Energy and Protein Intake during the First Week of the Pediatric Cardiac Intensive Care Unit Improves Hospital Outcomes

by

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Abstract

Provision of energy to critically ill children during hospitalization is important. However, too much or not enough energy impacts hospital outcomes. Nutrients can be delivered as enteral nutrition (EN) and/or parenteral nutrition (PN) to promote recovery post-surgery, preserve body weight, and improve hospital outcomes including decreased length of stay, ventilator support days, and infections. This study aimed to evaluate the energy and protein intake through EN or PN during the first week of Pediatric Cardiac Intensive Care Unit (PCICU) admission, and its association to hospital outcomes including hospital length of stay (LOS), PCICU LOS, ventilator support days, and infections. Changes in anthropometric z-scores were measured. All patients admitted to the PCICU between March 1, 2016 and June 30, 2018 with a PCICU stay of seven days were included. Demographics, clinical conditions, anthropometric measurements, total daily energy (kcal/kg/day) and protein (grams/kg/day) intake were collected from patient medical charts. A total of 253 patients were included and categorized as surgical (n=203) or non-surgical patients (n=50), and the analyses were independently performed. Energy requirement were estimated by two-thirds of basal metabolic rate from World Health Organization predictive equation (median 31kcal/kg/d) and compared patients receiving energy below or above the predictive value. For patients who had heart surgery, mean energy intake below 31kcal/kg/d was associated with longer PCICU LOS (11, IQR:6-17), total hospital LOS (27, IQR:15-49), and ventilator days (10, IQR:6-15) compared to those receiving energy greater than 31kcal/kg/d; (PCICU LOS 7, IQR:3-10; Hospital LOS 14, IQR:10-24; ventilator days 4, IQR:2-7; $p<0.001$, respectively). For non-surgical patients, no differences were observed in hospital outcomes in association with energy and protein intake ($p>0.05$). Patients receiving PN versus EN had similar hospital and PCICU LOS and infections rate. Patients receiving PN were on ventilation support for longer (7, IQR:5-14) compared to

patients receiving EN (5, IQR: 3-10). This study provides supportive evidence suggesting that providing energy, whether through EN or PN in the first seven days of PCICU admission reduces hospital LOS and promotes improved hospital outcomes.

Preface

This thesis is an original work by Luana Menegaz Boff. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, "Nutrition Improves Outcome," Pro00078007.

The study was designed by Dr. Bodil Larsen, Dr. Vera Mazurak, Gonzalo Guerra, and Luana Boff. Luana Boff wrote the study protocol, collected data, conducted the study, and completed statistical analysis with the revision of a statistician, Dr. Mohammadreza Pakseresh.

Author contributions for the manuscript-based thesis are as follows:

Chapter One of this thesis is a review of the literature to support the research problem. This literature search was conducted by Luana Boff and revised by co-authors Dr. Vera Mazurak, Dr. Bodil Larsen and Dr. Catherine Field.

Chapter Two of this thesis briefly describes the research plan for the study, its rationale, objectives, and hypothesis.

Chapter Three of this thesis is the original research study that intends to be published. In this chapter, Luana Boff performed data management including gathering patient data, statistical analysis, and writing the manuscript. Co-authors Dr. Vera Mazurak and Dr. Bodil Larsen, served as advisors and provided a critical review of the document. The statistical analysis was performed by Luana Boff and reviewed by Dr. Mohammadreza Pakseresh.

Chapter Four of this thesis is a summary of the research findings which includes a theoretical case study to confirm the consequences found in the research presented in chapter 3.

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LIST OF ABBREVIATIONS

ASPEN	American society of parenteral and enteral nutrition
BMR	basal metabolic rate
CPB	Cardiopulmonary bypass time
D	day
ECMO	extracorporeal membrane oxygenation
EN	enteral nutrition
G	grams
IC	indirect calorimetry
Kcal	kilocalories
Kg	kilograms
LOS	length of stay
MREE	measured resting energy expenditure
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
STAT	score
PICU	Pediatric intensive care unit
PCICU	pediatric cardiac intensive care unit
PN	parenteral nutrition
PRISM	score pediatric risk of mortality score

REE resting energy expenditure

RD registered dietitian

RQ respiratory quotient

RN registered nurse

WHO world health organization

Vent. Ventilator support

Chapter One: Introduction and literature review

1.1 Malnutrition in critically ill children with congenital heart disease (CHD)

Malnutrition affects 20 to 51% of critically ill children upon hospital admission and increases the risk of infection, morbidity, and mortality (Prieto and Cid 2011; de Souza Menezes, Leite, and Nogueira 2012). Critically ill children are at high risk for worsening nutritional status given their low energy reserves, low energy intake, and changes in energy expenditure dependent on the state of illness (Mehta et al. 2013). These conditions alter nutrient requirements and utilization. In addition, the presence of inflammation during illness can aggravate existing malnutrition and impacts hospital outcomes, including prolonged hospital length of stay (LOS), Pediatric Intensive Care Unit (PICU) LOS, extended periods on ventilator support, and increased number of infections (Delgado et al., 2008; Ellis, Hughes, Mazurak, Joynt, & Larsen, 2016). Studies have shown that malnutrition is associated with growth failure, poor wound healing, and impaired immune response in critically ill children undergoing surgery for congenital heart disease (CHD) (reviewed in Wong et al. 2015). Given the complex circumstances during admission to a pediatric cardiac intensive care unit (PCICU), multiple factors contribute to malnutrition. Optimal nutrition support becomes vital to alleviate the consequences of malnutrition. An adequate amount of energy is essential for organ function, preservation of lean body mass, and maintenance of immunological function. Given these factors, meeting energy requirements becomes especially critical as it can improve hospital outcomes (Larsen et al., 2013; Mehta & Compher, 2009).

1.2 Energy requirements during the critical illness

The energy requirements of a critically ill child are highly individualized. Metabolic response to injury and stress at surgery alters energy requirements characterized by changes in the metabolism of carbohydrates, protein and lipids (Evans et al. 2008). The severity of illness can impair immunological response, enhance systemic inflammation, and increase energy expenditure (Ellis et al. 2017; Martinez et al. 2015). Energy expenditure decreases during the first 2 to 3 days following admission, followed by increased energy expenditure (hypermetabolism) and catabolic responses, the intensity which depends on the severity of disease (Goday and Mehta 2015). Therefore, providing the optimal amount of energy remains challenging (Liusuwan et al. 2005; de Souza Menezes et al. 2012). Currently in the clinical setting, energy needs are determined through indirect measurement or are estimated by using predictive equations.

1.2.1 Energy expenditure: measured vs. estimated

In the clinical setting, indirect Calorimetry (IC) is the most accurate way to measure resting energy expenditure (MREE) and is a non-invasive method that measures the amount of oxygen (O_2) consumed and carbon dioxide (CO_2) produced. These values are used to calculate the respiratory quotient (RQ) to identify the substrates being predominantly oxidized by the patient (Mtaweh et al. 2018). For example, the RQ can indicate whether lipogenesis (energy excess) or catabolism (energy deficit) is occurring. An appropriate RQ ranges from 0.70 to 1.0, indicating a mixture of energy substrates (carbohydrate, protein, and fat) are being oxidized. An RQ greater than 1 indicates synthesis of lipids from glucose, and excess of calories. An RQ less than 0.7 indicates that fat is being oxidized and suggests a catabolic state or providing energy less than required to maintain energy balance and support growth (Walker & Heuberger, 2009; Liusuwan, Palmieri, Kinoshita, & Greenhalgh, 2005).

Indirect measures enable agreement between energy needs and provision of calories (i.e., feeding). The advantage of MREE is the ability to determine energy requirements at a given time precisely. However, direct measures are not feasible in many centers due to high cost, low equipment availability, and requirement of highly trained clinicians to perform the test. (Mtaweh et al., 2018;Martinez & Mehta, 2014;Liusuwan et al., 2005). When IC is not available or feasible, predictive equations are used to estimate energy needs.

Predictive equations estimate resting energy expenditure (REE) in critically ill children. Typically, these equations include a combination of weight, height, sex, and age. Despite applying similar variables, each equation can result in a different estimtes of caloric requirements. Table 1.1 compares the variables utilized in equations suggested by Schofield, Harris-Benedict, and the World Health Organization (WHO) for estimation of REE. The Harris-Benedict equation is based on weight, height, and age, while the WHO equation is based on weight and age. The Harris-Benedict equation is the oldest equation, and is currently still used in some clinical settings; however, is not considered appropriate for critically ill children due to significant overestimation (Finan, Larson, and Goran 1997). Further, these equations were derived using healthy populations as a reference, making them potentially inappropriate for use in critically ill pediatric patients who have different energy needs. The estimated value from predictive equations is taken as a point of reference to predict energy expenditure, whereas the actual value may be obtained by IC.

In all equations, calculations of energy expenditure are adjusted with activity and stress factors. The activity factor accounts for overall activity level, whereas the stress factor attempts to account for complex patient issues that may increase the metabolic rate. As assignment of both these factors is subjective, the resultant calculated energy requirement may not align with actual needs, due to high variability. Physicians are not consistently able to predict the metabolic state using stress factors (De Cosmi et al. 2017). For example, predicting energy expenditure using an assigned stress factor has been shown to miscalculate energy alterations by up to 50% in the ICU compared to indirect calorimetry measurements (Mehta et al. 2016).

Table 1. 1 Comparison of predictive equations.

Predictive Equations	**Variables in the equations** Weight	Height	Age
WHO 0-3 years [(60.9 x Wt) – 54]	✓	-	-
Scholfield 0-3 years [(0.167 x Wt) + (15.174 x Ht) – 617.6]	✓	✓	-
Harris-Benedict [66.473+(13.7516 x Wt) + (5.0033 x Ht) – (6.755 x age)	✓	✓	✓

WHO; World Health Organization. Examples of the equations for males.

Metabolic stress is highly variable in critically ill children and is dependent on many factors that alter metabolic rates including disease severity, the presence of sepsis, trauma, and life support (De Cosmi et al. 2017). Critically ill patients experience higher basal metabolic rates (BMR) due to inflammation, fever, or sepsis, whereas mechanical ventilation, sedation, dialysis, and intubation decrease metabolic rate (Martinez & Mehta, 2014). Extracorporeal Membrane Oxygenation (ECMO), which provides cardiac and respiratory support, may complicate the ability to estimate energy requirements as it decreases the energy demand of the heart and lungs. Life support performs the function of the organs, reducing tissue energy use to lowers total energy expenditure. Life support makes the calculation of energy requirements more challenging (Mehta et al. 2016). Formulas to predict energy expenditure in the critically ill pediatric population are generalized despite their use under different clinical conditions, which promotes an unreliable prediction of the real energy demands of each patient.

1.2.1.1 Studies comparing measured vs. predictive energy expenditure

To determine the differences between actual and estimations of energy requirement for critically ill children, a critical review was performed by searching the literature via systematic searches in different databases including: Cochrane Library, PubMed, OvidSP (Medline), EBSCO (CINAHL), and Scopus by using MeSH terms "Intensive Care Unit", "Pediatrics", "energy metabolism", "energy requirements", "energy expenditure" and synonymous terms. The reference list of relevant publications was also searched to find additional publications not captured by the search terms. Published literature was assessed to evaluate studies examining energy expenditure in pediatric populations (Table 1.2). For each study included, data were extracted on study design (predictive equations used and/or compared to indirect calorimetry) and outcome measurement (hypometabolic, hypermetabolic and an RQ when available).

