Summer 8-8-2018

Comparison of Nutrition Outcomes by Enteral Nutrition Feeding Method during Weaning from Parenteral Nutrition in Children with Intestinal Failure

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ABSTRACT

COMPARISON OF NUTRITION OUTCOMES BY ENTERAL NUTRITION FEEDING METHOD DURING WEANING FROM PARENTERAL NUTRITION IN CHILDREN WITH INTESTINAL FAILURE

by

Elizabeth K. Thomas

Objective: To evaluate the difference in time to achieve enteral autonomy, survival, and linear growth velocity by parenteral nutrition (PN) weaning strategy in children with intestinal failure.

Methods: Analysis of retrospectively reviewed medical record data included comparison of time to PN wean since the date of the first clinic visit, survival time, and differences in height *z*-scores between PN wean and two-years post-wean by whether an enteral tube feeding (TF) was used during the weaning process.

Results: 32 of 49 children (65%) received an enteral TF with or without oral diet during the two-year follow-up period. Median time to weaning did not differ significantly between those who received a TF (21.5 months [IQR;10.3, 37.8]) vs. oral diet alone (19.0 months [IQR; 14.5, 40.0]). The probability of survival did not differ by TF status with only one death in the TF group. Linear growth velocity between the time of PN weaning to two-years post-wean did not significantly differ by TF status. Children who weaned via oral diet alone had a similar decrease in height *z*-score vs. those who received a TF (-0.14 vs. -0.15, respectively); however, a greater increase in *z*-score between years 1 and 2 post-wean was observed (+0.27 vs. +0.11, respectively).

Conclusions: No association between weaning strategy and outcomes in children with IF was observed. Linear growth velocity declines during the first year after PN weaning but

rebounds in year two. Future studies should examine the long-term benefits of oral feeding vs. TF on intestinal adaptation.

COMPARISON OF NUTRITION OUTCOMES BY ENTERAL NUTRITION FEEDING METHOD DURING WEANING FROM PARENTERAL NUTRITION IN CHILDREN WITH INTESTINAL FAILURE

by
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A Thesis

Presented in Partial Fulfillment of Requirements for the Degree of

Master of Science in Health Sciences

The Byrdine F. Lewis College of Nursing and Health Professions

Department of Nutrition

Georgia State University

Atlanta, Georgia
2018

ACKNOWLEDGMENTS

I would like to express my deepest appreciation to my committee chair, Dr. Anita Nucci, who has offered endless support, guidance, and positivity throughout this process. Without her support, this thesis would not have been possible. I would also like to thank my committee members, Barbara Hopkins and Jessica White, for their assistance in writing this thesis. Their expertise and feedback has been invaluable. To Jane Anne Yaworski, thank you for continuously offering insight throughout data collection and analysis. Finally, I am grateful to my family, friends, and cohort members, without their encouragement, this thesis would not have been possible.

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ABBREVIATIONS

ASPEN	American Society for Parenteral and Enteral Nutrition
BMI	Body Mass Index
Ca	calcium
CDC	Centers for Disease Control and Prevention
Cl	chlorine
cm	centimeter
EN	Enteral Nutrition
ESPGHAN	The European Society for Paediatric Gastroenterology Hepatology and Nutrition
g	gram
GIR	Glucose Infusion Rate
GH	Growth Hormone
Gln	Glutamine
GLP-2	Glucagon-like peptide 2
Ht	Height
ICARE	Intestinal Care and Rehabilitation Center
IF	Intestinal Failure
IFALD	Intestinal Failure Associated Liver Disease
IV	Intravenous
K	potassium
Kcal	kilocalorie

Kg	kilogram
Mmol	millimole
Mo	month
MUAC	Mid-Upper Arm Circumference
Na	sodium
NEC	Necrotizing Enterocolitis
NFPE	Nutrition-Focused Physical Exam
PI	Principal Investigator
PICU	Pediatric Intensive Care Unit
PN	Parenteral Nutrition
SBBO	Small Bowel Bacterial Overgrowth
SBS	Short Bowel Syndrome
STEP	Serial Transverse Enteroplasty
TSF	Triceps Skinfold
UPMC	University of Pittsburgh Medical Center
WHO	World Health Organization
Wt	weight
Yr	year

CHAPTER I

COMPARISON OF NUTRITION OUTCOMES BY ENTERAL NUTRITION FEEDING METHOD DURING WEANING FROM PARENTERAL NUTRITION IN CHILDREN WITH INTESTINAL FAILURE

Introduction

Intestinal failure (IF) in the pediatric population is a clinical condition characterized by malabsorption, malnutrition, and growth retardation secondary to extensive loss of intestinal length or function.[1] Short bowel syndrome (SBS) occurs after massive resection of the small bowel, often due to necrotizing enterocolitis, intestinal atresia, midgut volvulus, or gastroschisis.[2] Resection is the most common cause of IF in children.[2] Many infants with SBS are born prematurely and at very low birth weight (<1,500 grams); most receive parenteral nutrition (PN) beginning within the first three days of life.[3] Children with IF caused by SBS undergo progressive intestinal adaptation of their remaining bowel over a period of a few months to years. During this time, medical and surgical management includes maintenance of fluid and electrolyte balance and enteral nutrition (EN) and PN support.[4] Adaptation is defined as an enhanced absorptive capacity of residual small bowel through increases in cellular proliferation, villus height, and crypt depth. The most effective strategy for stimulating intestinal adaptation, achieving intestinal rehabilitation, and reducing the risk of PN-related complications remains the provision of EN.[5]

Advances in neonatal intensive care, anesthesia, and surgical techniques have resulted in the survival of progressively smaller infants.[3] The incidence of SBS is

currently estimated to be 3 to 5 per 100,000 births per year and the prevalence of SBS has likely increased in recent years due to advances in medical and nutritional care.[3,6] Approximations of the prevalence of IF and SBS are difficult to determine in children as they are based on the number of patients receiving home PN, currently ~16,000, which is the therapy most often indicated for SBS.[3] Although cases of IF and SBS are rare, the human and societal costs are considerable with medical charges exceeding $500,000 in the first year of life and averaging ~$300,000 in subsequent years.[7] Children with IF are at risk for multiple complications including metabolic abnormalities, mechanical and infectious complications of central venous catheters, structural and functional bowel disorders, chronic liver disease and a lower quality of life.[3] Although the survival rate for pediatric patients with SBS has improved with the use of PN, many pediatric patients still fail to maintain adequate somatic growth, and the complications associated with its long-term use may be life-threatening.[8,9] Morbidity and mortality rates in patients with IF and SBS have been associated with many factors including: 1) age at the time of surgery, 2) residual bowel length, 3) function and adaptive capacity of the remnant bowel, 4) the ability to achieve enteral autonomy, 5) incidence of sepsis, and 6) the development of PN associated liver disease.[3,5]

