted in a number of subjects as the result of narcotic drugs prescribed for pain control. A change in taste was a common complication of cancer treatment in

study participants. Most subjects complained of a metallic taste with protein-rich foods which negatively impacted on the nutritional status often resulting in the subject being enterally fed in order to maintain growth.

Research by Skolin *et al* (2006) found chemotherapy -induced nausea, diarrhea and taste changes to occur during the induction and consolidation phases of treatment, in this study however nausea, diarrhea and taste changes were mostly reported during induction, consolidation and delayed intensification treatment.

There were no reports of osteoporosis or osteomalacia in the electronic files of subjects included in this study. Research by Salim *et al* (2013) reported a reduction of bone mass in children with ALL at diagnosis and during the first 6 months of chemotherapy. The possible long-term side-effects of corticosteroids and antiemetic were said to reduce the synthesis of collagen, causing a decrease in bone mass and an increase in bone loss which resulted in osteomalacia, osteoporosis and skeletal anomalies in children (Rosen *et al*, 2013). The prevalence of osteopenia and osteoporosis in children with ALL was noted during all phases of ALL treatment and throughout the post treatment period for up to age 20 years in the study by Salim *et al* (2014). In a similar study the fracture rate in children receiving treatment for ALL was reported to be 6 times more common than in healthy children of the same age (Salim *et al*, 2014 citing Rogalsky *et al*, 1986).

5.8. Nutrition support during treatment

Nutritional support can be defined as the provision of nutrients in place of or in addition to that provided by normal eating to ensure a balanced diet (Bauer *et al*, 2011). Adequate nutrition is an important concern in children with ALL as a good nutritional status helps them cope better with the side-effects of cancer therapy by decreasing their risk of developing infections which affects their growth, causes treatment delays and affects the overall quality of life (Nieuwoudt, 2011).

In this study information on current dietary intake, home feeding patterns, quality and quantity of food and food preferences, feeding environment, food allergies and intolerances were obtained from parents and caregivers during initial hospitalization for the initiation of induction treatment and during all treatment phases in order to assess the nutritional intake of patients. Oral feeding was generally recommended as the first option of feeding especially for children with a low nutritional risk. Nutrition support in the form of oral nutritional supplements in conjunction with an age-appropriate diet or enteral feeding in combination with an age-appropriate diet was only initiated based on weight loss, severity of treatment-related side-effects which caused a decrease in oral intake. In general, patients experienced phases of excessive intake when on steroids

followed by a reduced intake for the rest of the course of treatment. During the first phase of treatment (induction) subjects were treated with a high daily dose of steroids in order to induce remission, this increased their appetites, and minimized the symptoms of nausea and vomiting. After remission (from the consolidation phase onwards) steroid therapy was transient.

A few factors besides those directly related to the disease and its treatment such as unfamiliar foods and meal patterns, hospital routines, learned food aversions, feeding environment and meal timings also contributed to an inadequate food intake during the induction cycle. Subjects often had limited time to eat due to their treatment and investigation protocols coinciding with mealtimes. Extended periods of hospitalization especially during the induction phase resulted in subjects growing tired of the repetitive menus and they developed a food aversion to hospital meals. The Cancer and Leukemia in Childhood `Fit to eat` campaign which was launched in the United Kingdom as a result of parent complaints that hospital meals were unappealing, poorly prepared, not age-appropriate, lacked choice and was served cold or missed due to treatment and investigation protocols coinciding with mealtimes aimed at eliminating the inconsistencies in hospital food provision for children with cancer (Selwood *et al*, 2010). This campaign which was adopted by NHS hospitals in the United Kingdom are reviewing existing national nutritional guidelines to ensure that all children with cancer are given age-appropriate nutritious meals when they are in hospital.

Children who receive treatment for long periods of time are known to be more prone to having poor appetites and diminished energy intakes as the medications used in chemotherapy alter taste perceptions which include sourness, bitterness or a metallic taste when consuming foods. Changes in taste were directly linked to the development of anorexia which was described as a major cause of malnutrition in patients on cancer treatment (Owens *et al*, 2013). In this study the highest incidence of anorexia was reported during interim maintenance treatment. It has been established in the literature that the interim maintenance phase of chemotherapy is the most demanding phase of treatment causing a number of treatment-related side-effects and the least weight gain in children. As previously mentioned subjects were found to have the highest weight loss percentages during the consolidation (80%) and interim maintenance (65%) phases of treatment. It could therefore be argued that a decreased daily energy intake combined with treatment-related side-effects was contributing factors in weight loss in these subjects.

In some cases, the use of oral nutritional supplements as a means of nutrition support was started on a prophylactic or preventative basis rather than on a treatment basis for reasons of perceived

risk rather than actual risk. This study showed that a high proportion of subjects received some type of nutritional support (high calorie high protein diet and/ or oral nutritional supplements and /or enteral feeds) during the course of treatment in order to avoid nutritional depletion. Almost all subjects received at least one type of nutritional support during the entire course of treatment reflecting the intensity of the chemotherapy and duration of the treatment. The treatment could span around 2-3 years without much break between cycles in order to induce and maintain remission (Owens *et al*, 2013).