In total, 9 studies compared measured versus predicted energy requirements; 7 were prospective, and 2 were retrospective. Studies enrolled critically ill patients with a median age range of 5 months to 11 years. All studies compared predictive equations used in the clinical setting to MREE using IC. The metabolic state of patients in these studies was classified as hypermetabolic, when MREE/estimated REE was greater than 110%, hypometabolic when lower than 90%, or normal when MREE/estimated REE was between 90 to 110% of the predicted. When total energy requirements were calculated using predictive equations, there was a 3-30% error compared to measured values from IC.

When comparing measured vs. predicted, studies show that applying a stress factor with the assumption of hypermetabolism, overestimates energy needs (Table 1.2). Liusuwan et al. (2005) show that the use of Harris-Benedict predictive equation overestimated patient energy requirements by 29%, whereas the WHO equation allowed for estimation within the acceptable

10% deviation. This indicates that the WHO predictive equation most closely aligned with the MREE in this group of patients. Mehta et al. (2009) found that 42% of patients were provided more energy than needed when a stress factor of 1 to 1.5 was applied by the nutrition team. These results suggest that a stress factor accounting for the state of illness, presence of inflammation, age, type of disease, and use of life support should be carefully applied after extensive consideration of metabolic status. The assumption of hypermetabolism should not be applied to all critically ill children. Appropriate identification of the need for a stress factor may better enable clinicians to determine energy requirements. However, caution should be taken when selecting stress factors to add to energy prescriptions, as they may significantly overestimate energy needs (Mehta et al. 2017).

Mehta et al. (2012) reported an RQ of 0.94 (0.79-1.28) in critically ill infants, suggesting overfeeding in patients with an RQ ≥1.0. Liusuwan et al. (2005) reported a mean RQ of 0.88 (0.79-0.97), suggesting adequate feeding with mixed substrate oxidation. Framson et al. (2007) compared MREE to Schofield in children between 2 and 5 years of age at three time points during hospital stay, reporting a median RQ of 0.83, 0.83 and 0.88 (0.71-1.04) 24hr after admission, 48hr following the first measurement, and at discharge, respectively. In Larsen et al (2018), overestimation was more prevalent than underestimation when WHO equation was compared to MREE. In Framson et al. (2007), twenty percent of infants were classified as hypermetabolic (>110%), and 32% as hypometabolic (<90%) when predicted by Schofield, indicating 52% of patients were fed inappropriately.

Mehta et. al. (2011) showed a high incidence of overfeeding (83%) amongst pediatric patients when predictive equations were compared to MREE. In a separate study, Mehta et. a. (2009) analyzed 14 PICU patients using IC and they found patients to be hypermetabolic (50%), and hypometabolic (42%) when MREE was compared to estimations. Studies comparing predictive equations with MREE indicates that younger patients are more likely to have inaccurate estimations (Mehta et al. 2012; Al-Biltagi et al. 2017). In general, equations tend to overestimate or underestimate the energy needs of critically ill patients exemplifying the complexity of predicting energy requirements in critically ill children and potentially contribuiting to further consequences associated with inappropriate feeding.

1.2.2 Consequences of inappropriate feeding

There is considerable evidence that predictive equations over and underestimate the amount of energy required during critical illness. An energy imbalance, resulting from a deficient or excessive caloric intake, has negative consequences. Overfeeding a critically ill infant or child leads to metabolic complications including hyperglycemia, hyperlipidemia, and increased risk of infection (Liusuwan et al., 2005;Mencı, Urbano, Jose, Garcı, & Botra, 2017). During overfeeding, fat synthesis occurs mainly in the liver (Framson et al. 2007). Underfeeding also negatively impacts hospital outcomes of pediatric patients, by prolonging the need for mechanical ventilation, depleting fat and lean body mass stores, impairing the immune response, increasing susceptibility to infection, and delaying wound healing. The depletion of glucose stores increases protein breakdown to supply glucose to vital tissues (Moore et al. 2017)

In summary, future research is needed to determine more accurate energy estimations to be used in the hospitalized pediatric population. It may be beneficial to explore equations that better estimate energy expenditure. An understanding of energy metabolism and energy needs during illness is necessary to allow adequate metabolic support. Once energy requirements have been determined, the optimal route of nutrition delivery may be selected.

Table 1. 2 Summary of studies exploring energy expenditure in critically ill children.

Author, year	Population	Methods		Outcomes	
	N, Age	IC	Predictive Equations	Metabolic State	Mean RQ
Prospective Cohort					
Larsen et al., 2018	N=139, 10mo (0.03–204)	YES	WHO	Hypometabolism – 53% (Overfed) Hypermetabolism – 34.3% (Underfed)	–
Floh et al., 2015	n= 111, 5.3mo (0.8–10.5mo)	YES	Measures of REE by IC	REE decreased from 51to 41 kcal/kg/d Prevalence hypometabolism after CPB	–
Mehta et al., 2012	n= 26, 3.6 yrs (± 2.6y)	YES	WHO	Normal and Hypometabolism –73%	–
Mehta et al., 2011	n=29, 2yrs (0.1-28y)	YES	Schofield <15yrs, HB >15 yrs old, WHO (ht not available)	Hypometabolism –83% (Overfed)	0.94 (0.79-1.28)
Botran et al., 2011	n= 46, 7.5mo (0.08-16y)	YES	Measures of RQ by IC	High variability in EE	0.74 (0.67-0.87)
Mehta et al., 2009	n= 14, 11.2 y (0.13 - 32y)	YES	Schofield <15yrs, HB >15 yrs old, WHO (ht not available) SF based on Pediatric Risk Mortality III score	Hypermetabolism – 50% Hypometabolism – 42%	Hypermetabolic group 0.85 (±0.03) Hypometabolic group 0.94 (±0.06)
Framson et al., 2007	n= 44, 5.2yrs (0-17y)	YES	Schofield vs. MREE: 1st, 24h admission 2nd, 48h after 1st, 3rd, 24h before discharge of PICU	Hypometabolism in: 1st, 22% 2nd, 42% 3rd, 35%	1st. 0.83 (0.71-0.95) 2nd. 0.83 (0.73-0.90) 3rd. 0.88 (0.72-1.04)
Retrospective					
Neef et al., 2007	n= 84, 4 y	NO	WHO, delivery vs. prescribed	Hypermetabolism – 49.9% (Underfed) Hypometabolism –25% (Overfed) in the first 4 days	–
Liusuwan et al., 2005	n= 10, 5yrs (2-10 yr)	YES	HB, Mayes, WHO	Prevalence hypometabolism	0.88 (0.77–1.1)

d; day, EE; Energy Expenditure, HB; Harris-Benedict, ht; Height, h; hour, IC; Indirect Calorimetry, kcal; calorie, kg; kilogram, MREE; Measured Resting Energy Expenditure, mo; month, n; number, PICU; pediatric intensive care unit, REE; Resting Energy Expenditure, RQ; Respiratory Quotient, SE; Standard Equations, SF; stress factor, WHO; World Health Organization, y; year. CPB; cardiopulmonary bypass surgery.

1.3 Routes of nutrition delivery

Nutrition in the ICU is usually delivered through EN, PN or EN+PN. When no feeding is provided children are in NPO (nil per os). Enteral nutrition is the preferred route as it imitates the usual route of nutrient consumption and is used when the gut is functional. EN stimulates gut motility, hormone activity and immune response (Goday and Mehta, 2015). Although EN is the preferable route of nutrition delivery, PN is often chosen to support EN. PN is recommended to complement EN to reach nutritional goals or when EN is not feasible for nutritional support. PN is needed to deliver nutrients when no other route is available.

1.4 Protein requirements in critically ill children

The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends higher amounts of protein for critical illness than what is recommended for healthy children by the World Health Organization (WHO). The recommendations for healthy children are based on the Dietary Reference Intake (DRI), which is set based on age: 0-6mo (1.52 g/kg/day); 6mo-1year (1.2 g/kg/day); 1-3yrs (1.05 g/kg/day); 4-13y (0.95 g/kg/day); 14-18yrs (0.85 g/kg/day). For critically ill children, the recommendations of protein are based on collective evidence from randomized clinical trials, and the recommended range between of protein is 1.5-3.0 g/kg/d (Mehta & Compher, 2009; Coss-Bu et al., 2017). The 'adequate' amount of protein during illness remains unknown, but should follow individualized requirements accounting for risks associated with the time of delivery and route (Coss-Bu et al., 2017). During illness, depletion of body stores leads to a catabolic state increasing lean body mass wasting in patients who may already be malnourished. In addition, the lack of protein during this phase may promote the progression of a catabolic state

(PO and JE 1998). Providing protein to critically ill children upon admission has been shown to promote protein balance without adverse effects (de Betue CT, 2011).

1.4.1 Protein utilization, illness and inflammation

Protein turnover is a continuous process which includes synthesis and catabolism. In healthy children, protein synthesis exceeds breakdown, resulting in growth. However, during illness, protein turnover is increased and degradation exceeds synthesis leading to lean body mass depletion, growth failure, and poor hospital outcomes (Coss-Bu et al. 2017). During simple starvation, lean tissue is preserved, and fat is used for energy. However, during acute stress, such as surgery or trauma, protein reserves are broken down to supply the amino acids for the synthesis of proteins involved in tissue repair, wound healing, and acute inflammatory response. When energy supply does not meet metabolic needs, amino acids from protein stores are used for gluconeogenesis to provide energy and glucose for immune and other cells (Coss-Bu et al. 2017).

The severity of illness and the use of life support is also associated with protein catabolism and nitrogen loss. After surgery, stress hormones and local inflammatory cells (neutrophils and macrophages) produce cytokines and mediators which complicates normal protein utilization; these changes promote increased protein turnover. Plasma amino acids are used to synthesize acute phase proteins in the liver (Van Waardenburg et al. 2007). Therefore, the provision of an adequate amount of protein and energy may help to preserve LBM during critical illness.

1.5 Fluids and critically ill children

Critically ill children who undergo surgery frequently experience periods of fluid restriction (Rogers et al. 2003). In the PICU, nutrients are predominantly provided through tube feeding, and fluid restriction impacts the ability to provide nutrition support through EN and PN. Fluid balance is part of the management of medications and nutrition, and has been shown to contribute to hospital outcomes (Alobaidi et al. 2018; Raina et al. 2018; Bontant et al. 2015). The recommendations of fluid intake for maintenance are based on body weight and follows: the first 10kg (100ml/kg/d), 11-20kg (50ml/kg/d for each additional 1kg), and above 20kg (20ml/kg/d for each additional 1kg) (Goday and Mehta, 2015).

1.6 Controversies on feeding a child in the first week of admission to a PICU

Studies looking at feeding strategies conducted in adult populations may provide important information, however, cannot be directly applied to infants and children due to differences in energy reserves. Children have lower energy reserves compared to adults. Feeding critically ill children 24 hours after PICU admission is the best practice to preserve body weight and reduce complications including mortality (Joffe et al. 2016; Bağci et al. 2018). The clinical status of the patient determines the feeding modality of the patient (EN and PN). The most recent, multicenter, and a largest pediatric randomized clinical trial in nutrition 'Pediatric Early vs. Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC)', reported that withholding PN during the first week of admission was beneficial for critically ill children, reducing infections and decreasing PICU length of stay (Fivez et al. 2016). The participants included in the study were children identified as at risk for malnutrition or as malnourished based on the STRONG Kids malnutrition screening tool. Notably, this tool is known to overestimate nutritional risk (Oliveira et al. 2017). In this trial, children were randomly selected to receive PN or not within a week of PICU admission. All patients were enterally fed during the study to provide energy in the first week. However, each center provided energy based on their own protocols (center 1: used Scholfield predictive equation; center 2: energy predicted by weight such as for each 10kg a 100kcal/kg/d was given; and center 3: used 65% of BMR(WHO) when the MREE was not feasible). In addition, the assignment to receive PN was not based on patient needs, but rather on the randomization to receive PN in

24hours or after one week of PICU admission. Since individualized energy needs were not accounted for, patients who were randomized to receive PN in the first week may have been overfed.