Maintenance of nutritional status and growth in children with SBS can be difficult because of the potential clinical manifestations of the disorder, including feeding intolerance, altered intestinal motility, malabsorption of electrolytes and macro- and micronutrients,[10,11] and oral aversion.[12] The survival rate for many children with SBS, the avoidance of long-term PN associated complications such as central line catheter infections, liver disease, and death remain a constant concern and challenge for

healthcare providers.[13] The nutritional support of patients with SBS is complex and must be individualized based on the acute and chronic medical issues and conditions of each patient.[9] After patients are stabilized postoperatively, standard practice has been to gradually cycle PN hours downward while concurrently maximizing enteral tube feedings. Despite the use of PN and standard medical management, growth failure by anthropometry is still observed in a high percentage of patients. Rates of underweight (weight for age <5th percentile) and stunting (length or height for age <5th percentile) have been reported between 21-38% and 34-46%, respectively in this population.[3,9]

Interdisciplinary management of children with chronic intestinal disease is essential to improve the outcome of the disease process as it can result in cessation of PN support, accelerated growth, and improved survival.[9,14] Moreover, interdisciplinary care serves to enhance communication of the treatment plan to the patient/family as well as maintain the continuity of care throughout the entire treatment process. The high mortality rate of patients in the IF and SBS populations, who have been neither weaned from PN nor transplanted, emphasizes the critical importance of a concentrated effort toward the goal of eliminating PN support.[9] The initial publication of the Pediatric Intestinal Failure Consortium, which included 14 pediatric centers in the United States and Canada, reported that of 272 children examined retrospectively, breast milk was given to 52 (19%); twenty different infant formulas were used as the initial enteral diet and 40 different formulas were used overall.[3] While practice variations are expected, the effectiveness of these strategies it is important to compare to determine a best practice.[3]

The Intestinal Care and Rehabilitation Center (ICARE) at Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center (UPMC) has served as a

leading referral center for the evaluation and management of children with IF or SBS since 1996. Previous research conducted in Pittsburgh found that patients weaned from PN achieved 93% survival vs. 26% for those not weaned.[9] Children with SBS require months to years to adapt, and still others are never able to achieve enteral autonomy.[3,14] The confluence of factors such as diagnosis, intestinal anatomy, nutritional intake or growth status that contribute to the problem within this population is not yet understood. Nutrition management strategies vary between intestinal care centers and many practices are not evidence-based.[3] Therefore, we proposed the first observational retrospective study to evaluate the effectiveness of a standard PN weaning regimen using enteral tube feedings vs. a more direct approach of weaning to oral diet in a sample of infants and children with SBS. This research enables us to better understand factors that contribute to successful weaning from PN and develop a treatment approach to improve outcomes for these children.

The ICARE registry, which existed between 1996 and 2009, contains the nation's largest center database for children with IF/SBS (n=444). In 2010, the center clinicians adopted a regimen for patients with IF and SBS that involved weaning from PN directly to oral diet without the use of supplemental tube feedings. This change in the nutrition management protocol has provided us with the opportunity to assess the effect of using tube feedings vs. oral diet during weaning of PN on survival, nutritional intake, growth, and time to enteral autonomy. The benefits of using a regimen that does not incorporate supplemental tube feedings include: 1) reduced discomfort to children, 2) lower cost, 3) decreased stooling, 4) reduced risk of losing the suck/swallow reflex, and 5) less oral aversion. Continuous enteral feeding has been suggested to ensure better absorption of

calories. However, ultimately intestinal adaptation is what enables enteral autonomy and the discontinuation of PN. Early parabiotic mouse studies clearly showed the hormonal influence on intestinal adaptation.[15] We hypothesize that intermittent feeding provides an advantageous milieu for intestinal adaptation and that the introduction of oral feeding may outperform continuous tube feedings for this reason. By resuming the ICARE registry to include patients referred since 2009, we assessed this most recent change in practice and compared outcomes to those achieved using the previous standard of nutritional care.

Specific Aim: To describe and compare the effect of a PN weaning strategy with and without continuous enteral tube feedings on survival, nutrition intake, growth, and time to achieving enteral autonomy in children with IF.

Hypothesis 1: The time to achieve enteral autonomy will be shorter in patients who did not receive a continuous enteral tube feeding during the weaning process.

Null Hypothesis 1: The time to achieve enteral autonomy will not differ by PN weaning approach.

Hypothesis 2: Survival time will be longer in patients who did not receive a continuous enteral tube feeding during the weaning process.

Null Hypothesis 2: Survival time will not differ by PN weaning approach.

Hypothesis 3: Linear growth velocity will be greater in patients who did not receive a continuous enteral tube feeding during the weaning process.

Null Hypothesis 3: Growth will not differ by PN weaning approach.

We anticipated identifying a high percentage of children who remain on PN beyond the first year after initial surgery. We hypothesized that participants who were weaned from PN using a more direct approach to oral diet (without continuous enteral tube feeding) will have a shorter time to weaning than those who received enteral tube feedings during the transition process. The purpose of this study is to describe the medical, nutritional, and growth outcomes of children with SBS as they transition from PN to oral nutrition and to evaluate the effectiveness of various nutrition strategies on outcomes, including survival, nutrition intake, growth, and time to achieve enteral autonomy. Our future goal is to conduct a multicenter prospective study to assess nutritional interventions in children with intestinal failure that will shorten time on PN and reduce the morbidity and mortality associated with its use.

CHAPTER II

Review of Literature

Pediatric Short Bowel Syndrome

Short Bowel Syndrome is traditionally defined as a clinical condition resulting from extensive resection of the small bowel, congenital defect, or disease-associated loss of absorption that is characterized by inadequate absorption of enteral nutrients.[2,5,16,17] Most commonly, SBS occurs following significant injury to the gastrointestinal tract or intestinal failure, which is the reduction in functional intestinal capacity to maintain growth, hydration, and/or electrolyte balance requiring dependence on PN for greater than 4 weeks. [2,5,18] While SBS can be congenital or acquired, in pediatric patients, particularly infants, necrotizing enterocolitis (NEC) and subsequent surgical intervention is the most common cause, with 22% to 50% of SBS cases resulting from NEC.[2,5,19,20] Additional causes of SBS include intestinal atresia, abdominal wall defects, volvulus, Hirschsprung disease, and meconium ileus.[20,21] Though the etiology and pathophysiology of necrotizing enterocolitis are not fully understood, NEC is characterized by ischemia, severe damage or necrosis of intestinal cells, and ulcerative inflammation of the intestinal wall.[19,22] While NEC may be treated with conservative, symptomatic treatment, such as fasting, PN, fluid balance, and pain medication, bowel resection is often necessitated, leading to SBS.[22]