At the end of induction treatment five of the twenty subjects were found to have a loss in weight with no change in stature; three of the five subjects had a weight loss greater than 5%. The families of two of the three subjects with significant weight loss agreed to nasogastric tube insertion to supplement the oral intake of the subjects and one family refused. At the end of interim maintenance treatment the two subjects on nasogastric tube feeds showed a positive gain in weight and stature; which warranted stopping the nasogastric tube feed. The subject whose family refused nasogastric tube insertion continued to lose weight and did not gain height during the remaining course of treatment.

A study by Ijpma *et al* (2016) conducted on 60 adult patients with gastric cancer found the palatability of milk-based vanilla oral nutritional supplement to decrease over time, namely before, during and after chemotherapy; however the palatability of a milk based strawberry oral nutritional supplement was preferred before, during and after chemotherapy. It was therefore the recommendation of this study to offer a variety of types and flavors of oral nutritional supplements to malnourished cancer patients throughout the treatment period. In this study a variety of flavors of age-appropriate supplements were offered to subjects to prevent taste fatigue and improve acceptance. The vanilla flavored oral nutritional supplement was best tolerated by all subjects during the entire course of treatment. In light of this finding, more research is needed to investigate the taste and smell changes in pediatric cancer patients undergoing chemotherapy.

Enteral feeding in the form of a nasogastric tube feed was commenced in subjects with suboptimal intake. Weight loss as a result of a poor oral intake and poor acceptance to an oral nutritional supplement was the main reasons for starting an enteral feed for subjects in this study. Jeejeebhoy and Keith (2005) and Sala *et al* (2004) supported enteral feeding of cancer patients and also mentioned the enteral route to be more practical, have a lower risk of infection and safer (maintains gut integrity and reduces the risk of bacterial translocation). Parenteral nutrition was

not prescribed as route for nutrition support in subjects in this study, as all subjects had normal gastrointestinal function.

During the consolidation, interim maintenance, delayed intensification and maintenance cycles of treatment nutrition intervention sessions with the dietitian were missed due to the multitude of tests, procedures and visits of subject`s to other specialties. During the above mentioned treatment cycles subjects were only referred to the dietitian service if they were to be started on an oral nutritional supplement or already receiving an oral nutritional supplements or were to start an enteral feed.

In summary it has been widely recognized in the literature that the nutritional status of a child is likely to be affected by cancer at some point during the disease. The results of this study showed that some phases of treatment may increase the risk for weight loss. In this study pediatric subjects on treatment for ALL underwent changes in nutritional status as manifest by a reduction in growth, weight gain and weight loss. Although the anthropometric z-scores did not significantly change between diagnosis and the end of treatment, the percentage weight loss of patients during cycles was significant. Malnutrition in children with cancer should not be accepted or tolerated as an unavoidable process at any stage of the disease. Early nutrition intervention should be considered to prevent weight loss or excessive weight gain as a result of treatment-related complications and all nutritional concerns should be measured within the perspective of the child`s growth and development. Social and emotional issues also need to be addressed during and after treatment to ensure that children with cancer can function normally within the school system and society at large. Although the sample of subjects in this study was small it showed that the growth of children with ALL in the United Arab Emirate has a pattern different to that in most developing countries where malnutrition is common. More research is needed within the context of the United Arab Emirates to analyze the impact of nutrition intervention strategies during treatment on the morbidity, mortality and quality of life of pediatric cancer survivors.



CHAPTER 6

THE DEVELOPMENT OF A NUTRITION SUPPORT PROTOCOL

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The development of a nutrition support protocol

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy treated at Sheikh Khalifa Medical City (SKMC). Patients on treatment (chemotherapy) for ALL developed numerous physical, medical and nutrition related conditions as a result of the treatment which affected their tolerance to meals and feeds. This made nutritional support extremely challenging.

In this study treatment delays between treatment phases occurred as a result of neutropenia, diarrhea, skin rash, fever, vomiting, thrombocytopenia, upper respiratory tract infection and elevation in liver enzymes. The most common reasons for treatment delays between treatment phases were neutropenia, diarrhea and fever. At the start of consolidation treatment 40% of subjects experienced a delay; at the start of interim maintenance treatment 30% of subjects experienced a delay; at the start of delayed intensification 10% of subjects experienced a delay and at the start of maintenance treatment 20% of subjects experienced a delay.

Subjects also experienced the greatest number of treatment-related complications during the induction, consolidation, interim maintenance and delayed intensification phases of treatment and the lowest number during the maintenance phase. During the induction phase the most common nutritionally related complications were appetite changes, nausea, vomiting, diarrhea, anorexia, hyperglycemia, taste changes, tumor lysis syndrome and constipation. During the consolidation phase the most common nutritionally related complications were appetite changes, nausea, vomiting, diarrhea, anorexia, taste changes, constipation, mucositis, stomatitis and pharyngitis. During the interim maintenance phase the most common nutritionally related complications were appetite changes, nausea, vomiting, diarrhea, anorexia, taste changes, constipation, mucositis and stomatitis. During the delayed intensification phase the most common nutritionally related complications were appetite changes, vomiting, diarrhea, anorexia, taste changes, constipation, mucositis and stomatitis. During the maintenance phase there was an absence of nutritionally related complications.