The ASPEN guidelines do not recommend withholding PN for one week to patients who are less than 30 days old, malnourished, or at risk for malnutrition. At this point, feeding or not using PN in the first week of PICU admission remains controversial. Currently, there is a lack of evidence on the timing of PN administration, an appropriate amount of energy and protein required to nourish critically ill children. These information is needed to develop evidence based guidelines for feeding critically ill children.

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Chapter Two: Research plan

2.1 Rationale

Provision of energy is crucial for the treatment of a critically ill child admitted to Pediatric Intensive Care Units (PICU); they are at high risk for worsening nutritional status during their hospital stay (Mehta, Christopher, & Duggan, 2015; Delgado et al., 2008; Leong, Field, & Larsen, 2013; Larsen et al., 2018; de Neef et al., 2008). During disease, depletion of energy and protein stores occur rapidly. To maintain the nutritional status, and prevent malnutrition (De Cosmi et al., 2017; Mehta et al., 2013) an optimal amount of energy and protein is required after admission to PICU. An optimal energy intake has been associated with lower hospital length of stays (Larsen et al., 2018); however, the association between energy intake during the first week of PCICU admission, regardless of route of delivery, and its association with hospital outcomes has not been fully investigated.

To provide optimal amount of energy to a critically ill child, MREE should be applied; however, predictive equations are often applied in the absence of IC (Framson et al., 2007; Mehta et al., 2017). These equations frequently over or under-estimating energy requirements (as revised in chapter one). Researchers have found that an excess of energy or an energy deficit is associated with worse hospital outcomes (Larsen et al., 2013; Kyle, Jaimon, & Coss-Bu, 2012; Mehta, 2015). The amount of energy a critically ill child requires is influenced by several factors including certain medications, clinical status, and whether the child is on life support; these may lower energy needs (Kaufman, Vichayavilas, Rannie, & Peyton, 2015). Current guidelines recommend meeting the requirements early and selecting the appropriate route and timing for nutrition supply. Enteral nutrition (EN) is the preferable route of delivery; however, parenteral nutrition (PN) is used to support EN or exclusively when EN is not possible.

Recently, a multicenter trial questioned the benefits of giving PN to critically ill patients during the first week of admission to PICU (Fivez et al., 2015). The authors Fivez et al. reported that withholding PN for one week after PICU admission reduced the number of infections, PICU and hospital LOS. However, aspects of their methodology is questionable, the amount of energy provided to the patients was not standardized in the study and energy needs were based on each center's protocol (Center 1: used Scholfield predictive equation; Center 2: energy predicted by weight such as for each 10kg a 100kcal/kg was given; and Center 3: used 65% of BMR(WHO) when the MREE was not feasible). Furthermore, predictive equations used in center 1 and 2 are known to overestimate energy needs (chapter one). EN was provided to all patients, and patients were randomly assigned to receive additional PN without consideration of the patient energy needs. PN was then either delivered in the first 24hours or after one week of admission to PICU. Fifty five percent of the patients who were randomized to receive PN after one week were discharged on day 4, indicating that they may have been been appropriately fed with EN alone.

The nutritional approach used may have affected the clinical significance of their findings, disfavoring PN. Insufficient research has been done in homogeneous populations evaluating the effects of energy delivery during the first week of admission and hospital outcomes including hospital and PCICU LOS, ventilation days, and infections. This presents an opportunity to evaluate energy and protein intakes during the first week of PCICU admission, and to determine the association between intake and hospital outcomes. The evaluation of the energy and protein intake during the first week of PCICU admission will provide evidence to future guidelines and support future clinical trials.

2.2 Objectives and hypothesis

The overall aim of this research is to evaluate whether energy and protein intakes, regardless of route of delivery (EN or PN) during the first 7 days of PCICU admission is associated with hospital outcomes including hospital and PCICU LOS, ventilation days, and infections.

Hypothesis:

It was hypothesized that energy intake during the first 7 days of PCICU admission would be associated with positive hospital outcomes, and patients receiving PN in the first 7 days would have similar outcomes as EN. This hypothesis was tested by achieving the following objectives:

Objectives:

i) To determine the association between energy intake (kcal/kg/d) during the first 7 days after PCICU admission and hospital LOS, PCICU LOS, ventilator days.

ii) To determine the association between protein intake (g/kg/d) during the first 7 days after PCICU admission and hospital LOS, PCICU LOS, ventilator days.

iii) To identify the differences in hospital outcomes between patients who received above or below 2/3BMR(WHO).

iv) To explore whether patients receiving PN present with worse hospital outcomes compared to patients receiving only EN.

v) To explore changes in nutritional status using an anthropometric measure of z-score over three time points: admission to PCICU, discharge from PCICU, and discharge from the hospital.

vi) To evaluate fluid balance to assess fluid restriction during the first week in the PCICU.

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Chapter Three: Energy and protein intake in the first week of pediatric cardiac intensive care unit admission matters

3.1 Introduction

Children admitted to Pediatric Cardiac Intensive Care Units (PICU) are at risk for worsening nutritional status due to rapid depletion of energy stores (Pollack et al. 1981; Mehta et al. 2013). Providing excessive amounts of energy or not providing enough energy to a critically ill child negatively impacts hospital outcomes including hospital length of stay (LOS) (Mehta, Christopher, and Duggan 2015). Provision of an optimal amount of energy to critically ill children requires measuring resting energy expenditure (MREE) by indirect calorimetry (IC). However, when IC is not available, energy expenditure is estimated using predictive equations. The underlying disease processes may elevate metabolic rate, while the need for life support (e.g. ventilator support, sedation, paralytics) may decrease energy requirements. This can result in challenges in determining energy requirements in the hospitalized critically ill child. Overfeeding or underfeeding impact hospital outcomes including extended days in the PICU and in hospital, increased number of days on ventilator support, and an increased number of infections (reviewed in Chapter One).

The American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines suggest the use of the World Health Organization (WHO) predictive equation to estimate energy when IC is not available (Mehta et al. 2017). Previous studies in the pediatric cardiac population have proposed the use of 2/3BMR(WHO) to prevent risks of overfeeding children when on life support during PICU stay (Lewis et al. 2018; Leong, Field, and Larsen 2013). A review of studies that have compared measured to estimated energy requirements shows the best agreement between the

WHO predictive equation and actual energy needs compared to other estimates (reviewed in Chapter One).

Nutrition in the PICU is preferably provided through enteral nutrition (EN) if the gut is functional; however, if nutrition goals are not reached by EN, parenteral nutrition (PN) may be used to supplement EN, or provided exclusively to reach energy and protein goals (Mehta et al. 2017). Recently, a randomized multicenter trial questioned the benefits of PN in a pediatric ICU population during the first week of admission. The PEPaNIC study evaluated the effects of withholding PN during the first week of admission to pediatric intensive care units (section 1.6 in Chapter One). Energy requirements provided during the study were estimated using standard practice at each center (Belgium: 100kcal per kg body weight, Canada: 65% of WHO when IC was not feasible, and Netherlands: Schofield equation). This study showed that withholding PN support, whether feeding EN or not for one week, resulted in fewer infections and shorter hospital length of stay.

Questions that arose with regards to evidence-based practice presented a unique opportunity to determine provision of sufficient energy and protein, regardless of route of delivery would be associated with positive hospital outcomes including shorter PCICU and hospital LOS, fewer days on ventilator support, and fewer infections. This study aimed to evaluate the association between the provision of energy and protein in the first week to PCICU and hospital outcomes, while considering whether nutrition is delivered through EN or PN. It was hypothesized that energy intake during the first week of PCICU admission is associated with positive hospital outcomes, and patients receiving PN would have similar outcomes as EN.

3.2 Methods

3.2.1 Study design

This observational study was conducted in the PCICU at the Stollery Children's Hospital in Edmonton (Alberta, Canada). The University of Alberta Health Research Ethics Board approved the study protocol (Pro00078007) on November 20, 2017. Informed consent was waived; and there was no intervention. The study was conducted between March 1, 2016, and June 30, 2018. All patients admitted to the PCICU with a LOS equal to or greater than seven days were included. If a patient was less than 30 days old (neonate) and admitted to the PCICU and transferred back within a week to the neonatal intensive care unit (NICU), they were also followed until completion of one week. The exclusion criteria included patients that stayed less than seven days in the PCICU, were on full oral intake, and patients arriving from other units or centers.

3.2.2 Data Collection

Data was collected in two parts. For patients admitted between March 1, 2016, to December 31, 2017, data was collected retrospectively from electronic (Metavision) and paper charts from medical records. For those patients admitted between January 1, to June 30, 2018, data were collected daily on the unit from nutrition care plans and bedside patient charts. All patient information was entered and stored in a secured web application database (REDCap: Research Electronic Data Capture (Appendix D), and the data was transferred to the statistical program for analyses (SPSS for Windows).

3.2.3 Patients characteristics

The patients included in this study were between ages 0 to 17 years old. All patients admitted to the PCICU presented with a heart defect coming from post-cardiac operation support or various reasons related to the underlying defect. For all the patients, demographic (age in months, sex) and anthropometric (weight, height or length) characteristics were collected. A registered nurse (RN) calculated inotrope scores for each of the seven days during PCICU stay, and the Pediatric Risk of Mortality (PRISM) score.

For patients who underwent cardiac surgery, clinical severity of the specific cardiac operation was determined by the Society of Thoracic European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score (STAT Score) calculated by a pediatric intensivist upon admission. Clinical information regarding the surgical procedure was collected including single or double ventricle physiology, cardiopulmonary bypass time (CPB time) duration in minutes, cross-clamp duration in minutes, second cross-clamp, presence of necrotizing enterocolitis (NEC), chylothorax, cardiac arrest, open chest, and use of life support such as inotropic support, dialysis, and extracorporeal membrane oxygenation (ECMO).

3.2.4 Energy and Protein Intakes in the first seven days

Standards for determining energy requirements in the Stollery Children Hospital, Edmonton, Alberta, Canada are to either measure resting energy expenditure by indirect calorimetry (IC) or to provide two-thirds of the basal metabolic rate determined using the WHO predictive equation (2/3BMR(WHO). The 2/3BMR(WHO) was calculated for all the patients to provide a predicted value. The daily amount of energy (kcal/kg/d) and protein (g/kg/d) received, prescribed by the attending RD was collected. The study was started on PCICU admission (indicated as Day 0) until the seventh day in the unit (indicated as Day 6).

The amount of nutrients provided to each patient was recorded from the daily prescriptions including all sources of energy and protein from EN, PN, and/or IV dextrose solutions given during the first seven days in the PCICU from patient's electronic records (Metavision). The feeding modality of the patients was from PN (fed through exclusively parenteral route), EN (fed through exclusively enteral route), combinations of PN+EN (fed from the enteral and parenteral route), or NPO (not fed). For analyses, patients were categorized into two groups: patients receiving PN at any point during seven days were categorized as being in the PN group, and patients who were exclusively fed through EN were classified as EN group (no PN). For all patients, daily monitored fluid balance (ml/d) from fluid input and fluid output was recorded (fluid balance = fluid input – fluid output).