Full-term infants typically have between 200 and 250 cm of small bowel at birth, while those with SBS have a portion of small bowel that is nonfunctional or removed.[2,19] The resulting anatomy of the gastrointestinal tract typically falls into one of three

categories: jejuno-colic anastomosis, end-jejunostomy, or jejuno-ileal anastomosis. The pathophysiology of SBS varies widely depending on the amount and portion of intestine resected. [2,19,23] Jejuno-colic anastomosis results from removal of the ileum and often ileocecal valve leaving the remaining jejunum and colon.[24] Patients with removal of the ileum, colon, and some portion of the jejunum have an end-jejunostomy, and those with a primarily jejunal resection with more than 10 cm of ileum and colon remaining have a jejuno-ileal anastomosis.[24] Because the portion and length of remaining bowel is indicative of absorption, hormone and enzyme production and secretion, and adaptive capacity, the length of small bowel remnant remaining is one of the essential variables predicting survival and weaning of PN.[2,23] The potential problems associated with resection of various portions of the small intestine are shown in Appendix A

Treatment of SBS is focused on maintenance of normal growth and development and restoration of full EN, and prognosis is closely related to 1) age at the time of surgery, 2), site and amount of bowel resected, 3) function (absorption and motility of the remnant bowel), (4) adaptive capacity of the remnant bowel, 5) injury to the bowel (due to infections, bacterial overgrowth, ischemia, stricture), and 6) whether complications (liver disease, recurrent line infections, and loss of vascular access) associated with chronic PN occur.[5,19,21]

Intestinal Adaptation

Following intestinal resection, there is decreased mucosal surface area and decreased intestinal transit time, which results in reduced intestinal absorption of nutrients.[19,25] Intestinal adaptation is an innate response that includes both anatomic and

physiologic changes of the intestine whereby the bowel attempts to regain absorptive capacity and transit time comparable to the level prior to resection. [2,19,23,26] Adaptation begins immediately following the resection and continues for at least two years, sometimes extending to more than three years.[2,19,23,26] While the physiologic changes are poorly understood, intestinal adaptation is known to be affected by EN, circulating gut hormones, and endogenous luminal secretions.[19] Beginning EN as early as is medically feasible is integral to intestinal adaptation.[19] Furthermore, circulating enteroglucagon and luminal cholecystokinin and secretin stimulate intestinal cell proliferation, and these luminal secretions are stimulated by enteral nutrition.[19]

While the degree of adaptation depends on the site and length of the remaining bowel, some degree of adaptation can occur no matter the remaining length of bowel remaining.[19,23] When comparing resection of various portions of the small intestine, absorptive and adaptive capacity of each section of the intestine must be considered. The ileum is responsible for fluid and electrolyte management, absorption of a multitude of nutrients, including vitamin B12, A, D, E, and K, phosphorus, and zinc, and has a greater capacity for adaptation both structurally and functionally, so resection of portions of the duodenum or jejunum are better tolerated in terms of nutrient and electrolyte maintenance than ileum resection.[2,23] Overall, intestinal adaptation results in increased small bowel surface area, villus length, intestinal crypts, and length and diameter of the remaining intestine that ultimately leads to increased surface area for digestion and absorption.[19]

Treatment Strategies

Pharmacologic Intervention

Many clinical manifestations of SBS can be treated with pharmacologic interventions.[19] Gastric hypersecretion is a common result of intestinal resection and further inhibits absorption because the increased acidity inactivates pancreatic enzymes and precipitates bile acid while also damaging the intestinal epithelium.[5,19] Therefore, gastric hypersecretion should be managed quickly with an H_2 receptor antagonist or proton-pump inhibitor.[5,19] Intestinal transit time is reduced in SBS resulting in decreased nutrient absorption and often excess stool.[19] Pharmacologic intervention can be used to slow transit time, optimize absorption, and encourage weaning from parenteral nutrition more quickly.[19]

Small bowel bacterial overgrowth (SBBO), a common problem in SBS, occurs when excess bacteria exists in the small intestine.[19,27] While some patients may tolerate SBBO and benefit from the production of the production of short chain fatty acids, others may experience feeding intolerance, abdominal distention, gassiness, diarrhea or increased ostomy output, or early satiety and may have further reduced nutrient absorption.[5,19,20] Furthermore, SBBO is associated with villous atrophy and mucosal inflammatory response, and the risk for developing a bloodstream infection is higher in patients with SBS and SBBO than those without SBBO.[28] Pharmacologic intervention is necessary to reduce bacterial overgrowth and promote mucosal health and feeding tolerance, but large randomized control trials evaluating antimicrobial treatment are lacking.[5,19,29] Diagnosing SBBO is challenging because the associated symptoms are often indistinguishable from IF, an endoscopy procedure to obtain luminal samples is

invasive, and breath hydrogen tests may be unreliable in SBS patients.[20] Therefore, SBS patients with symptomatic SBBO or an anatomic predisposition to SBBO are treated with cycled antimicrobials.[20,29] Antimicrobials are given for a one to two week cycle each month, and a different antimicrobial is prescribed at each monthly administration to avoid bacterial resistance.[20,29] Pharmacologic interventions for the management of SBBO symptoms include stool bulking agents used to limit bacterial translocation, glutamine supplementation to increase intestinal immunity, and probiotics; however, data detailing the risks and benefits of glutamine and probiotic supplementation are limited.[29]

Surgical Management

Surgical intervention may be indicated to promote intestinal adaptation and enteral autonomy. [19,26] These interventions include procedures to increase intestinal surface area for absorption, improve motility through the small intestine, and slow intestinal transit time. [19,26] Surgical interventions may also be used to lengthen the intestine through serial tapering enteroplasty (STEP) or Bianchi procedures.[19,26] If other medical or surgical interventions are unsuccessful or additional complications arise, isolated intestinal transplantation is a possiblity.[26] Additionally, for patients who have developed end-stage liver disease related to long-term PN therapy, intestine-liver transplantation may be considered.[24] While surgical intervention may be necessary, to promote intestinal adaptation, it should be withheld for at least one year following small bowel resection.[19]

Nutrition Therapy

Appropriate nutrition therapy for pediatric short bowel syndrome is integral for promoting intestinal adaptation, managing fluid and electrolytes, reducing infection and disease associated with intestinal resection and PN, and improving overall health outcomes. Nutrition management includes recommendations for macronutrient composition of PN and EN as well as micronutrient, hormonal, and trophic supplementation.