In this study, subjects often experienced a lack of appetite which was exacerbated by nausea, vomiting, mucositis, stomatitis, taste changes, constipation, diarrhea and metabolic abnormalities. Nutrition support in the form of a high calorie high protein diet with snacks and / or the addition of a standard or high calorie high protein age-appropriate oral nutritional supplement and/ or the introduction of a nasogastric tube feed either as a sole source of nutrition or as an overnight feed was initiated when a subject showed signs of weight loss as a result of the treatment. Total parenteral nutrition was not prescribed for any subjects in this study as subjects

responded well to dietary supplementation with oral nutrition supplements and enteral feeds. Nutrition support was also not initiated in subjects who were able to maintain normal growth during treatment. To date there are no universally agreed criteria for the duration of nutrition support, timing and type of formula composition for use in pediatric oncology due to the broad scale of the disease and complexity of treatment modalities and their side-effects (Bauer *et al*, 2011).

In this study the distribution of anthropometric z-scores found the highest percentage of stunting during the start and end of consolidation (10%) and interim maintenance treatment (10%). There was a low percentage of underweight during all phases of treatment. The highest percentage of overweight was at the start (10%) and end (10%) of induction treatment and at the end of maintenance treatment (10%). Weight loss expressed as a percentage of body weight provided a more accurate estimate of the true significance of weight loss in subjects during cancer treatment (chemotherapy) in this study. A weight loss of greater than 5% of body weight over a period of one month is considered a sign of nutritional deprivation even when the subject is not classified as undernourished by anthropometric parameters (Bauer *et al*, 2011; Jeejeebhoy and Keith, 2005). At the end of the induction phase 15% of subjects lost more than 5% of their body weight; at the end of consolidation treatment 40% of subjects lost more than 5% of their body weight; at the end of the interim maintenance treatment 25% of subjects lost more than 5% of their body weight and at the end of the delayed intensification and maintenance phases of treatment none of subjects lost more than 5% of their body weight.

From the results of this study a significant improvement in weight was observed during the induction, consolidation, interim maintenance and delayed intensification phases of treatment as a result of nutritional support in the form of an oral nutritional supplement and or an enteral feed. Aggressive nutritional support in the form of enteral feeding enabled subjects who experienced a significant weight loss during the second phase of treatment (consolidation) to successfully reach normal growth centiles during the third stage (interim maintenance) and fourth stage of treatment (delayed intensification). A significant improvement in the longitudinal growth was also observed in subjects during the interim maintenance, delayed intensification and maintenance phases of treatment at initiation of nutritional support in the form of enteral feeds. This suggests the positive effect of nutritional support in preventing further nutritional depletion and counteracting undernutrition *per se*.

Within the health care environment it is common practice for dietitians to document the positive outcomes of the medical nutrition therapy they provide so as to develop nutrition protocols to standardize the nutrition practice guidelines within similar populations. The main aim of this nutrition support protocol is to assist healthcare professionals involved in the management of pediatric cancer (ALL) to optimize the nutritional status of patients by using clinical experience and evidence based guidelines alongside accepted best practice in order to maximize treatment outcomes and enhance the quality of life of these patients. Figure: 1 below illustrates a nutrition support protocol for the management of Acute Lymphoblastic Leukemia in childhood.