3.2.5 Hospital Outcomes

The number of days a patient was in hospital was calculated starting on admission to the PCICU (Day 0) until discharge from the hospital. For patients who stayed more than 60 days (n=34), data were censored at day 60. Intubation and extubation dates were collected to calculate the number of days on a mechanical breathing machine. Infection was determined by the presence of positive cultures in the respiratory system, blood, urine, wound, and/or stool, during the study period.

3.2.6 Anthropometric measurements

Anthropometric measurements, weight, length (less than two years old) and height (greater than two years old) were used to calculate z-scores using the website PedTools.com. The gestational age was obtained for patients less than two years old to calculate the z-scores using corrected age. Calculations used for analysis included weight z-scores, height z-score, weight-for-length z-score (for patients under two years old), and BMI z-score (for patients between 2-17 years). Appropriate growth charts according to patient condition, age, and sex were applied to determine z-scores for each patient. WHO Growth Standard 2006 (0 to 24 months old), CDC Growth Chart 2000 (2 to 17 years old), and Zemel 2015 growth charts (Down Syndrome, 0 to 36 months and 2 to 20 years old) were applied. Anthropometric measurements were performed by a registered dietitian (RD) on PCICU admission, PCICU discharge, and hospital discharge. For patients transferred from the PCICU directly to another hospital, assessments were recorded at the time of discharge.

3.2.7 Statistical Analysis

Statistical analyses were performed using SPSS version 24 (IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered statistically significant. Data were assessed for normality using the Shapiro-Wilk test. For non-parametric variables, median and interquartile range (IQR) are presented. For continuous variables Mann-Whitney U test was performed and for categorical variables Chi-square test was performed. For parametric variables, mean and standard deviation is reported and paired-sample t-test was used to evaluate changes over time (anthropometric z-scores of three time points).

Separate linear regression models were used to predict hospital LOS, PCICU LOS, and ventilator days. The mean energy intake over the seven days and mean protein intake were evaluated as predictors of hospital outcomes. Univariate linear regression analyses were performed to first identify predictors of hospital outcomes. Significant independent variables were entered in the multivariate analyses. Patients were categorized as surgical or non-surgical based on admission records since a patient undergoing surgery presents many confounding variables that can impact hospital outcomes. Analyses was conducted for surgical and non-surgical patients separately. For surgical patients, multiple regression models were adjusted for age, sex, single or double ventricle, STAT score, and CPB time. For non-surgical patients, regression models were adjusted for age and sex

Mann-Whitney U test was used to compare the differences in hospital outcomes between patients who had energy intake below or above the predicted value (2/3BMR(WHO). The same test was applied to identify if hospital outcomes were different in patients receiving PN versus EN

3.3 Results

3.3.1 Patients characteristics

A total of 253 patients with a cardiac defect were included in the study (surgical n=203 and non-surgical n=50) (**Figure 3.1**). The majority of patients were male (n=145, 57%) with a median age of 1.8 months (IQR: 0.2 – 6.0). One hundred and eight (43%) patients admitted to PCICU were less than 30 days old, 115 (45%) were between 1 to 24 months, and 30 (12%) older than 24 months of age. The median energy and protein intake over the first seven days for the entire cohort, was 29 kcal/kg/d (IQR:19–43) and 1.2 g/kg/d (IQR: 0.6–1.7), respectively. The overall energy estimation using 2/3BMR(WHO) was 31 kcal/kg/d (IQR: 29–34). The median fluid balance was 15 ml/d (IQR: -33–134) (**Table 3.1**). The presence of positive cultures (infection) was present in 108 (42%) patients and was higher in non-surgical patients (n=34, 68%). The overall characteristics of surgical and non-surgical patients are presented in Table 3.1, analyses of non-surgical patients showed that energy nor protein was significantly different in hospital outcomes with any of the nutritional variables assessed. Therefore, the analyses presented in this chapter were focused on surgical patients. The non-surgical patient supplementary information is found in Appendix B and C. The cohort who had heart surgery are presented in **Table 3.2**.

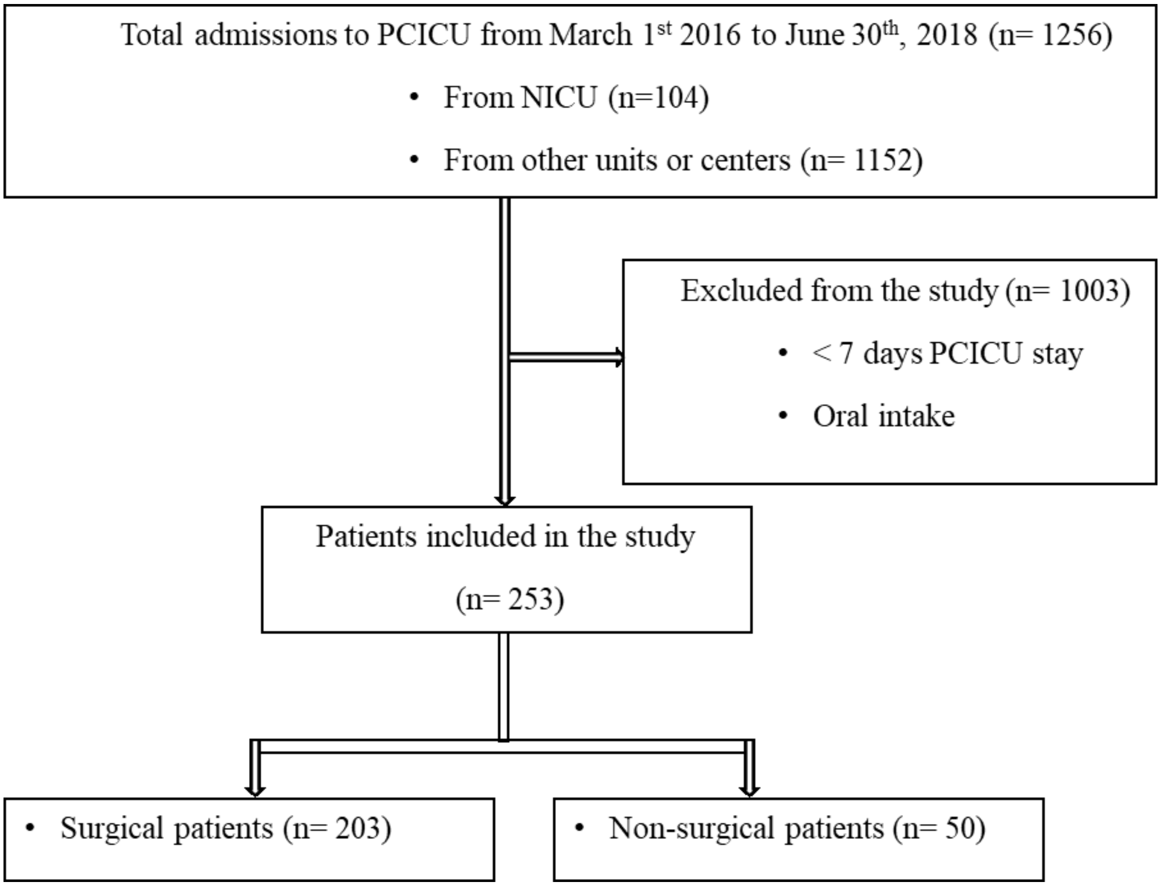

Figure 3. 1 Flow diagram of inclusion and exclusion of patients admitted to the PCICU

Table 3. 1 Characteristics of the children admitted to the PCICU

Characteristics	All patients (n =253)	Surgical patients (n = 203)	Non-surgical patients (n = 50)
Male sex, n (%)	145 (57%)	114 (56%)	31 (62%)
Age, mo., median (IQR)	1.8 (0.2–6.0)	0.9 (0.2–3.9)	8.0 (2.8–24.0)
Newborn, < 30d, n (%)	108 (43%)	102 (40%)	6 (3%)
Children, 1mo – 24mo, n (%)	115 (45%)	83 (33%)	32 (12%)
Children, > 24mo, n (%)	30 (12%)	18 (7%)	12 (5%)
GA, weeks, median (IQR)	39 (37–39)	39 (37–39)	39 (37–40)
Wt admission, kg, median (IQR)	3.9 (3.2–6.4)	3.7 (3.2–5.0)	7.0 (4.2–11.4)
Nutritional, median (IQR)			
Cumulative Energy intake (kcal)	204 (138–304)	196 (135–279)	281 (162–377)
Mean Energy intake (Kcal/kg/d)	29 (19–43)	28 (19–39)	40 (23–54)
Predicted 2/3BMR(WHO) (kcal/kg/d)	31 (29–34)	31 (29–33)	34 (30–36)
Mean Protein intake (g/kg/d)	1.2 (0.6–1.7)	1.1 (0.6–1.6)	1.3 (0.6–1.8)
Cumulative Protein intake (g)	8.2 (4.6–11.9)	8.0 (4.8–11.7)	9.5 (4.5–12.6)
Mean Fluid Balance (ml/d)	15 (-33–100)	0.8 (-41–73)	97 (24–184)
Hospital Outcomes, median (IQR)			
Hospital LOS, d	21 (13–38)	20 (12–36)	25 (15–42)
PCICU LOS, d	9 (5–14)	8 (4–13)	12 (8–19)
Ventilator, d	7 (4–12)	6 (4–12)	7 (4–12)
Deceased, n (%)	17 (7%)	12 (6%)	5 (10%)
Positive Culture, n (%)	108 (42%)	74 (36%)	34 (68%)
Respiratory	72 (28%)	44 (21%)	28 (56%)
Blood	19 (7%)	13 (7%)	6 (12%)
Urine	18 (7%)	11 (5%)	7 (14%)
Wound	14 (5%)	12 (6%)	2 (4%)
Peritoneal Fluid	5 (3%)	5 (3%)	-
Drainage	1 (1%)	1 (1%)	-
Stool	1 (14%)	-	1 (2%)
Biochemistries			
Glucose	7.0 (6.2–8.4)	7.2 (6.3–8.5)	6.5 (5.9–7.7)
Lactate	1.2 (0.9–1.7)	1.3 (1.0–1.7)	1.1 (0.9–1.5)
CRP	40 (6–79)	40 (19–71)	33 (8–95)

Values are presented in median (IQR) and percentage; mo: months; BMR: basal metabolic rate; LOS: length of stay;

Table 3. 2 Clinical characteristics of the children who underwent surgery

Surgical Characteristics	No.(%) or Median (IQR)
Single Ventricle	48 (19%)
CPB, min	113 (86–154)
X Clamp, min	59 (38–86)
X Clamp	174 (69%)
2nd X Clamp	35 (18%)
Post-op	
ECMO, y	31 (12%)
Dialysis, y	20 (8%)
NEC, y	5 (2%)
Open chest, y	78 (31%)
Chylothorax, y	20 (8%)
Cardiac Arrest, y	24 (9%)
Highest Lactate	4.6 (2.7–7.2)
Inotrope, y	172 (68%)
Inotrope Score	6.5 (3.7–9.1)
PRISM score	6 (3–10)
STAT score, n (%)	
STAT score 0	23 (11%)
STAT score 1	24 (11%)
STAT score 2	39 (19%)
STAT score 3	25 (12%)
STAT score 4	72 (34%)
STAT score 5	26 (12%)

Values are presented in median (IQR) and percentage. y: yes; CPB: cardiopulmonary bypass time; X Clamp: cross-clamp time; ECMO: extracorporeal membrane oxygenation; NEC: necrotizing enterocolitis. (Surgical characteristics data was available in n=193 surgical patients); STAT score: Society of Thoracic European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score

3.3.2 Energy and protein intake

Univariate analyses were performed to detect relationships between variables. Within this analyses, energy intake, age, CPB time, and single ventricle predicted hospital LOS (**Table 3.3**), energy intake, protein intake, age, STAT score, and CPB time predicted PCICU LOS (**Table 3.4**), and energy intake, protein intake, age, and CPB time predicted ventilator days (**Table 3.5**). When the variables were entered in the multivariate analyses, the models show that energy remained predictor of hospital LOS, PCICU LOS, and ventilator days. Since protein intake was correlated with energy, it was removed from the multivariate analyses.