Intestinal failure-associated liver disease is common in patients with SBS relying on PN, and intravenous (IV) lipids are closely associated with its development.[5] The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommends lipid dosage in the PN solutions be between 0.5 g/kg/day and 1 g/kg/day to reduce the risk for essential fatty acid deficiency while also reducing the risk for Intestinal Failure Associated Liver Disease (IFALD).[5] Though closely managing lipid content of PN is necessary to prevent complications, the inevitable calorie deficit is most often replaced with dextrose.[5] A.S.P.E.N., the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), and the American Academy of Pediatrics recommend limiting the glucose infusion (GIR) rate to 12-14 mg/kg/min to prevent hepatic steatosis.[5] If meeting energy needs at this GIR is impossible, increases in PN glucose content should be made with close monitoring for hyperglycemia and liver disease.[5]

When beginning trophic EN feeding in patients with short bowel syndrome, continuous EN is arguably most appropriate to promote better tolerance, improved absorption, and continuous saturation of carrier proteins in the intestinal lumen.[5,20,21,23,30]

Human milk or an amino acid-based formula is the optimal choice for enteral feeding and may reduce the duration of PN.[5,21,23] At initiation of EN, human milk should be provided for all infants when available because it contains growth factors, immunoglobins, long-chain fatty acids, and free amino acids that promote intestinal adaptation. [20,30] Protein concentration and caloric density of breast milk is limited, so hydrolyzed protein may be added after considering growth parameters and blood urea nitrogen levels.[20]

When breast milk is not available, in older children, or with a protein allergy, an elemental amino-acid based formula is appropriate.[20] Amino-acid based formulas contain long-chain and medium-chain triglycerides that promote intestinal adaptation and ensure direct absorption by enterocytes.[5,21,23,30] Macronutrient composition should include a 30%:70% ratio of medium-chain triglycerides to long-chain triglycerides to promote fat absorption.[5] It is recommended that EN begin at a concentration of 20 kcal/30 mL and be increased by 0.5 to 1 mL/kg/day to reduce the risk of volume-related complications.[23]

Because micronutrient absorption will differ depending on the type of bowel resected and may be hindered by a variety of medical complications associated with SBS, nutrient supplementation must be monitored closely and supplemented as necessary, particularly when PN is discontinued.[19,21] To differing degrees, patients with SBS will likely have decreased fat-soluble vitamin absorption due to bile acid deficiency; therefore, vitamins A, D, E, and K require supplementation in water-soluble form.[21] Depending on the remnant bowel and degree of adaptation, phosphorus, magnesium,

selenium, copper, iron, calcium, zinc, and vitamin B12 may also necessitate supplementation (Appendix A).[19,21,24,31]

Growth hormone (GH) has been shown to promote mucosal cell proliferation, increase mucosal height, and increase water, sodium, and amino acid absorption in patients with SBS.[5,32] Unfortunately, data supporting the benefits of GH on improving tolerance of EN and increasing body weight, lean body mass, and fat-free mass in pediatric patients are inconclusive; therefore, GH is not approved for use in the pediatric population.[5]

Glutamine (Gln), a nonessential amino acid that is utilized as a major fuel for intestinal mucosal cells and immune cells, is found abundantly in human milk; however, Gln is not included in standard IV amino acid solutions. While Gln is adequately produced during times of health, supplementation during catabolic conditions may be necessary.[33] Multiple studies suggest Gln supplementation enhances gut mucosal growth, repair, and function, increases duodenal villus height, reduces intestinal mucosa atrophy, improves nitrogen balance, and decreases gut-origin sepsis.[5,33] Despite these known benefits of supplemental Gln, a multicenter clinical trial of extremely low birth weight infants found that PN supplemented with Gln did not decrease mortality, increase tolerance of enteral feeds, effect growth, or reduce incidence of late-onset sepsis.[34] Supplemental Gln is currently not approved for pediatric use; though, additional studies are ongoing.[5]

Glucagon-like peptide 2 (GLP-2) is a trophic peptide produced by mucosal cells in the ileum and proximal colon and pancreatic cells that has been shown to stimulate crypt cell proliferation and increase villus growth in the jejunum and ileum.[5,33,35] GLP-2

is often diminished in patients with small bowel resection, but its use is not approved for pediatric patients since there are no pediatric studies examining the safety and efficacy of GLP-2 supplementation.[5]

Soluble fiber slows gastric emptying and intestinal transit, which are necessary to increase absorption in patients with SBS.[5] Additionally, soluble fiber is metabolized by colonic bacteria to produce short-chain fatty acids, which can be used as an energy source for colonocytes and promote sodium and water absorption.[5] Several studies indicate a potential role of supplemental soluble fiber in improving diarrhea associated with SBS.[5,21,36]

Pediatric Nutrition Assessment

As defined by the Academy of Nutrition and Dietetics, a nutrition assessment is the process "to obtain, verify, and interpret data needed to identify nutrition related problems, their causes, and significance."[37,38] Because of the intensive growth and development occurring through infancy and childhood, pediatric patients are particularly vulnerable to nutrition-related concerns and malnutrition.[38] A comprehensive nutrition assessment is imperative for pediatric patients, especially those with nutrition-related chronic conditions like SBS.[38] Nutrition assessment is comprised of five categories: food/nutrition-related history; anthropometric measurements; biochemical data; medical tests and procedures; nutrition-focused physical findings; and patient history. Data can be obtained from the medical record, through patient and caregiver interviews, and in the nutrition-focused physical assessment.[38] Often, extensive information can be gleaned from the patient's medical record, particularly if the patient's medical history includes

past visits to specialty clinics or other providers.[38] In the record, the following should be noted: reason for clinic visit or referral; medical history, surgeries, and nutrition-related conditions; current medications, supplements; laboratory data, medical tests, and procedures; Tanner stage; growth history; anthropometric measurements with growth chart plots and z scores; and prenatal and birth history.[38]

Anthropometric Measures

Anthropometric measures are essential for observing growth changes over a continuum of time and should be assessed at admission, throughout hospital stay, and prior to discharge.[38] Often, correct anthropometric measures are difficult to obtain due to contractures, poor cooperation, or clinician error.[38] This increases the importance of routine anthropometric measures.

Length and Height

Traditionally, for children < 24 months old, length should be recorded using a solid length board or infantometer with two clinicians present, one to hold the head of the patient while the other places the patient's feet at a right angle with legs straight against the lower plate.[38] Length is recorded to the nearest 0.1 cm, and the process should be repeated to ensure accuracy.[38] For patients > 2 years old, height should be measured using a fixed stadiometer or vertical measuring tape secured to a solid surface.[38] The patient should stand looking straight ahead with heels together and heels, buttocks, shoulders, and head resting against the solid surface where the measuring tool is located.[38] Height is recorded to the nearest 0.1 cm, and the process should be repeated to

ensure accuracy.[38] In patients with limitations hindering the ability to use a standard measuring method, alternative methods, such as knee height measure, arm span, and tibial length, should be used.