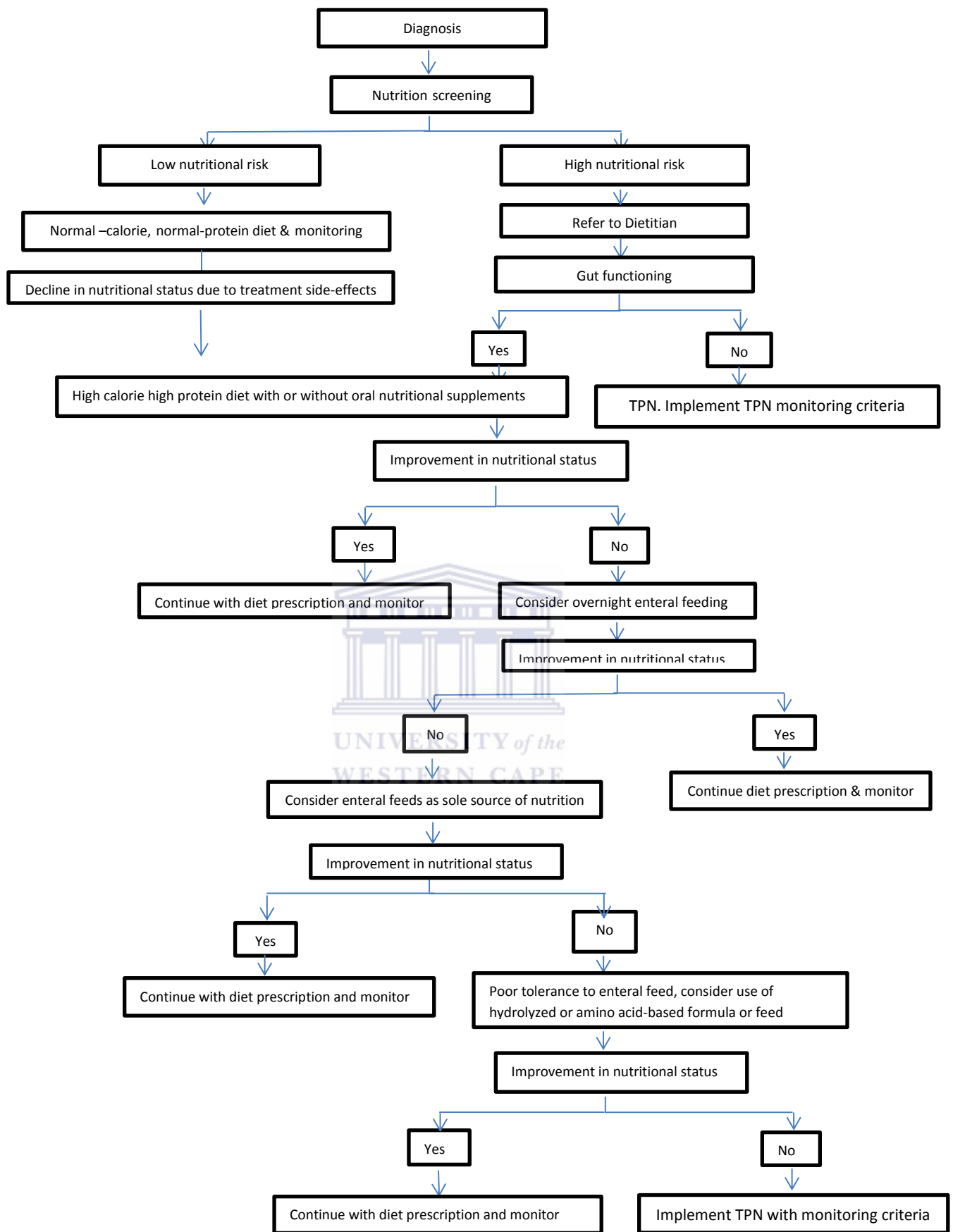


Figure: 1 A nutrition support protocol for the Management of Acute Lymphoblastic Leukemia in Childhood.

In order to accomplish this task the nutrition protocol needs to provide the necessary tools for nutrition management which includes screening, assessment, intervention and evaluation.

Early identification of undernourished patients from diagnosis and throughout the length of the treatment process can be accomplished by nutritional screening (Bauer *et al*, 2011).

Nutrition screening tool

In 2015 a screening tool for childhood cancer called SCAN was developed and validated for use in this population by Murphy *et al*. Incorporation of this tool into the patient`s electronic medical record at SKMC will improve the screening of each subject at diagnosis and during each treatment visit to ensure that the nutrition interventions in place are suitable and effective. The early identification of nutritional risk is paramount in providing a high standard of nutrition care that can often prevent the need for more aggressive nutritional support later during the treatment phase. In order for a validated screening tool to be effective updated anthropometric measurements for weight and height is of paramount importance during each outpatient or treatment visit.

Nutrition assessment

Current methods of assessing the nutritional status of children involve the following (Nieuwoudt, 2011; Ladas *et al*, 2005):

- Anthropometry: a combination of objective anthropometry (weight, height, BMI).
- Biochemical and immunologic measurements (visceral proteins (prealbumin, transferrin and retinol binding protein); blood glucose levels; hemoglobin; hematocrit; lymphocyte count; lipid profiles)
- Clinical assessment to find signs and symptoms of nutrient deficiencies or excesses (the absence or presence of oedema, cachexia, obesity, skin changes, dry mucous membranes, petechiae or ecchymoses, healing of wounds, glossitis, stomatitis and cheilosis and the evaluation of body composition- including fat and muscle stores).
- Dietary history (home feeding regimes, food preferences, types and textures, food allergies, food intolerances, feeding environment, problems when chewing or swallowing, religious and cultural food habits, feeding skills of the child based on the child`s age, stooling habits).

Once a patient has been screened, assessed and his/her nutrition risk has been determined the nutritional care protocol will be followed. If a subject is at high nutritional risk early nutritional

intervention will be considered to prevent further weight loss and nutritional deterioration. The decision for nutritional support will involve discussion with the multidisciplinary team, the dietitian and the family of the subject. The level of intervention will vary depending on the individual subject's nutritional status. Further nutrition support may be accomplished in the following ways to maintain body stores as close to ideal as possible, minimize weight loss and promote appropriate age related growth and development: by oral intake (diet alone or a combination of diet + oral nutritional supplement); by enteral nutrition and by parenteral nutrition.

Oral intake

Oral feeding will be recommended as the first method of choice especially for ALL subjects with a low nutritional risk. This will involve individualized meal plans to accommodate personal food preferences to achieve realistic achievable nutritional goals. Nutrition education on age-appropriate, energy dense foods (based on the subject's culture and traditions) will be provided to caregivers. If a subject's oral intake deteriorates during treatment the introduction of small frequent meals, in addition to an oral nutritional supplement will be considered. There is a wide range of oral nutritional supplements available in a variety of styles (milk based or juice based or as a milkshake) and flavors and energy densities (1 kilocalorie per milliliter or 1.5 kilocalorie per milliliter).

In some cases, the modification of food textures maybe required to facilitate chewing and swallowing to accommodate mucositis and stomatitis (side-effects of cancer treatment). Dry mouth and changes in taste perception may affect oral intake of meals and snacks. Excessive weight gain as a result of steroid treatment may develop; nutrition education on healthy eating should be shared with the family to enable them to provide the subject with healthy meals and snacks.

Enteral feeding

Enteral feeding will be provided for those subjects with suboptimal intake and a normal gastrointestinal tract. Subjects with swallowing difficulties or mucositis will be fed with the use of a nasogastric tube for duration of up to 3 weeks or by a gastrostomy tube if the duration of feeding is expected to be greater than 3 weeks. Feeds maybe administered as a continuous feed (18 or 20 hours) or as bolus feeds every 3 to 4 hours or at night only so as to maintain an oral intake during the day. Enteral feeding is always considered to be more practical and safe in children with cancer than parenteral nutrition regimes.