Age, sex, STAT score, single ventricle and CPB time were included in all multiple linear regression models since these may influence hospital outcomes.

In multiple linear regression, energy was a significant predictor of hospital LOS, PCICU LOS, and ventilator days. Energy, STAT score, and single ventricle explained 17.6% of the variability in hospital LOS (**Table 3.6**). Energy, age, and STAT score explained 20.7% of the variability in PCICU LOS (**Table 3.7**). For ventilator days, energy explained 11.2% of the variability in days on ventilator support (**Table 3.8**).

Table 3. 3 Regression analysis of predictors of hospital length of stay in patients with a heart defect in surgical patients

Univariate analyses		Surgical patients (n=203)			
Predictors		**B Coefficient**	**95% CI**	**p-value**	**r^2**
Energy (kcal/kg/d)		-0.355	-0.511, -0.199	**<0.001**	0.091
Protein (g/kg/d)		-3.424	-7.079, 0.230	0.066	0.017
Age, mo.		0.161	0.068, 0.253	**0.001**	0.055
Sex		-0.690	-5.589, 4.210	0.782	0.000
PRISM Score		0.294	-0.201, 0.788	0.243	0.007
STAT Score		-0.824	-2.597, 0.950	0.361	0.005
CPB time		0.058	0.020, 0.096	**0.003**	0.046
Single Ventricle		7.188	1.519, 12.858	**0.013**	0.030
Multivariate analyses					
Model					
1	Energy (kcal/kg/d)	-0.364	-0.525, -0.202	**<0.001**	0.096
2	Age, mo.	0.111	0.013, 0.208	**0.026**	0.119
	Energy (kcal/kg/d)	-0.298	-0.468, -0.128	**0.001**	
3	Age, mo.	0.123	0.026, 0.221	**0.014**	0.139
	Energy (kcal/kg/d)	-0.258	-0.431, -0.085	**0.004**	
	Single ventricle	5.925	0.203, 11.064	**0.042**	

Variables from the regression analyses. CI: confidential interval; mo.: month, CPB: cardiopulmonary bypass time; STAT score: Society of Thoracic European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score. PRISM score: Pediatric Risk of Mortality socre.

Table 3. 4 Regression analysis of predictors of PCICU length of stay in patients with a heart defect in surgical patients (203)

Univariate analyses		Surgical patients (n=203)			
Predictors		**B Coefficient**	**95% CI**	**p-value**	**r^2**
Energy (kcal/kg/d)		-0.257	-0.357, -0.157	**<0.001**	0.114
Protein (g/kg/d)		-5.924	-8.167, -3.681	**<0.001**	0.119
Age, mo.		0.144	0.085, 0.202	**<0.001**	0.105
Sex		-0.992	-4.166, 2.182	0.538	0.002
PRISM Score		-0.051	-0.373, 0.270	0.754	0.000
STAT Score		-1.317	-2.453, -0.182	**0.023**	0.028
CPB time		0.036	0.011, 0.061	**0.005**	0.042
Single Ventricle		0.472	-3.259, 4.204	0.803	0.000
Multivariate analyses					
Model					
1	Age, mo.	0.149	0.085, 0.212	**<0.001**	0.109
2	Age, mo.	0.113	0.047, 0.178	**0.001**	0.162
	Energy (kcal/kg/d)	-0.187	-0.299, -0.075	**0.001**	
3	Age, mo.	0.094	0.028, 0.161	**0.006**	0.186
	Energy (kcal/kg/d)	-0.204	-0.316, -0.092	**<0.001**	
	STAT Score	-1.312	-2.459, -0.166	**0.025**	
4	Age, mo.	0.076	0.007, 0.144	**0.030**	0.204
	Energy (kcal/kg/d)	-0.186	-0.298, -0.073	**0.001**	
	STAT Score	-1.572	-2.737, -0.406	**0.009**	
	CPB time	0.026	0.000, 0.052	**0.048**	

Variables from the regression analyses. CI: confidential interval; mo.: month, CPB: cardiopulmonary bypass time; STAT score: Society of Thoracic European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score. PRISM score: Pediatric Risk of Mortality socre.

Table 3. 5 Regression analysis of predictors of ventilator days in patients with a heart defect in surgical patients

Univariate analyses		Surgical patients (n=195)			
Predictors		**B Coefficient**	**95% CI**	**p-value**	**r^2**
Energy (kcal/kg/d)		-0.219	-0.318, -0.119	**<0.001**	0.089
Protein (g/kg/d)		-2.758	-5.061, -0.456	**0.019**	0.028
Age, mo.		0.089	0.024, 0.153	**0.007**	0.037
Sex		-0.560	-3.655, 2.535	0.721	0.001
PRISM Score		0.244	-0.067, 0.554	0.123	0.012
STAT Score		-0.194	-1.300, 0.912	0.730	0.001
CPB time		0.027	0.003, 0.051	**0.026**	0.027
Single Ventricle		0.985	-2.620, 4.590	0.590	0.002
Multivariate analyses					
Model					
1	Energy (kcal/kg/d)	-0221	-0.325, -0.177	**<0.001**	0.089

Variables from the regression analyses. CI: confidential interval; mo.: month, CPB: cardiopulmonary bypass time; STAT score: Society of Thoracic European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score. PRISM score: Pediatric Risk of Mortality socre.

Table 3. 6 Multiple linear regression of predictors of hospital length of stay in patients with a heart defect in surgical patients

N = 203	B Coefficient	95% CI	p-value	r^2
Energy (kcal/kg/d)	-0.253	-0.433, -0.074	**0.006**	0.176
Age, mo.	0.095	-0.014, 0.204	0.086	
Sex	-0.460	-5.460, 4.539	0.856	
STAT Score	-1.895	-3.766, -0.025	**0.047**	
CPB time	0.031	-0.009, 0.072	0.130	
Single Ventricle	6.980	0.854, 13.106	**0.026**	

Variables from the regression analyses. CI: confidential interval; mo.: month, CPB: cardiopulmonary bypass time; STAT score: Society of Thoracic European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score.

Table 3. 7 Multiple linear regression of predictors of PCICU length of stay in patients with a heart defect in surgical patients

N = 203	B Coefficient	95% CI	p-value	r^2
Energy (kcal/kg/d)	-0.184	-0.300, -0.068	**0.002**	0.207
Age, mo.	0.080	0.009, 0.150	**0.027**	
Sex	-1.382	-4.614, 1.851	0.400	
STAT Score	-1.571	-2.781, -0.362	**0.011**	
CPB time	0.025	-0.002, 0.051	0.067	
Single Ventricle	0.464	-3.497, 4.424	0.818	

Variables from the regression analyses. CI: confidential interval; mo.: month, CPB: cardiopulmonary bypass time; STAT score: Society of Thoracic European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score.

Table 3. 8 Multiple linear regression of predictors of ventilator days in patients with a heart defect in surgical patients

N = 195	B Coefficient	95% CI	p-value	r^2
Energy (kcal/kg/d)	-0.174	-0.293, -0.056	**0.004**	0.112
Age, mo.	0.044	-0.030, 0.118	0.245	
Sex	-1.646	-4.953,1.662	0.327	
STAT Score	-0.405	-1.619, 0.809	0.511	
CPB time	0.016	-0.011, 0.042	0.251	
Single Ventricle	-0.158	-4.180, 3.863	0.938	

Variables from the regression analyses. CI: confidential interval; mo.: month, CPB: cardiopulmonary bypass time; STAT score: Society of Thoracic European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score.

3.3.3 Energy intake compare to predicted 2/3BMR(WHO)

The energy intake compared to the predicted value revealed that 119 (47%) were provided less than predicted, 98 (39%) were provided more, and 36 (14%) were in the recommended range of feeding from 90% to 110% of predicted energy intake (2/3BMR(WHO). The median of predicted energy intake for surgical patients was 31kcal/kg/d. Patients receiving below predicted value stayed significantly ($p<0.001$) longer in hospital, PCICU, and had more ventilator days compared to patients receiving equal or greater than the predicted value (**Table 3.9**). The clinical conditions of the patients receiving above 2/3BMR(WHO) were similar. The maximum energy intake among the patients receiving above 2/3BMR(WHO) are shown in Appendix 3.

Table 3. 9 Comparison of hospital outcomes between patient's energy intake below or above of 2/3BMR(WHO) in surgical patients

Hospital Outcomes n=203	**Surgical**		
	<31kcal/kg/d n=113	≥31kcal/kg/d n=90	P value
HLOS, d	27 (15–49)	14 (10–24)	**< 0.001**
PCICU, d	11 (6–17)	7 (3–10)	**< 0.001**
Vent, d	10 (6–15)	4 (2–7)	**< 0.001**
Infections, n (%)	43 (38%)	31 (34%)	0.596

Values are presented in median (IQR) and percentage.
P values < 0.05 are significant from the Mann-Whitney U test for continues variables and Chi-square for categorical variables.
Surgical patients on ventilator support above and below were n=89 and n=106, respectively.
PN and EN < 31kcal/kg/d was n=86 and n=25, respectively
PN and EN ≥ 31kcal/kg/d was n=52 and n=37, respectively
NPO was n=3

3.3.4 Route of nutrition delivery

The overall feeding modalities, PN was the first route of delivery for 162 (64%) patients, 87 (34%) received EN, and 4 (2%) patients were NPO for seven days due to clinical practice (**Figure 3.2)**. The proportion of daily nutrition delivery during the first week of PCICU admission can be seen in **Figure 3.3**.

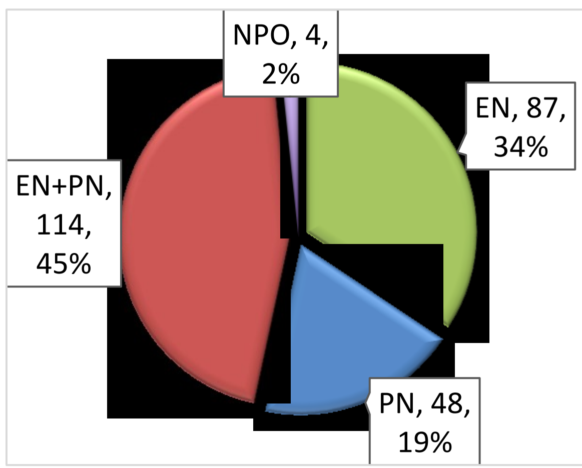

Figure 3. 2 Distribution of feeding modalities between all patients. PN: parenteral nutrition; PN+EN: parenteral and enteral nutrition EN: enteral nutrition; NPO: no nutrition