Weight

Weight is a necessary parameter when assessing growth and nutrition; however, weight can fluctuate widely depending on time of day, intake, IVs, and scale used, among other factors, so weight should be recorded at all clinician interactions. [38] In infants, weight should be measured naked or with a dry diaper using a pan scale.[38] Pan scale weight is recorded to the nearest 10 g.[38] Weight for children greater than two years of age should be measured using a platform scale with minimal excess weight from clothing and shoes. Platform scale weight is recorded in kilograms to the nearest one decimal place.[38] If a weight is unable to be obtained by traditional methods, a bed scale, wheelchair scale, or hold and subtract method may be used.[38]

Mid-Upper Arm Circumference and Triceps Skinfold

When there is concern that weight measures may be inaccurate or fluctuating due to fluid changes, Mid-Upper Arm Circumference (MUAC) and Triceps Skinfold (TSF) are easily obtainable measures that can be used as predictors of malnutrition risk and mortality.[38] These measures are often better at predicting body composition and malnutrition because unlike weight and BMI, they are more indicative of muscle and fat mass.[38]

Weight for Length

For patients less than two years of age, weight for length is a comparison used to assess proportionality and linearity of growth using the World Health Organization 0-to 24-month growth charts.[38] Weight for length and growth chart plots can be used to assess linearity of growth over time.

Body Mass Index

Proportionality and acceptability of weight and height for patients older than two years is assessed using body mass index.[38]

$$\text{BMI} = \text{Weight in kg/Height in m}^2$$

BMI can be used to assess trends over time and visualize growth patterns. However, BMI may be skewed in individuals who have increased muscle mass or short stature, so additional measures like MUAC and TSF should be gathered during the assessment to determine if BMI is an adequate measure of growth.[38]

Growth Charts

Growth charts provide necessary data for determining pediatric nutrition status. Pediatric growth rate varies widely through the growth process, so differing growth are used depending on the age of the patient. For term infants up to two years of age, the 2006 WHO charts are most appropriate because they were developed using data from exclusively breastfed children from diverse backgrounds and geographic regions. Growth charts from the WHO can be used to determine percentiles, and *z* scores are available for boys and girls for weight for age, length for age, head circumference for age, and weight

for length.[38] At two to twenty years of age, patients are plotted on the Centers for Disease Control and Prevention (CDC) growth charts published in 2000.[38] CDC growth charts are available for boys and girls for weight for age, stature for age, and BMI for age.[38] For patients born prematurely or those with Down syndrome, Turner syndrome, Cerebral palsy, Prader-Willi syndrome, Achondroplasia, Noonan syndrome, or Williams syndrome, specialty growth charts exist that correspond with various growth differences in these populations.[38]

Nutrition-Focused Physical Exam

The nutrition-focused physical exam (NFPE) is a system-based examination of each region of the body to evaluate nutrition status.[39] The exam focuses on anthropometric measurements, visualization, assessment of subcutaneous fat and muscle stores, and assessment of the hair, eyes, oral cavity, skin, and nails for micronutrient deficiencies.[38] The NFPE is completed using inspection and palpitation, though percussion and auscultation may be included if deemed necessary.[38]

In infants and toddlers, fat stores should be assessed by palpating the orbital, buccal, triceps, ribs, and buttocks.[38] As fat stores are depleted, bony prominences become more protuberant, depressions between bones are more apparent, and less fat is found pinching and rolling skin together.[38] Muscle store assessment includes the temples, muscles surrounding the clavicle, shoulders, muscles overlying the scapula, quadriceps, and calves, and loss of muscle stores results in more apparent bony prominences and less resistance when muscular regions palpated..[38] Micronutrient assessment is completed by

visually observing the eyes and oral cavity and by visually observing the hair and nails and palpating the skin (Appendix A).[38]

Malnutrition

Pediatric malnutrition is defined by A.S.P.E.N. as an imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein or micronutrients that negatively affect growth, development, and other relevant outcomes.[40] In patients with chronic conditions or who require long-term nutrition support, nutrition-related issues are a concern, and patients with intestinal failure are at a higher risk for malnutrition.[38,41] In the United States, most malnutrition results directly from acute or chronic illness, and in critically ill patients, malnutrition is associated with longer periods of ventilation, higher-risk of hospital-acquired infection, longer pediatric intensive care unit (PICU) and hospital stay, and increased mortality.[38,42] Because of the adverse outcomes associated with malnutrition in critically ill patients, it is recommended that patients in the PICU undergo a thorough nutrition assessment within 48 hours of admission and weekly throughout hospitalization.[42] While a standardized method for diagnosing pediatric malnutrition has not been established, several indicators have been identified for assessment and diagnosis. These include food and nutrient intake, assessment of energy and protein needs, growth parameters, weight gain velocity, mid-upper arm circumference, and handgrip strength.[40] When determining a pediatric malnutrition diagnosis, a nutrition assessment with data from five domains: 1) etiology and pathogenesis, 2) chronicity, 3) anthropometric measurements, 4) growth, and 5)

developmental and functional outcomes, should be collected to ensure accuracy and completeness.[38]

Attention should be paid to those patients considered at-risk by A.S.P.E.N. criteria. Nutritionally-at-risk neonates who are at high nutrition risk are those born at less than 28 weeks gestational age, of extremely low birth weight less than 1000 g, establishing feeds after an episode of necrotizing enterocolitis or gastrointestinal perforation, or with severe congenital malformations like gastroschisis.[43] Infants at moderate risk are those born preterm between 28 and 31 weeks, at a weight less than the 9th percentile, at a very low birth weight of 1000-1500 g, or with an illness or congenital anomaly that compromises feeding.[43] Children considered nutritionally-at-risk are those with a weight for length or weight for height or sex less than the 10th percentile or greater than the 95th percentile, body mass index for age or sex less than the 5th percentile or greater than the 85th percentile, increased metabolic requirements, impaired ability to ingest or tolerate oral feedings, documented inadequate provision of or tolerance of nutrients, or inadequate weight gain or a significant decrease in usual growth percentile.[40,41]

Etiology and Pathogenesis

Malnutrition can be classified as illness or non-illness-related and can be further specified as acute or chronic.[38] Illness-related malnutrition is related to one or more disease, illness, or trauma and results in nutrient imbalance from decreased intake, increased needs, increased losses, and/or altered utilization of nutrients.[38] Non-illness-related malnutrition is linked to environmental or behavioral factors that result in

decreased nutrient intake and can be associated with adverse developmental and/or physiologic outcomes.[38] Malnutrition that has been present for less than three months is considered acute malnutrition and is most commonly seen using the measures of weight/age, weight/length, or BMI.[38] Malnutrition that has endured for more than 3 months is considered chronic malnutrition and is often seen in a skewed linear growth pattern or stunted growth.[38]

Anthropometric Measurements

Anthropometric measurements are necessary for a malnutrition diagnosis and therefore should be recorded regularly and accurately.[38] Measures like weight, length/height, and mid-upper arm circumference should be plotted on growth charts to determine growth.[38] *Z* scores for body mass index for age (weight for length, < 2 years) or weight for age should be used to further assess patients who may fall on extreme ends of the spectrum, and head circumference for patients < 36 months of age should be documented.[42]

Growth

When anthropometric measures are plotted on a growth chart, the corresponding *z* score is used to determine the degree of malnutrition.[38] A diagnosis can be further supported using multiple data points over time.[38] The criteria for malnutrition diagnosis based on anthropometric measures appear in Appendix B.