The recommended criteria for starting enteral feeding according to Bauer *et al* (2011) are:

- Weight two centiles below height centile.
- Percentage weight for height < 90% of the ideal.
- Decrease in current percentiles for weight or height of two centiles.
- Total weight loss > 5% since diagnosis.
- Reduced oral intake of < 70% of estimated average requirement for > 5 days.

Enteral nutrition as a sole source of nutrition or as an overnight enteral feed has been found to be safe and effective in the home environment for pediatric cancer patients who are unable to consume an adequate oral diet. It also has a lower risk for infection, preserves gut integrity and reduces bacterial translocation and is thus recommended since it is more practical and safer than parenteral nutrition (Bauer *et al*, 2011 citing Rickard *et al*, 1986). Multiple studies have found success in improving the nutritional status of children by means of nasogastric tube feeds, during intensive cancer treatments including bone marrow transplantation with minimal complications (Selwood *et al*, 2011 citing De Swarte-Wallace *et al*, 2001; Pietsch *et al*, 2000; den Broeder *et al*, 1998).

Enteral formulas containing intact protein was reported to be well tolerated by children during chemotherapy however following chemotherapy protein hydrolysate and amino acid based formulas were found to be better tolerated as children as children may display reduced gastrointestinal motility with a risk for malabsorption (Selwood *et al*, 2011 citing Ward, 2003).

Nasogastric and nasoduodenal feeding is recommended for short duration feeding as these feeding devices cause nasal discomfort, recurrent pulmonary aspiration and easy tube dislodgment (El- Matary, 2008). For long duration feeding, gastrostomy (a feeding tube which is inserted directly into the stomach through an opening in the anterior abdominal wall) or jejunostomy (a tube inserted directly into the small intestine) feeding tubes are recommended.

The side-effects of cancer treatments such as nausea, vomiting and diarrhea pose limitations to the use of enteral nutrition support in cancer patients however the use of prokinetic agents and post pyloric feeding has been reported in the literature to minimize vomiting (Barbosa *et al*, 2012). Enteral nutrition is discouraged in cancer patients with mucositis and enteral tube insertion is not recommended in children with neutropenia or thrombocytopenia as these children have an increased risk of bleeding during feeding tube insertion (El- Matary, 2008). A study conducted by Barbosa *et al* (2012) found malnourished children with cancer to show improved

growth parameters, in terms of z-scores for weight-for-age and BMI, with initiation of enteral nutrition during cancer treatment.

Total parenteral Nutrition

Total parenteral nutrition is recommended for those subjects whose enteral feeding regimes cannot provide adequate nutrition. A risk benefit analysis needs to be performed to justify the use of parenteral nutrition in cancer subjects because of its life threatening complications. The choice of central versus peripheral parenteral nutrition depends on the length of therapy. Peripheral parenteral nutrition is recommended for short term therapy which usually lasts between 7 to 10 days. Parenteral nutrition therapy requires more monitoring than enteral nutrition and carries the highest incidence of septic complications (Nieuwoudt, 2011). Most studies aiming to assess the effectiveness of TPN in pediatric cancer patients have found a positive effect on reversing malnutrition during the initial phase of treatment (Andrassy *et al*, 1998; Rickard *et al*, 1986; Donaldson *et al*, 1982). TPN is however associated with liver disease which remains a dreaded complication of parenteral nutrition in children and the risk of refeeding syndrome remains a serious complication in aggressive nutritional rehabilitation (by the enteral and/or the parenteral route) in severely malnourished children with cancer (Nieuwoudt, 2011).

Once the nutrition support plan has been implemented a plan for monitoring is vital in order to evaluate the effectiveness of the nutrition support. Nutrition screening is also important during all phases of treatment to ensure that the nutrition support plan in place meets the nutritional goals of the patient. Weight and height measurements should be updated during each outpatient visit to reassess the ongoing nutritional status of the patient.

In conclusion numerous factors must be considered when addressing the nutritional concerns of pediatric cancer patient. This nutrition support protocol, if approved by the pediatric healthcare team at SKMC, will serve as an important tool to improve the quality of care of children on cancer therapy.

CHAPTER 7
CONCLUSION
RECOMMENDATIONS



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7.1. Conclusion

It has been widely recognized in the literature that the nutritional status of a child is likely to be affected by cancer at some point during the disease. The results of this study showed that some phases of treatment may increase the risk for weight loss. In this study pediatric subjects on treatment for ALL underwent changes in nutritional status as indicated by a reduction in growth, weight gain and weight loss. Although the anthropometric z-scores did not significantly change between diagnosis and the end of treatment, the percentage weight loss of patients during cycles was significant. Malnutrition in children with cancer should not be accepted or tolerated as an unavoidable process at any stage of the disease. Early nutrition intervention should be considered to prevent weight loss or excessive weight gain as a result of treatment-related complications and all nutritional concerns should be measured within the perspective of the child's growth and development. Social and emotional issues also need to be addressed during and after treatment to ensure that children with cancer can function normally within the school system and society at large. Although the sample of subjects in this study was small it showed that the growth of children with ALL in the United Arab Emirate has a pattern different to that in most developing countries where malnutrition is common. More research is needed within the context of the United Arab Emirates to analyze the impact of nutrition intervention strategies during treatment on the morbidity, mortality and quality of life of pediatric cancer survivors.