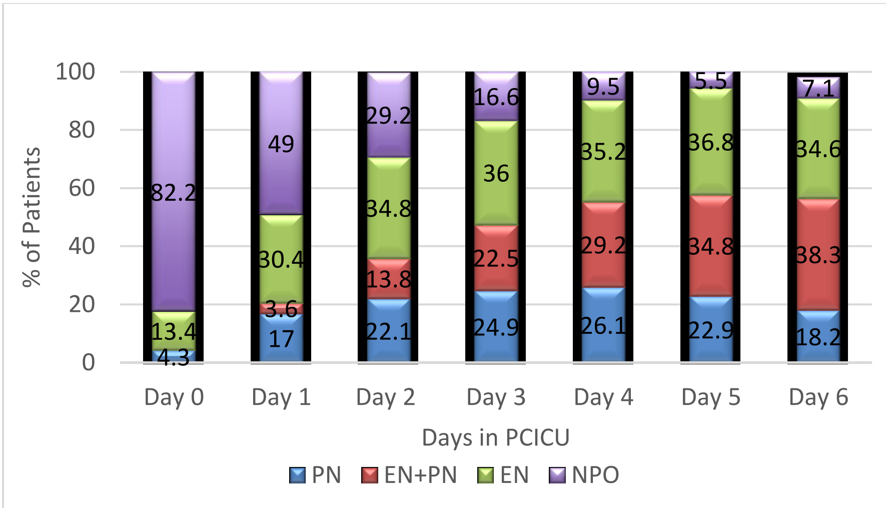

Figure 3. 3 Characteristic of feeding modality of the patients in the first week of admission to PCICU. Percentage of nutrition delivery in the first week of admission (n=253)

3.3.5 PN vs. EN in surgical and non-surgical patients

Mann-Whitney U test was conducted to determine differences between patients receiving PN versus EN. There were no significant differences in hospital LOS, PCICU LOS, and infections (**Table 3.10**). Patients on PN had more ventilator days

Table 3. 10 Comparison of PN vs. EN and hospital outcomes in surgical and non-surgical patients

	Surgical		
Hospital Outcomes	PN Group (n=138)	EN Group (n=62)	p value
HLOS, d	21 (13–37)	18 (11–31)	0.125
PCICU LOS, d	8 (4–14)	9 (7–13)	0.216
Vent, d	7 (5–14)[a]	5 (3–10)[a]	**0.006**
Infections, n (%)	47 (34%)	25 (40%)	0.393

Values are presented in median (IQR) and percentage. P values < 0.05 are significant from the Mann-Whitney U test for continues variables and Chi-square for categorical variables.
HLOS: hospital length of stay; PCICU LOS: pediatric cardiac intensive care unit; Vent, d: Ventilator support days.
[a] n of patients on ventilator support: PN n=134, EN n=59, the sum of days (PN=1466, EN=482)

3.3.6 Anthropometric measurements in all patients

A total of 63 (25%) of patients had all anthropometric measurements taken (weight, height or length) at three time points during the study. The changes in z-score over time in hospital indicate that patients, who had their anthropometrics measured, became significantly (p<0.001) more malnourished during their hospital stay (**Table 3.11**). For weight-for-height z-score, 63 patients significantly decreased their z-score from PCICU Admission, PCICU discharge and hospital discharge (-0.01, -0.11, -1.87, p<0.001, respectively). For BMI z-score, calculated for patients older than 5 years old, only two patients had complete measurements on the three time points. Collectively, these results show a decline in nutritional status by decreasing weight during a hospital stay in this study.

Table 3. 11 Changes in Anthropometric Z-scores during Hospital stay

Z-scores	PCICU Admission		PCICU Discharge		Hospital Discharge	
	n	Mean (±SD)	n	Mean (±SD)	n	Mean (±SD)
Weight	137	-0.66 (±1.32)	137	-0.87 (±1.48)*	129	-1.60 (±1.25)*
Height	99	-0.87 (±1.62)	99	-1.00 (±1.48)	64	1.40 (±1.44)*
Weight/Height	97	-0.01 (±1.58)	97	-0.11 (±1.81)	63	-1.87 (±7.19)*
BMI	4	1.19 (±1.54)	4	-0.17 (±0.78)	2	0.24 (±0.14)

Values are represented in mean (±SD); *P<0.001 are significant from Paired-sample t-test for continues variables. BMI, body mass index

3.4 Discussion and conclusion

This observational cohort study confirms our hypothesis that energy intake during the first week of PCICU is associated with positive hospital outcomes, and patients receiving PN had similar hospital outcomes compared to patients receiving EN including hospital LOS, PCICU LOS and infections after cardiac surgery. Patients receiving PN stayed longer on ventilator support.

In the present analysis, overall energy intake was negatively associated with hospital LOS. Although the same changes were observed for protein intake, which was significantly associated with PCICU LOS after cardiac surgery, protein was colinear with energy intake. It is known that critically ill children have lower energy reserves and they are at high risk for depleting protein and energy reserves during stays in the PICU (Kyle, Jaimon, and Coss-Bu 2012). However, protein requirements after cardiac surgery remain unknown, and recommendations are based on limited evidence (Mehta and Compher 2009). Our results contribute to the evidence base by presenting the median of protein intake during the first week of PCICU admission associated with PCICU LOS and ventilator days.

In this center, the standard care for providing energy requirements is MREE via IC when feasible or estimating using 2/3BMR(WHO). This equation has been suggested by previous studies in cardiac children (Leong, Field, and Larsen 2013). In our study, cardiac critically ill children who received energy of less than 2/3BMR(WHO) presented poorer hospital outcomes compared to those who received an equal or greater amount. The patients receiving equal or greater than the predicted median value had shorter hospital LOS, shorter PCICU LOS, and fewer days on ventilation support.

When the patients were compared based on their feeding modalities, EN or PN, no significant differences were found in hospital LOS, PCICU LOS and infections between groups supporting our hypothesis. The PEPaNIC study (n=1440) provided energy based on predictive equations, and less than 10% of the patients had resting energy requirements measured using IC (Fivez et al. 2016). The study questioned the benefits of PN due to concerns about overfeeding. Knowing that available predictive equations tend to overestimate energy requirements (as discussed in chapter one), patients who were randomized to receive PN in addition to EN in the first 24hours may have been overfed based on the equations used in the study, and patients randomized to receive PN after one week were possibly adequately fed through enteral support. In addition, a study evaluating the risk of infection in patients receiving PN, complications presented were associated with the excess of energy prescribed and not with the PN route per se (Dissanaike et al. 2007), which aligned with other studies showing the safety of PN when energy provision is appropriate (Kagan, Theilla, and Singer 2016). Therefore, evidence from our study does not support the results of the PEPaNIC study. Providing an appropriate amount of energy, whether delivered through EN or PN, improves hospital outcomes.

The imbalance between energy required and energy intake influences nutritional status and can be evaluated by anthropometric measurements (Mehta et al. 2015; Lewis et al. 2018; De Cosmi et al. 2017). However, for cardiac patients, these values may be influenced by fluid excess or fluid restriction after a heart surgery due to provision of diuretics to maintain normal fluid balance. In this study, anthropometric measurements were collected at three time points, which allowed us to evaluate the nutritional status over time using the anthropometric z-scores. A decline in z-scores was observed during hospital stay (60 days period). Our study suggests that weight loss occurs during the hospital stay and more research is needed to evaluate better ways to identify a deterioration on nutritional status in this population. We evaluated weight-for-height z-score, which have not been previously reported in cardiac critically ill children over time. Recording weight and height z-score alone at a single point in time, as is generally reported, does not give the whole picture, and the longitudinal assessment is a strength of this study (Peres et al. 2014).

An additional strength of this study was the ability to gather data on all patients admitted to PCICU in a period over two years. A robust approach with a broad range of variables was collected, data of energy and protein intake during the first week of PCICU admission in a homogeneous patient population allowed us to find associations between energy and hospital outcomes. Moreover, this study was exclusively focused on cardiac pediatric population, whereas other studies have included pediatric populations with diverse clinical conditions.

A limitation of our study is the retrospective approach, the anthropometric measurements collected from 2016 to 2017 were done by different clinicians, and we were not able to obtain weight, height or length from all patients due to data not being available on hospital discharge. However, anthropometric measurements collected from 2018 (prospectively) was collected during the study period by the RD. The inability to measure resting energy expenditure resulted in the application of 2/3BMR(WHO), which is not specific for cardiac patients (Walker and Heuberger 2009).

Future research needs to investigate the optimal ways to predict energy requirements to meet the patient needs specific to clinical condition, considering energy deficits, energy excess, and micronutrient status. Malnutrition occurs in critically ill patients, and depletion of nutritional status should be considered in all studies evaluating nutrition support. Failure to access weight and z-scores is common, therefore, anthropometric measurements should be precisely done at discharge follow up.

In conclusion, this study provides supportive evidence suggesting that providing energy during the first seven days of PCICU admission reduces hospital LOS, PCICU LOS, and ventilator days. Energy intake during the first week was associated with improved hospital outcomes, including PCICU and hospital LOS, and ventilator days. First, energy requirement should be determined individually by measuring energy expenditure if feasible or by applying a validated accurate predictive equation. Then the feeding modality should be determined.

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Chapter Four: Final Considerations

4.1 Summary of the results

The overall aim of this research was to evaluate energy and protein intakes, and route of delivery (EN or PN) during the first 7 days of PCICU admission and its association with hospital outcomes including hospital and PCICU LOS, days on ventilator support, and presence of infections. It was hypothesized that it is energy intake during the first 7 days of PCICU admission that is associated with positive hospital outcomes and patients receiving PN in the first 7 days would have similar outcomes as EN. What we found supports that energy intake provided at or above 2/3BMR(WHO) in the first week of admission to PCICU is associated with improved hospital outcomes.

The objectives of this thesis were:

i) To determine the association between energy intake (kcal/kg/d) during the first 7 days after PCICU admission and hospital LOS, PCICU LOS, ventilator days and infections:

When regression analyses were performed, it was found that energy intake during the first week of admission is a predictor of positive hospital outcomes and it is associated with shorter hospital LOS in patients who underwent heart surgery. For non-surgical patients energy was not associated with hospital LOS.

ii) To determine the association between protein intake (g/kg/d) during the first 7 days after PCICU admission and hospital LOS, PCICU LOS, ventilator days and infections:

Protein intake correlates with energy intake; they are both associated with PCICU LOS and ventilator days. The univariate analyses show that protein was associated with PCICU LOS and ventilator days; however, it was not associated with hospital LOS.

iii) To identify the differences in hospital outcomes between patients who received above or below 2/3BMR(WHO):

The results demonstrate that patients receiving energy intake below 2/3BMR(WHO) presented with longer hospital and PCICU LOS, and longer ventilator days when compared to patients receiving above the median value. The incidence of infections was not statistically different between groups.

iv) To explore whether patients receiving PN present with worse hospital outcomes compared to patients receiving only EN:

Patient receiving PN nutrition did not present significant differences in hospital LOS, PCICU LOS and infections compared to those who received only EN. The patients receiving PN spent more time on ventilator support.

v) To explore changes in nutritional status using the anthropometric measure of z-score over three time points: admission to PCICU, discharge from PCICU, and discharge from the hospital:

These results show a decline in anthropometrics measurement z-scores over time; these changes were statistically significant decreased between PCICU admission, PCICU discharge, and hospital discharge. Further, in cardiac surgical patients, malnutrition may be influenced by fluid restriction and profound inflammation.

vi) To evaluate fluid balance to assess fluid restriction during the first week in the PCICU:

Cardiac surgical patients are fluid restricted, and the fluids presented on the descriptive analyses only demonstrates the fluid balance of the week. The normal fluid intake ranges from 120ml to 160ml/kg/d. However, these patients may receive multiple diuretics to maintain normal fluid balance. Although these patients are fluid restricted, energy amount could be delivered by concentrating nutrients from the feeding modalities (EN and/or PN) to reach nutrition goal.