Developmental and Functional Outcomes

While handgrip strength can be used to assess functional status of patients greater than six years old with minimal physical or developmental limitations, often developmental and functional status is assessed through observation, care with the medical team, and/or a caregiver interview.[38] A pediatric patient with malnutrition may have decreased mobility, muscle loss, or weakness, which may result in vent dependence, immune dysfunction, cognitive and developmental delays, or delayed wound healing.[38]

Pediatric Nutrition Requirements

Pediatric Critically Ill Patient

When determining a pediatric patient's energy expenditure, indirect calorimetry is the most precise method because it accounts for the metabolic alterations that may occur throughout the course of an illness.[40,42] Moreover, indirect calorimetry is independent of nutrition status, diagnosis, or severity of the illness.[42] When indirect calorimetry is unavailable, predictive equations for energy and protein may be used. Evaluation of energy and protein needs regularly is important to adjust for changing needs throughout the course of illness and to ensure adequacy of energy intake.[42] Despite evidence that most predictive equations are inaccurate, according to A.S.P.E.N., if indirect calorimetry is unavailable, the Schofield or Food Agriculture Organization of the United Nations/WHO equations are suggested for use without inclusion of a stress factor.[42] Upon determining energy requirements, it is necessary to ensure that patients receive at least two-thirds of energy requirements by the end of the first week in the PICU.[42]

Adequate protein intake attenuates the loss of lean muscle mass and is necessary to achieve positive or neutral nitrogen balance. The Recommended Dietary Allowance and WHO recommendations should not be used to determine protein needs in critically ill patients because they were developed for use in healthy children.[42] A minimum recommendation has been made by A.S.P.E.N. at 1.5 g/kg/day, but optimal protein intake may be higher, particularly in young children, critically ill patients, and patients receiving mechanical ventilation.[42] While clinical expertise should be considered, the safety of protein intake of greater than 3 g/kg/day in children older than one month of age has not been established, so particular care and monitoring should be in place when protein needs are expected to be >3 g/kg/day.[42] Recommended predictive equations for the pediatric critically ill patient appear in Appendix C.

Premature Infant

Infants born prematurely have increased nutrient requirements compared to infants born at term, and adequate nutrient provision is necessary to promote growth similar to that of the in utero growth of a normal fetus.[44] According to ESPGHAN guidelines, enteral energy requirements for neonates are 110-135 kcal/kg, and protein requirements are 3.5-4.0 g/kg.[45,46] Because enteral nutrition promotes dietary induced thermogenesis, enteral needs are 10% higher than parenteral needs.[45] Parenteral energy requirements are 110-120 kcal/kg, and protein requirements are 1.5-4.0 g/kg (Appendix C).[31,45]

Pediatric Nutrition Support

Parenteral Nutrition

Parenteral nutrition has dramatically changed the course of treatment for pediatric SBS and is an imperative piece of medical management.[19,47] Patients with short bowel syndrome require supplemental PN to ensure sufficient growth and development.[47] Following intestinal resection, three distinct phases of intestinal adaptation and nutritional needs are noted. The phase immediately following intestinal resection is characterized by watery diarrhea, high gastric output, and significant fluid and electrolyte loss.[2,5] While in this phase, PN is imperative for fluid and electrolyte management and maintenance of growth and development.[5,19] Initially, fluid replacement is based on the amount lost from ostomies, fistulas, or drainage tubes and is replaced at 1 mL for every mL of fluid lost.[5] The second phase of SBS is known as the transition phase and nutritional support becomes the primary focus, particularly introduction of EN.[2,19] This phase generally occurs over one year or longer and is characterized by intestinal adaptation and mucosal hyperplasia.[2,19] During the transitional phase, continuous enteral feedings should begin at a low rate.[19] As tolerance increases and adaptation occurs, enteral feedings can be advanced while PN is reduced.[19] The third and final phase following intestinal resection includes weaning of PN and complete enteral autonomy, and few adaptive changes or improvement are seen in phase three.[2,19]

Though necessary for survival and growth, the duration of PN is associated with increased morbidity and risk for serious complications like sepsis and cholestasis.[47] Moreover, throughout the course of PN, complications like exhausted venous access routes, infectious complications, PNALD, and IFALD may arise. Historically, liver

failure has been responsible for 67% to 89% of deaths among PN-dependent patients with SBS.[23,47] For these reasons, patients requiring PN should be monitored closely and advanced to enteral nutrition as quickly as medically feasible.[5,9,47]

Enteral Nutrition

When oral intake is not feasible, enteral nutrition is the preferred method for feeding in critically ill patients.[42] However, for patients with short bowel syndrome, enteral feeding is not practicable at initiation of nutrition support.[47] Following intestinal resection, structural and functional intestinal adaptation of the remnant bowel occurs leading to improved nutrient and fluid absorption.[48] This includes bowel lengthening and thickening, increases in villus height and crypt depth, increased nutrient transporter expression, accelerated crypt cell differentiation, and slowed transit time.[48] While intestinal length and quality of remnant bowel are integral in influencing the time at which EN can be initiated, early achievement of EN fosters intestinal adaptation and rehabilitation and should be strongly pursued as clinical circumstances allow.[5] Regardless of remnant bowel length, enteral autonomy is achievable for most patients. [5,47]

While advancing EN, special attention should be paid to stool output, vomiting, and irritability to determine if advancement is appropriate.[5] Stool output >40 mL/kg is a contraindication to increasing enteral feeds and suggests that fluid and electrolyte replacements are necessary.[23,42] If stool output is between 30 and 40 mL/kg body weight, EN should be advanced cautiously.[42] If feeding intolerance is suspected, it is recommended that feeds be reduced rather than stopped, unless there is evidence of underlying systemic illness or sepsis.[20] A stepwise algorithmic method with the

assistance of a multidisciplinary nutrition support team is appropriate for use to advance EN.[42] As EN is advanced and reaches >20% of nutrition intake, PN volume and duration should be reduced isocalorically.[5] It is necessary to ensure sufficient calories are absorbed, so malabsorption should be evaluated and considered when increasing calories provided by EN.[23]

As EN is advanced and tolerated, bolus oral feedings, at a volume of what is being tolerated continuously or less, should be introduced three to four times a day to promote oral-motor development and mimic normal infant eating patterns.[5,21,30] Patients may have oral aversion due to delayed oral feeds, intubation, and cardiovascular instability; feeding therapy may be necessary to encourage oral intake.[5]