7.2. Recommendations

Cancer during childhood can negatively affect a child's ability to achieve normal growth and development. In this study cancer treatment in the form of chemotherapy independently affected a child's nutritional status during stages of treatment. Undernutrition during cancer treatment can increase morbidity and mortality (Ladas *et al*, 2005) which in turn decreases the quality of life by increasing hospital admission. On the other hand, over nutrition during cancer treatment has been found to increase the risk of morbidity, mortality and chemo induced toxicity (Tan *et al*, 2013). Appropriate nutritional care, comprising nutritional assessment and nutritional intervention, is therefore becoming increasingly important to maintain optimal growth and development during all stages of cancer treatment.

7.2.1. Nutrition screening tool

In children the first measurable sign of undernutrition is a decrease in body weight. It is therefore pivotal that during cancer treatment undernutrition be promptly detected and treated so as to avoid changes in the normal growth and development of a child.

The first step in the management of malnutrition is the prompt detection of patients who are malnourished or at risk for malnutrition through the process of nutritional screening. Nutritional screening is generally carried out by members of the nursing team at first contact with the patient (McCarthy *et al*, 2012). The tool used for screening should be quick, simple to complete and validated for use in children with cancer. To date there is only one nutrition screening tool called SCAN which has been designed and validated to detect undernutrition in children with cancer. However this tool cannot be used to detect patients at risk for obesity during cancer treatment (Murphy *et al*, 2015).

At Sheikh Khalifa Medical City (SKMC) the nutrition screening tool currently incorporated into the electronic pediatric patient chart has not been validated for use in children which makes it an inaccurate and unreliable tool in detecting the nutritional risk of pediatric patients receiving treatment. This is a limiting factor for improving the nutritional support of children on cancer treatment. It is therefore recommended that the Nutrition Screening Tool for Childhood Cancer (SCAN) be incorporated in to the electronic patient record at SKMC to improve the nutrition screening process. Nutritional risk screening is essential for the care of pediatric cancer patients at diagnosis and at regular intervals (start and end of each phase of treatment) in order to identify children at risk.

7.2.2. Anthropometric measurements

The most sensitive indices for growth in children include weight and height-for-age and body mass index. In this study, growth was assessed by extrapolation of recorded weight and height data from the WHO growth charts within the electronic medical record at diagnosis and at the start and end of each treatment phase. Updated weight and height measurements are required throughout the duration of treatment in order to accurately assess the patient`s growth. It has been noted that in this study more attention was given to recording an updated weight than a height; as chemotherapy drug doses are based on a patient`s weight rather than height.

7.2.3. Nutrition support

Nutrition support is initiated based on the results of the nutritional assessment which includes weight loss, excessive weight gain, nutritional intake and the gastrointestinal side-effects of the cancer treatment. This study showed that a high proportion of patients experienced a multitude of treatment-related side-effects which affected their oral intake; nutritional support was therefore initiated in order to prevent nutrition depletion. This observation reflected the need for a nutrition support protocol for patients on cancer treatment once malnutrition has been identified. Figure 1 above was developed based on the results and experience obtained with the study.

7.2.3. Cook to order service

The food service delivery system in use at SKMC does not provide suitable age-appropriate meals and flexibility in meal timings to meet the individual needs of a child with cancer. This leads to a high level of dissatisfaction with food provision to children with cancer in hospital. In order to address these inconsistencies in food provision to children with cancer in hospital it is recommendation of this study to provide a `cook to order service` which allows patients to order meals off a `room service menu throughout the day to accommodate treatment timings, food preferences and child friendly portion sizes to suit each age group and appropriate crockery and cutlery for children. The oncology dietitian will need to work closely with the chef to discuss the individual needs of the children on cancer treatment and would help the oncology dietitian to re-channel her resources towards more appropriate referrals than completing menus with personal food preferences.

7.2.4. Biochemistry

It is recommended that a test for prealbumin be added to the routine laboratory tests completed at the start and end of each phase of treatment. Medical staff working in pediatric oncology will need to be educated on the benefits of using prealbumin versus albumin as a marker for nutritional status as serum albumin levels do not reflect recent dietary intake and may be found to be normal in patients with severe protein energy malnutrition. Prealbumin is a more sensitive marker to assess the nutritional status of children receiving chemotherapy as chemotherapeutic drugs have the ability to negatively affect the nutritional intake of a child within a short time of starting chemotherapy.

7.2.5. Food diary

The use of a three day food record diary is recommended to accurately assess the dietary intake of pediatric patients on cancer treatment during the consolidation, interim maintenance and delayed intensification and maintenance cycles when patients are at home. The food diary will be useful to the caregiver as it does not rely on his or her memory to recollect the dietary intake of the child between treatment sessions and it will be useful to the dietitian/healthcare professional during the nutrition assessment session to obtain a realistic view of the patient's actual intake versus perceived intake. The food diary will allow the dietitian to correctly assess and validate the dietary intake of a child on treatment for cancer.



CHAPTER 8

LIMITATIONS OF THE STUDY



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Limitations of the study

Although this retrospective study has reached its aim there were some unavoidable limitations. This chapter discusses the limitations of this study.