In summary, the results confirm our hypothesis that energy intake is associated with positive hospital outcomes and impacts hospital LOS. Patients receiving nutrition either through enteral or parenteral route were similar in terms of hospital outcomes. Benefits of providing PN in the first week has been questioned and the lack of evidence in the literature to the application of a late PN strategy derived from the results of the PEPaNIC study by some physicians to clinical practices. Our study evaluated how many critically ill children did not receive PN for one week, the amount of energy intake, protein intake, and the hospital outcomes associated with the feeding practice applied to each individual patient according to standard clinical practice. The results from chapter three enabled evaluation of each patient individually based on the standard clinical practice applied.

4.2 Application of observations

Many patients in this study were in energy deficit. One patients was chosen from the cohort study as an example case study to evaluate the nutritional and clinical consequences from energy and protein deficit during the first week of PCICU admission. The criteria to select the case was based on the following:

1- Weight and height measured at three time-points
2- A decrease in z-score derived from anthropometrics (length and weight)
3- Energy intake less than predicted requirement of 2/3BMR(WHO).

The patient characteristics are shown in **Table 4.1**, and the anthropometric measurements in **Table 4.2**.

Table 4. 1 Case study characteristics and hospital outcomes compared to cohort

Patient characteristic		
Sex	Male	
Gestational Age, weeks	38+3days	
Age, days	5 days	
Heart Defect	HLHS (single ventricle)	
STAT score	5	
Hospital outcomes	**Case study**	**Median (IQR)**
PCICU LOS	12	8 (4-13)
Hospital LOS	48	20 (12-36)
Ventilator days	10	6 (4-12)
Postoperative open chest	yes	78 (31%)
Peak lactate of 7 days	6.1	4.6 (2.7-7.2)
CRP, mean	35	40 (19-71)

HLHS: Hypoplastic Left Heart Syndrome; CPB: cardiopulmonary bypass, X-Clamp: cross-clamp

Table 4. 2 Anthropometric measurements of a critically ill child.

	Wt	Lt	Wt Z-score	Lt Z-score	Wt/Lt Z-score
PCICU ADMISSION Day 0	3.10kg	53 cm	-0.05	2.17	-3.08
PCICU Discharge Day 12	2.88kg	54cm	-1.45	1.65	-4.88
Hospital Discharge Day 48	3.33kg	54cm	-2.87	-1.12	-3.00

Wt:weight; Lt: length; Wt/Lt: weight-for-length

4.2.1 Energy Provided vs. Estimated, in the first week of PCICU

The amount of energy provided to this neonate in the first week of PCICU stay was compared to 2/3BMR(WHO) predictive equation. The cumulative energy deficit was 149kcal/d, which represents a total energy deficit of 462kcal during the first week of admission to PCICU (**Table 4.3**).

Table 4. 3 Energy Intake of a critically ill child.

	First week on PCICU							
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Cumulative
Energy Intake (kcal/kg/d)	5	8	8	8	4	9	12	54
Protein Intake (g/kg/d)	0	0	0	0	0	0	0	0
Estimation of Energy kcal/kg/d (2/3 BMR - WHO)	29	29	29	29	29	29	29	203
Daily Energy Deficit (Estimation – Intake)	24	21	21	21	25	20	17	149
Total Energy Deficit	149kcal/kg/d x wt. (3.1kg) = 462 Kcal							

Values from actual intake. BMR: basal metabolic rate; WHO: world health organization

4.3 Discussion

This critically ill neonate admitted to the PCICU did not receive enteral (EN) or parenteral nutrition (PN) for seven days. The amount of energy intake presented during the first week was from intravenous dextrose solutions. Although predictive equations are inaccurate, we compared the energy intake to 2/3BMR(WHO) as a starting point. This critically ill child received an average energy intake of 7 kcal/kg/d is one quarter of the predicted value (29 kcal/kg/d). The cumulative energy deficit of 462 kcal may represent significant nutritional consequences to hospital outcomes (**Table 4.1**).

Provision of appropriate energy during PCICU stay is important to support metabolic responses to illness. The energy deficit that occurs during seven days manifests as a noticeable change in anthropometric z-scores and longer compared to the median value hospital LOS and PCICU LOS. This critically ill child presented with severe malnutrition based on the classification weight-for-length below -3.00. During hospitalization, this child remained malnourished, experiencing a decline in z-score and nutritional deficit (energy intake and protein intake). It may lead to the nutritional and clinical consequences such as loss of lean body mass, muscle weakness, infections, immune dysfunctions, delay in wound healing, which prolong hospital LOS (Mehta et al., 2013; Grippa et al., 2017).

Other factors should be investigated in terms of metabolic response to illness such as inflammation, wound healing, and recovery from heart surgery in the absence of energy. The combination of the severity of disease and metabolic dysregulation (e.g., high lactate, high glucose, high triglycerides) may have impeded initiating EN (Schwalbe-Terilli et al., 2009). However, the possible reasons for not initiating PN are unknown.

Our results show that patients receiving PN did not have worse hospital outcomes compared to patients receiving only EN. The in the case study may have benefitted from PN to provide nutrients. The PEPaNIC study, the late PN strategy, reported that patients receiving PN after one week presented fewer new infections and had shorter PICU and hospital stay compared to those receiving PN within the first 24h of admission (Fivez et al. 2016). That study included pediatric patients from newborn to adolescents who were randomly selected to receive PN or not during the first week of admission rather than based on individual physiological needs. In contrast, the ASPEN guidelines are intended for pediatric populations older than one month of age and applying the late PN strategy for children at risk or malnourished is not recommended. Furthermore, neonates have physiological differences and a higher risk for malnutrition compared to children older than a month (Mehta et al. 2017). Although the PEPaNIC study presented a subgroup of neonates, they were still randomized to receive PN within 24h or 7 days.

Feeding modalities continue to be discussed by experts (as presented in Chapter One). However, after surgery or admission to PICU feeding should start within 24-48 hours to avoid further complications (Wang, Li, & Guo, 2018). Studies have shown that NPO is required for surgical procedures and it can continues after surgery (Brunet-wood et al., 2016). In our study, 16% of the patients remained in NPO until day 4 and 4 (2%) patients were in NPO during the first week of PCICU admission.

4.4 Final comments and future directions

Collectively, the results of this thesis can be used to inform future research for pediatric patients as we have identified that energy intake matters, and it is crucial during the first week of admission to a PCICU due to metabolic alterations in response to the severity of illness. Our findings in Chapter three highlights the needs for new research investigating optimal nutrition delivery in terms of optimal ways to predict energy requirements, protein requirements, feeding modalities and timing of delivery in specific populations. Providing adequate energy is well accepted as the first step of nutrition provision; however, if energy is limited, other nutrients will be compromised such as proteins, lipids, and micronutrients necessary to metabolic functions. Therefore, further investigation is required to examine better ways to provide the adequate amount of energy to critically ill children to improve hospital outcomes.

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Appendix

Appendix 1: Case Report Form

Study ID: _______________

Demographics

Female /Male   Day of birth: _________ Admission Age: ______(yr) GA: ____

Weight

PCICU Adm: ______Kg   Disch: ______Kg   HOSP Disch: ______ Kg

Height:

PCICU Adm: ______cm   Disch: ______cm   HOSP Disch: ______cm

Z-Scores

	Wt	Ht	Wt/Lngth	BMI
PCICU Adm				
PCICU Disch				
HOSP Disch				

Hospital Outcomes

Pre PCICU   NICU LOS _____ (d)   REFERAL HLOS _____(d)

PCICU Adm:_______   Disch:_______   = LOS______(d)

Hosp Adm:________   Disch:_______   = LOS______(d)

Vent. Support: YES / NO: Intubation date: ___ Extubation date:___ = LOS_(d)

Positive Cultures: YES / NO: Respiratory - Urine - Stool - Wound - Blood

Energy and Protein Intake

	PICU						
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Date							
Energy kcal/kg/day							
Protein g/kg/day							
Enteral (EN)							
Parenteral (PN)							
EN + PN							
NPO							
Fluid In							
Fluid out							
Fluid Balance							

Surgical information

Pre-op (If in NICU or Referal site)

Heart Defect:_________________________

Mechanical ventilation: ______days

Inotropic support (Y / N)

NEC (Y / N)

ECMO (Y / N)

Highest lactate:_____

Intra-op

Type of repair:_________________________

Single ventricle physiology (Y / N)

CPB:_______min Cross clamp (Y / N) Cross clamp: _______min 2nd CPB run (Y / N)

Post Op

STAT Score:________

ECMO (Y / N)

Dialysis (Y / N)

NEC (Y / N)

Chest open (Y / N)

Chylothorax (Y / N)

Cardiac arrest (Y / N)

PRISM:_______

Inotrope Score:_______

Other reason for admission: ______________________

Appendix 2: Tables from regression analyses of non-surgical patients

Table A.1 Predictors of hospital length of stay in non-surgical patients

Univariate analyses	N=50			
Predictors	**B Coefficient**	**95% CI**	**p-value**	**r^2**
Energy (kcal/kg/d)	-0.056	-0.257, 0.146	NS	0.006
Protein (g/kg/d)	-1.797	-7.504, 3.910	NS	0.008
Age, mo.	0.070	-0.024, 0.164	NS	0.045
Sex	5.618	-3.878, 15.114	NS	0.029
PRISM Score	0.285	-0.609, 1.179	NS	0.008

NS: not significant

Table A.2 Predictors of PCICU length of stay in non-surgical patients

Univariate analyses	N=50			
Predictors	**B Coefficient**	**95% CI**	**p-value**	**r^2**
Energy (kcal/kg/d)	-0.110	-0.263, 0.042	NS	0.042
Protein (g/kg/d)	2.514	-6.869, 1.841	NS	0.027
Age, mo.	0.071	0.000, 0.142	0.050	0.078
Sex	8.983	2.032, 15.934	0.012	0.123
PRISM Score	0.189	-0.500, 0.879	NS	0.006

NS: not significant

Table A.3 Predictors of ventilator days in non-surgical patients

Univariate analyses	N=35			
Predictors	**B Coefficient**	**95% CI**	**p-value**	**r^2**
Energy (kcal/kg/d)	0.192	-0.050, 0.435	NS	0.073
Protein (g/kg/d)	1.963	-3.689, 7.615	NS	0.015
Age, mo.	-0.025	-0.129, 0.080	NS	0.007
Sex	-0.736	-9.643, 8.172	NS	0.001
PRISM Score	0.187	-0.609, 0.982	NS	0.007

NS: not significant

Table A.4 Multiple linear regression of predictors of hospital length of stay in non-surgical patients

	B Coefficient	95% CI	p-value	r^2
N=50				
Energy (kcal/kg/d)	0.054	-0.185, 0.292	NS	0.070
Age, mo.	0.077	-0.034, 0.188	NS	
Sex	5.191	-4.565, 14.947	NS	

NS: not significant

Table A.5 Multiple linear regression of predictors of PCICU length of stay in non-surgical patients

	B Coefficient	95% CI	p-value	r^2
N=50				
Energy (kcal/kg/d)	-0.006	-0.179, 0.166	NS	0.179
Age, mo.	0.059	-0.021, 0.139	NS	
Sex	8.145	1.083, 15.207	NS	

NS: not significant

Table A.6 Multiple linear regression of predictors of ventilator days in non-surgical patients

	B Coefficient	95% CI	p-value	r^2
N= 35				
Energy (kcal/kg/d)	0.207	-0.074, 0.488	NS	0.075
Age, mo.	0.011	-0.104, 0.126	NS	
Sex	0.618	-8.420, 9.657	NS	

NS: not significant

Appendix 3: Tables of comparison of all patients, non-surgical patients and 2/3BMR(WHO)

Table A.7 Comparison of hospital outcomes between below or above 2/3BMR(WHO) in all patients