Medical and Nutritional Outcomes

Survival

Morbidity and mortality are high in infants and children with SBS.[16] Comprehensive, longitudinal, multidisciplinary care has resulted in improved outcomes in many cases, but[21] despite improvements in care, mortality rates still consistently range between 20-30%.[7] A 1972 study found survival rates for pediatric IF to be 54%.[49] Whereas, more recent studies have found survival rates to have improved to 70-100%.[3,14,50] A large retrospective cohort study found cholestasis and age-adjusted small bowel length to be significant predictors of mortality in pediatric SBS, and the SBS case fatality rate was 37.5%.[16] In this study, gestational age, number of septic episodes, and etiology of SBS were not significant predictors of mortality.[16] Additional studies have found hepatobiliary disease, episodes of sepsis, length of remaining small bowel, and loss

of the ileocecal valve to be significant contributors to increased incidence of morbidity and mortality among patients with SBS.[9] While survival rates have increased and mortality and PN-associated morbidity have decreased, it appears that reducing the time to enteral autonomy will further improve survival.[9]

Nutrition Intake

Following resection, most intestinal rehabilitation centers initiate continuous rather than bolus feeds because they are believed to be tolerated better, promote intestinal adaptation, and result in increased body weight and enteral retention of formula and nutrients.[30,51] Few studies exist comparing nutritional value and absorption of EN with oral intake.[23] A randomized crossover study of adults with SBS evaluated nutrient absorption by mode of nutrition therapy and found significantly greater absorption of carbohydrates, protein, and lipids with a tube feeding alone or a tube feeding alongside oral feeding than with oral feeding alone.[17]

Depending on the type of bowel resected, various micronutrient deficiencies may present. Deficiencies appear to be more prevalent after transition from PN to EN, but the risk for deficiency still exists with PN use.[21] A longitudinal study of 30 children with IF found that patients receiving partial PN had a high prevalence of micronutrient deficiencies, including copper (56%), iron (46%), selenium (35%), and zinc (31%).[52] Another study found that after achieving enteral autonomy, vitamin D deficiency increased from 20% to 68%, and zinc deficiency increased from 31% to 67%.[52]

Growth

Meeting nutrition requirements and ensuring optimal growth can be challenging in pediatric patients with SBS because of fluid loss, nutrient malabsorption, electrolyte malabsorption, and PN-associated complications.[10,11,13,16] Growth and development should be evaluated routinely to promote positive health outcomes. A study of pediatric patients on long-term PN found that 75% exhibited failure to thrive, often related to inadequate protein supplementation.[53] In a study of very low birth weight preterm infants, those with short bowel syndrome were more likely to have growth delay with shorter lengths and smaller head circumferences than those without SBS, and between 18 and 22 months, 74% were below the 10th percentile on at least one growth parameter (weight, length, or head circumference).[54] After the onset of SBS, one study found that at six months, 76.5% of patients were classified as failure to thrive.[16] At one year, patients exhibiting failure to thrive diminished to 68.3% and 47.6% at two and one-half years or later.[16] The increased incidence of failure to thrive (body weight <5%) is indicative of the challenges of ensuring needs are met.[16]

Achievement of Enteral Autonomy

Though PN is necessary to sustain growth and development in patients with SBS, promoting enteral autonomy by reducing the duration of PN may decrease complications and improve survival for pediatric patients with SBS while also promoting intestinal adaptation and maintenance of structural and functional integrity of the remaining bowel.[20,21,23] Many studies have found intestinal length to be the primary predictor of enteral autonomy.[16,55,56] Other contributing predictors of enteral autonomy noted have

been percent of daily energy intake tolerated through the enteral route, presence of the ileocecal valve, and underlying NEC. [16,55,56] A 2008 retrospective study found that those patients weaned from PN by two and on-half years after referral to a multidisciplinary intestinal rehabilitation center achieved 95% survival after five years compared to 52% for those patients not weaned from PN.[9] A 2014 retrospective study found 78%, in total, were weaned from PN, and while the primary predictor of PN wean was intestinal length, of those with less than 50 cm of intestinal length, 71% weaned from PN, indicating that achievement of enteral autonomy is still possible for patients regardless of intestinal length.[47] Another retrospective cohort study found that over an average of 5.1 years, 64% of pediatric SBS patients had successfully weaned from PN, and presence of the ileocecal valve and age-adjusted bowel length were significant predictors of enteral autonomy.[16] A multicenter, retrospective cohort analysis of 272 infants found that 43% achieved enteral autonomy, and achievement of enteral autonomy was promoted with preservation of the ileocecal valve, longer bowel length, and underlying NEC.[55] While many studies indicate the role of the ileocecal valve in achieving enteral autonomy, others have shown that the ileocecal valve is not a contributing factor in reducing PN dependence.[16,55,56]

CHAPTER III

Materials and Methods

Study Design

The project is an observational retrospective study with a large cohort of infants and children who have SBS/IF. Study variable data were extracted from an existing registry. The de-identified registry was reviewed to obtain demographic characteristics, medical history, modes of nutrition therapy, nutritional intake, and growth starting at the time of referral and quarterly or biannually thereafter until achievement of enteral autonomy, intestinal transplantation, or death.

Sample Population

The Intestinal Care and Rehabilitation Center (ICARE) at Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center (UPMC) is staffed by an interdisciplinary team of pediatric specialists including gastroenterologists, pediatric surgeons, transplant surgeons, clinical dietitians, a clinical nurse specialist, a social worker, and an occupational therapist. Each patient is evaluated with a history and physical examination, review of pertinent laboratory data, and nutritional assessment. Subsequently, a coordinated treatment plan and goals are constructed, implemented and communicated to referring physicians. Families are recruited and consented for select components of their child's medical information to be included in the ICARE registry at the time of a regularly scheduled clinic visit. Based on ICARE registry data from 2008, the mode of nutritional therapy for the vast majority of patients referred to the center is

PN with or without enteral supplementation (~85%), followed by oral intake alone (~10%) and enteral tube feedings with or without oral intake (~5%).[5] Eligibility criteria for the current study includes: 1) referral to the ICARE center between 2006 and 2015, diagnosis with SBS or Intestinal Failure at <12 months of age, 2) weaned from PN while receiving medical care by the ICARE center team, 3) receipt of a continuous tube feeding with or without oral diet or oral diet alone during weaning, and 4) minimum of one year of follow-up data after PN weaning. Children were excluded from the current study if PN was weaned prior to referral, if the child received an intestinal transplant, if a tube feeding was received after PN weaning, if tube feedings were provided as bolus feedings with an oral diet during weaning, or if PN was not weaned prior to data analysis.