8.1. Sample size

The first limitation was the sample size. Although all patients included in the study have the same type of cancer, have undergone cancer treatment under the same protocols and policies and data gathering are the same; the sample size was small. A larger sample size with a multicenter approach is needed for better understanding of the effect of ALL on the nutritional status of children undergoing treatment in the United Arab Emirates.

8.2. Study Design

The second limitation was the study design. In this study a retrospective study design was used to collect data from electronic patient medical records as it is less expensive to conduct since outcome and exposure has already occurred and the resources are mainly directed at data collection and analysis. A major disadvantage of this type of study design is that the outcome assessment cannot be controlled and therefore has to rely on others for record keeping. This study was therefore limited by the detail of anthropometric measurements obtained from electronic patient chart review. Although a hospital protocol exists for routine growth measurements (weight, length/height, head circumference) not all of these were routinely measured by staff. In particular length/height and head circumference was not routinely measured as inpatients receiving induction chemotherapy or as outpatients on their routine visits to receive chemotherapy. Weight measurements were seen as the main priority as the weight of a patient was needed to determine the appropriate drug dose for chemotherapy; the accuracy of length measurements recorded in the electronic patient records during treatment was therefore questionable.

8.3. Diet history

The third limitation of this study was the information pertaining to the dietary intake of a patient prior to diagnosis and during treatment (consolidation, interim maintenance, delayed intensification and maintenance treatment). In this study information on current dietary intake, home feeding patterns, quality and quantity of food, food preferences, feeding environment, food allergies and intolerances were obtained from parents and caregivers during initial hospitalization to start induction treatment and during each treatment session. Self-reporting of

dietary intake was limited by the individual`s memory and the emotional influence of the disease on the caregiver. Post remission most parents and caregivers were apprehensive about the patient`s nutritional intake as they wanted to avoid the child`s hospitalization for further evaluation as it was emotionally overwhelming for the family.

8.4. Serum albumin

The forth limitation of this study was the use of serum albumin levels as an indicator of nutritional status. Many studies reject albumin as an indicator of nutritional status due to its long half-life of 20 days. Low albumin levels may occur in patient`s undergoing treatment as a result of the chemotherapy and/ or use of corticosteroids. Serum albumin levels can also be affected by many other factors besides nutrition such as inflammation, all of which result in a low sensitivity and specificity to changes in nutritional intake. Inflammation is known to contribute to a net protein loss as a result of catabolism therefore albumin levels must be analyzed in relation to C-reactive protein levels in order ascertain whether the low albumin levels are as a result of a poor nutritional status or as a result of inflammation.





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APPENDICES



UNIVERSITY *of the*
WESTERN CAPE

APPENDIX I: Letter to Institutional review board research Ethics Committee

Looventhree Pillay

Senior Dietitian

Sheikh Khalifa Medical City

PO Box 767879

Abu Dhabi, UAE

17 May 2015

The Chairperson

The Institutional Review Board Research Ethics Committee

Sheikh Khalifa Medical City, Managed by Cleveland Clinic

PO Box 51900

Abu Dhabi, UAE

RE: Letter of Request to conduct research at Sheikh Khalifa Medical City

Dear Sir / Madam

I am currently a final year MSc student at the University of Western Cape (South Africa). As part of the fulfillment of my degree I will need to complete a research project and write it up as a thesis. I wish to apply for permission to conduct this research at SKMC. The topic of my study is to investigate the nutritional status of children between the ages of 1-14 years old who have been newly diagnosed with acute lymphoblastic leukemia. I wish to conduct a retrospective study by reviewing anthropometric measurements (weights and heights) of patients from the electronic patient charts. The purpose of my study is to develop a comprehensive nutritional care program for patients diagnosed with acute lymphoblastic leukemia at Sheikh Khalifa medical City.

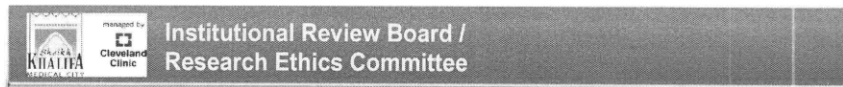
I am looking forward to receiving a positive response towards my request.

Thank You

Kind Regards

Looventhree Pillay

APPENDIX II: Approval letter from Institutional review board research Ethics Committee



APPROVAL LETTER



14th June 2015

Ms Looventhree Pillay
Senior Clinical Dietitian
Department of Clinical Nutrition
SKMC, Abu Dhabi, UAE

Ethics Approval Reference No: <i>Please quote this ref # in all correspondence</i>	REC-14.06.2015 [RS-380]
Research Title:	The nutritional status of children (1-14 years old) newly diagnosed with Acute Lymphoblastic Leukemia (ALL) at Sheikh Khalifa Medical City.

Dear Ms Pillay,

Thank you for submitting your research project for IRB review and approval.

An expedited review of the submitted documents was done and the proposal was found to be merely a chart review of pediatric patients with Acute Lymphoblastic Leukemia (ALL) seen and diagnosed at Sheikh Khalifa Medical City aiming to confirm a need for comprehensive nutritional care program for these patients.

Since no ethical issues from IRB's perspective was noted, the proposal was approved as designed highlighting strict compliance on the confidentiality linked to the participant's data.