Hospital Outcomes	N=253 <31kcal/kg/d n=132	≥31kcal/kg/d n=121	P value
HLOS, d	25 (15–44)	16 (11–28)	**< 0.001**
PCICU LOS, d	11 (7–19)	8 (3–12)	**< 0.001**
Vent, d	10 (6–15)	5 (2–8)	**< 0.001**
Infections, n (%)	54 (41%)	54 (45%)	NS

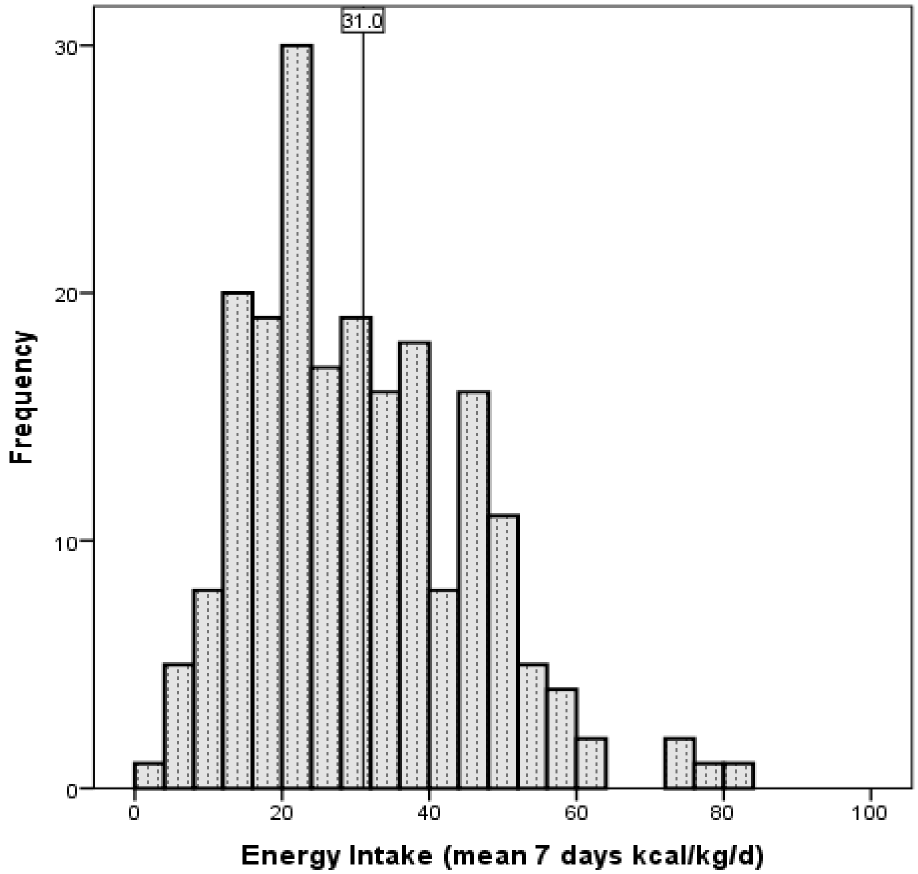
Values are presented in median (IQR) and percentage. Patients on ventilator support above and below were n=106 and n=124, respectively. Median 2/3BMR(WHO). P values < 0.05 are significant fromt he Mann-Whitney U test for continues variables and Chi-square for categorical variables. NS: not significant

Table A.8 Comparison of hospital outcomes between patients below or above 2/3BMR(WHO) in surgical and non-surgical patients

Hospital Outcomes	Non-Surgical <34kcal/kg/d n=20	≥34kcal/kg/d n=30	P value
HLOS, d	21 (17–45)	32 (17–41)	NS
PCICU, d	12 (9–23)	10 (8–17)	NS
Vent, d	9 (5–15)	7 (4–10)	NS
Infections, n (%)	12 (60%)	22 (73%)	NS

Values are presented in median (IQR) and percentage. P values < 0.05 are significant from the Mann-Whitney U test for continues variables and Chi-square for categorical variables. NS: not significant. Non-surgical patients on ventilator support above and below were n=19 and n=16, respectively.

Table A.9 Distribution of surgical patients energy intake below or above predicted 2/3BMR(WHO)



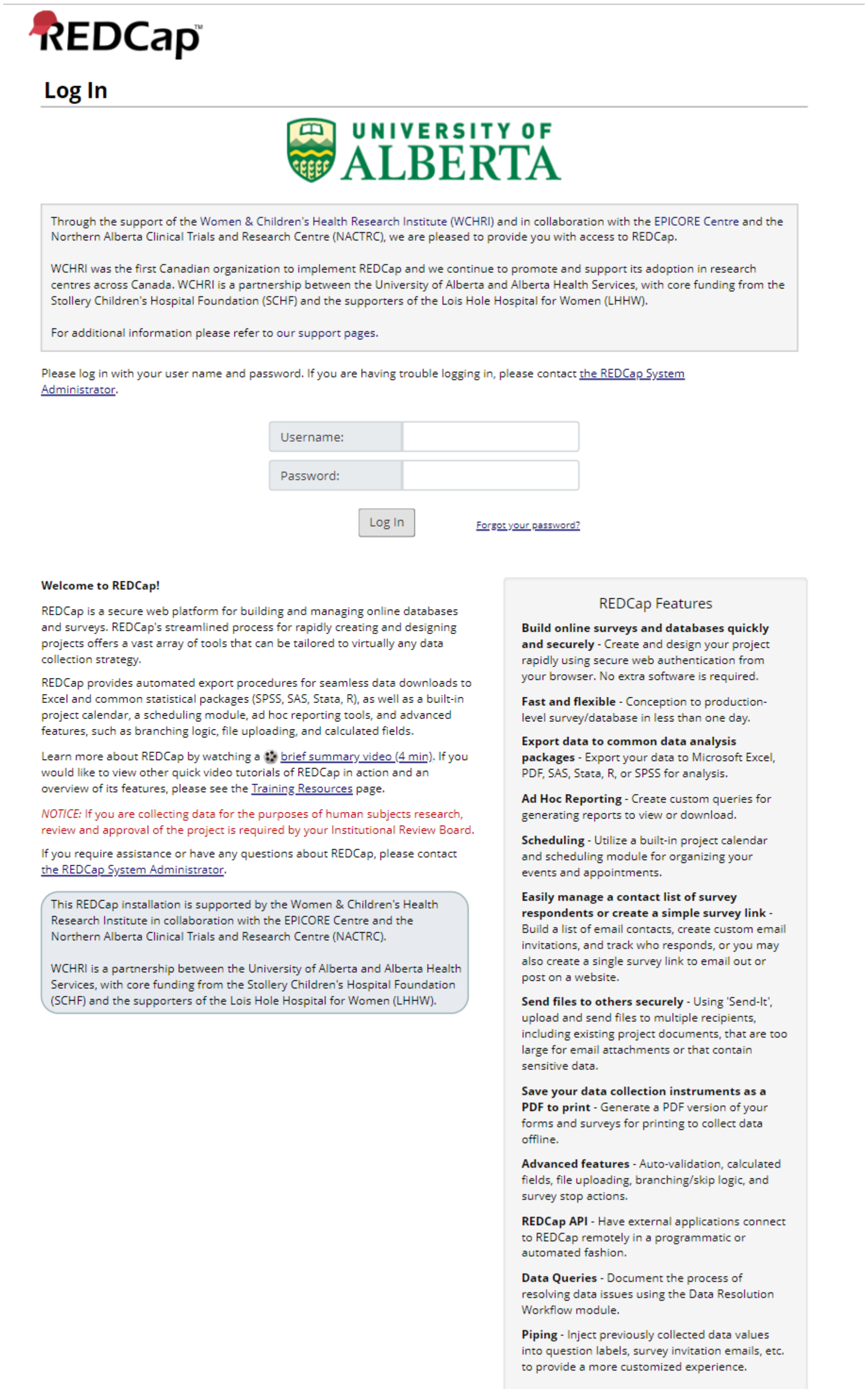
Appendix 4: Table of PN vs. EN in non-surgical patients

Table A.10 Comparison of PN vs. EN and hospital outcomes in non-surgical patients

	Non-Surgical		
Hospital Outcomes	PN Group (n=19)	EN Group (n=30)	p value
HLOS, d	32 (17–37)	24 (12–52)	NS
PCICU LOS, d	12 (9–19)	11 (9–23)	NS
Vent, d	9 (4–12)	7 (4–11)	NS
Infections, n (%)	11 (58%)	23(77%)	NS

Values are presented in median (IQR) and percentage. P values < 0.05 are significant from the Mann-Whitney U test for continues variables and Chi-square for categorical variables. NS: not significant HLOS: hospital length of stay; PCICU LOS: pediatric cardiac intensive care unit; Vent, d: Ventilator support days.

Appendix 5: REDCap online databases



REDCap

Log In

UNIVERSITY OF ALBERTA

Through the support of the Women & Children's Health Research Institute (WCHRI) and in collaboration with the EPICORE Centre and the Northern Alberta Clinical Trials and Research Centre (NACTRC), we are pleased to provide you with access to REDCap.

WCHRI was the first Canadian organization to implement REDCap and we continue to promote and support its adoption in research centres across Canada. WCHRI is a partnership between the University of Alberta and Alberta Health Services, with core funding from the Stollery Children's Hospital Foundation (SCHF) and the supporters of the Lois Hole Hospital for Women (LHHW).

For additional information please refer to our support pages.

Please log in with your user name and password. If you are having trouble logging in, please contact the REDCap System Administrator.

Username:

Password:

Log In

Forgot your password?

Welcome to REDCap!

REDCap is a secure web platform for building and managing online databases and surveys. REDCap's streamlined process for rapidly creating and designing projects offers a vast array of tools that can be tailored to virtually any data collection strategy.

REDCap provides automated export procedures for seamless data downloads to Excel and common statistical packages (SPSS, SAS, Stata, R), as well as a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields.

Learn more about REDCap by watching a brief summary video (4 min). If you would like to view other quick video tutorials of REDCap in action and an overview of its features, please see the Training Resources page.

NOTICE: If you are collecting data for the purposes of human subjects research, review and approval of the project is required by your Institutional Review Board.

If you require assistance or have any questions about REDCap, please contact the REDCap System Administrator.

This REDCap installation is supported by the Women & Children's Health Research Institute in collaboration with the EPICORE Centre and the Northern Alberta Clinical Trials and Research Centre (NACTRC).

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REDCap Features

Build online surveys and databases quickly and securely - Create and design your project rapidly using secure web authentication from your browser. No extra software is required.

Fast and flexible - Conception to production-level survey/database in less than one day.

Export data to common data analysis packages - Export your data to Microsoft Excel, PDF, SAS, Stata, R, or SPSS for analysis.

Ad Hoc Reporting - Create custom queries for generating reports to view or download.

Scheduling - Utilize a built-in project calendar and scheduling module for organizing your events and appointments.

Easily manage a contact list of survey respondents or create a simple survey link - Build a list of email contacts, create custom email invitations, and track who responds, or you may also create a single survey link to email out or post on a website.

Send files to others securely - Using 'Send-It', upload and send files to multiple recipients, including existing project documents, that are too large for email attachments or that contain sensitive data.

Save your data collection instruments as a PDF to print - Generate a PDF version of your forms and surveys for printing to collect data offline.

Advanced features - Auto-validation, calculated fields, file uploading, branching/skip logic, and survey stop actions.

REDCap API - Have external applications connect to REDCap remotely in a programmatic or automated fashion.

Data Queries - Document the process of resolving data issues using the Data Resolution Workflow module.

Piping - Inject previously collected data values into question labels, survey invitation emails, etc. to provide a more customized experience.