Kindly note that approval was granted on the understanding that the research team complies on the applicable guidelines and regulations governing the conduct of clinical trials¹ particularly as to the following:

- *Any amendments or significant change which occurs in connection with this study and/or which may alter its ethical consideration, premature suspension or termination of the study must be reported immediately to the Research Ethics Committee Office.*
- *IRB has an authority to suspend or terminate approval of this research study if not being conducted in accordance with the IRB's requirements or has been associated with unexpected serious harm to subjects.*

¹ <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

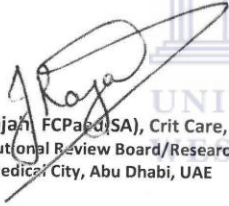
- *The investigator should provide the Research Ethics Committee office with a **final report** within **three (3) months** after Termination or Completion of a research study or the investigator's part of the research study.*
- *The investigator should comply with the REC's request for progress report whenever the future audits on any REC approved studies are required. A completed Progress Report Form (attachment 1) should be submitted to the REC office.*
- *Research office should also be notified of the arrangements for publication or dissemination of the research including any feedback to participants.*

SKMC Institutional Review Board/Research Ethics Committee (IRB/REC) has been organized and operates according to the Good Clinical Practice (GCP) Guidelines.

- *Granted an authorization to conduct human subjects research by Health Authority Abu Dhabi (HAAD) - Research Authorization #2011.01.*
- *Received accreditation from the Office for Human Research Protections (OHRP), US Department of Health and Human Services (HHS). <http://ohrp.cit.nih.gov/search/search.aspx>*
 - *Institution Registration # IORG0006896 expires 20 May 2018*
 - *IRB Registration # 00008262*
 - *Federal Wide Assurance (FWA) # FWA00018992 expires 14 June 2017*

On behalf of the IRB/REC members, wishing you all the best towards a successful completion of this research project.

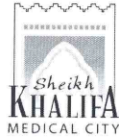
Sincerely,


Dr. Jaishen Rajan, FCPaed(SA), Crit Care, DA
Chairman, Institutional Review Board/Research Ethics Committee
Sheikh Khalifa Medical City, Abu Dhabi, UAE



Attachment: 1. Progress Report by the Principal Investigator

JR/doree



managed by
**Cleveland
Clinic**

Clinical Dietetics Department

17 May 2015

To Whom It May Concern:

I thereby confirm that the research project undertaken by Looventharee Pillay as fulfillment of her MSc degree will not impact on her current clinical workload.

The purpose of her study once completed will benefit the department as it involves the development of a comprehensive nutritional care program for pediatric patients diagnosed with acute lymphoblastic leukemia at Sheikh Khalifa Medical City.

Truly yours,



Jillian Rigg
Manager
Clinical Dietetics Department



APPENDIX III: Approval from UWC Ethics Committee to conduct the research

[Home](#) **MISS L PILLAY (LOOVENTHAREE)**

Programme:

Programme: MSc Nutrition Management
Year Started: 2013
Faculty: FACULTY OF COMMUNITY AND HEALTH SCIENCES
Department: SCHOOL OF PUBLIC HEALTH

Supervisors:

Supervisor: DR ERNESTA KUNNEKE [EKUNNEKE@UWC.AC.ZA]
Co Supervisor: MS NASHEETAH SOLOMONS [NSOLOMONS@UWC.AC.ZA]

Thesis Title: [View Detail](#)

The development of a nutritional support protocol for children with Acute Lymphoblastic Leukemia (ALL): Twenty case studies from Sheikh Kalifa Medical {Please click **VIEW DETAIL** for more.}

Progress Report: [View History](#)

Year: 2016 [Email me a Progress Report Template](#) [Upload a completed Progress Report](#)

Supervisor	SHD Committee
Status	Approved
Date	2016/10/29
Comment	Finalise thesis for Nov submission-examiners to be appointed

Examination:



APPENDIX IV: Data Collection Form

Patient Number:

Gender (circle): Male Female

Cancer Diagnosis: Acute Lymphoblastic Leukemia (ALL)

High risk Y N Low Risk Y N

Date of Birth: dd/mm/yyyy

Age at diagnosis: in years and months

Date of diagnosis: dd/mm/yyyy

Anthropometrics:

WHO growth charts	Admission Date : Age:	Induction Date: Age:	Consolidation Date: Age:	Delayed Intensification Date: Age:	Maintenance Date: Age:
Weight (kg) Wt-for-age z-score					
Height (cm) Ht-for-age z-score					
HC (cm) HC for age z-score					
Wt-for-Ht z-score					
BMI-for-age z- score					

Laboratory values:

	Admission	Induction	Consolidation	Delayed Intensification	Maintenance
	Date:	Date:	Date:	Date:	Date:
Creatinine (micromole/L)					
Urea (mmol/L):					
Total protein (g/L)					
Albumin (g/L)					
MCV (fL):					
MCH (pg):					
MCHC (g/L):					
Platelets					
WBC					
RBC					
Hgb (g/L)					
Hematocrit (L/L)					
Neutro (%)					
Lymph (%)					
Mono (%)					
Blasts (%)					

APPENDIX V: Excel Spread Sheet for Data Analysis

ALL PATIENT LIST final - Excel

1	PATIENT LIST																
2	KM	DOB	SEX	age	TREAT	Date of tr	weight	height	HC	BMI	wt for age	ht for age	BMI for age	weight change	height change	diet prescription	treatment delays
30	vomiting	nausea	diarrhea	constipation	total protalbumin	gluc	WBC	platelets	Hgb	Alk Ph	AST	ALT					

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Sheet1 Sheet2 Sheet3

READY 100%