Procedures and Measures

The study principal investigator (PI) and student PI extracted select data variables from the ICARE registry for the purpose of the current study. Data included the following variables:

- Demographic characteristics (gender, race, gestational age, age at first ICARE visit, medical diagnoses)
- Intestinal characteristics (small bowel length and anatomy, percent of small bowel remaining after initial surgery*)
- Physical assessment by systems at the time of referral (presence of liver disease [serum total bilirubin >5] and lung disease)
- Anthropometric indices (weight, length/height, weight for length/height, and head circumference measures, BMI, percentiles, *z*-scores)**

- Mode of nutrition therapy (PN, EN, oral diet) and percent of total daily calories from parenteral and enteral sources
- Transplant status
- Death
- Nutritional outcomes (enteral autonomy [>3 months off of PN], transition from enteral tube feeding to oral feeding)

*The percent of small bowel remaining after initial surgery was estimated using normal values for intestinal length identified by Touloukian.[57]

**Weight (kilograms) was measured with a digital medical scale, height (centimeters) was determined using a stadiometer. Infants and toddlers (newborn to 18 months) had their weight and length measured using a digital infant scale and recumbent length board. Gestation adjusted weight-for-age, length/height-for-age and weight-for-length/height percentiles were determined using gender specific WHO/CDC growth charts for infants birth-24 months and 2-20 years.[58]

Data Management and Analysis

Data were cleaned and examined for missing data, outliers, and meeting the assumptions of normality prior to analysis. Demographic and clinical characteristics, modes of nutrition therapy, and linear growth were described using frequency statistics. Demographic, anthropometric, and clinical characteristics were compared between feeding method using an independent samples t-Test for continuous variables that were normally distributed (gestational age, weight z-score at baseline, height z-score at

baseline, height z-score at year 1 post-wean, height z-score at year 2 post-wean, difference between height z-score from time of weaning and year 1 post-wean, and difference between height z-score from time of weaning and year 2 post-wean) or the Mann Whitney U test for variables that were skewed (age at referral, total bilirubin, direct bilirubin, total small bowel length, percent small bowel remaining, and time to PN wean from initial visit). The Chi-square test was used to determine differences by tube feeding status for categorical variables (gender, race, presence of ileocecal valve, and intestinal procedures).

The Kaplan-Meier survival statistic was used to examine the difference in survival by mode of nutrition therapy during weaning at two-years post-wean. The z-score statistic was used to standardize values of relative position on a percentile growth curve to obtain an overall assessment of growth in the sample population, which includes children of varying age and gender. The positive or negative trends in growth velocities and z-scores between baseline measurements and those taken at subsequent time points were assessed over a two-year period after PN weaning using the repeated measures test.

CHAPTER IV

Results

The electronic medical records of 114 patients initially seen at the ICARE center between June 2006 and November 2015 were reviewed. At the time of the review, 38 patients had not weaned from PN, 24 patients had undergone intestinal transplant, 4 patients received bolus tube feedings during the weaning process, and 3 patients were lost to follow up within the first year after the initial visit. The final sample included 45 patients with short bowel syndrome or intestinal failure who met the study inclusion criteria. Twenty-one of the 45 patients (47%) received a continuous enteral tube feeding with an oral diet during the weaning process while 24 patients (53%) were weaned directly to an oral diet without tube feeding support. The majority of the participants were male (64%), Caucasian (73%), and non-Hispanic (100%). The demographic, anthropometric, and clinical characteristics of the sample population at the time of referral by mode of nutrition therapy during PN weaning are shown in Tables 1 and 2. Several differences between feeding groups were observed. A higher percentage of children in the oral diet vs. TF group were male (79% vs. 48%, respectively; p=0.027). Children weaned to an oral diet were younger than those who received a tube feeding (1 to 2 months vs. 6 months, respectively; p=0.029). In addition, children weaned to an oral diet had a higher serum direct bilirubin level at the time of referral than those who received a continuous tube feeding (1.9 mg/dL vs. 0.1 mg/dL, respectively; p=0.045).

The majority (64%) of the children weaned from PN who were referred to the ICARE center between 2006 and 2009 (n=22), received a continuous tube feeding during

the weaning process. Those who were referred between 2010 and 2015 (n=23) were primarily weaned directly to oral diet (70%). Time to complete the weaning process from the date of the initial visit did not differ significantly between patients who received a continuous enteral tube feeding and those who received only oral diet (p=0.345). The median time for patients who received a tube feeding was 14.0 months (Interquartile Range [IQR]; 9.5, 36.0) while the median time for patients who did not receive an enteral tube feeding was 21.5 months (IQR; 14.5, 41.0). No patient deaths occurred within the first two years after PN weaning; therefore, the probability of survival did not differ significantly between patients who received an enteral tube feeding during weaning and those who did not.

Mean height z-score values did not differ between children who did and did not receive a continuous enteral tube feeding during the PN weaning process at baseline (p=0.608), year one post-wean (p=0.220), or year two post-wean (p=0.126). Repeated measures analysis of linear growth between the time of PN weaning to two-years post-wean was not significant for either feeding method (TF, p=0.116; oral diet, p=0.436). Patients who weaned from PN directly to an oral diet had a smaller decrease in *z*-score from the time of weaning to year one than those who received a continuous enteral tube feeding (-0.05 vs. -0.43, respectively; Table 3) and a larger increase in *z*-score from year one to year two after PN wean (+0.22 vs. +0.02, respectively; Table 4). The mean change in height z-score from time of weaning to year one post-wean was not significantly different between feeding method groups (p=0.228). The same was true for year one post-wean to year two post-wean (p=0.251). The mean height *z*-scores for those

who received a continuous enteral tube feeding with an oral diet compared to those who consumed an oral diet only over the two-year follow-up period are shown in Figure 1.

Table 1: Demographic and Anthropometric Characteristics of the Intestinal Care and Rehabilitation Center Sample Population by Feeding Method during Parenteral Nutrition Weaning

Characteristic	Tube Fed n = 21	Oral Diet n = 24	P-Value
Gender n (%)			
Male	10 (48)	19 (79)	
Female	11 (52)	5 (21)	**0.027**
Gestational age (weeks)*	34.3 ± 4.1	33.5 ± 4.5	0.542
Age at referral (years)**	0.5 (0.2, 2.2)	0.10 (0.00, 0.30)	**0.029**
Race n (%)			
Caucasian	16 (76)	17 (71)	
Black	4 (19)	6 (25)	
Asian	0 (0)	1 (4)	
Native American	0 (0)	0 (0)	
Other	1 (5)	0 (0)	
Wt *z*-Score at Baseline*	-1.29 ± 1.98	-0.69 ± 1.25	0.242
Ht *z*-Score at Baseline*	-1.76 ± 2.75	-1.25 ± 1.85	0.463

Ht - height, Wt - weight

*Mean ± Standard Deviation

**Median (Interquartile Range, 25%, 75%)

Table 2: Baseline Clinical Characteristics of the Intestinal Care and Rehabilitation Center Sample Population by Feeding Method during Parenteral Nutrition Weaning

Characteristic	Tube Feeding (n = 21)	Oral Diet (n = 24)	P-Value
Serum Total bilirubin (mg/dL)*	2.9 (0.4, 7.3)	3.8 (2.2, 5.0)	0.393
Serum Direct bilirubin (mg/dL)*[+]	0.1 (0.1, 2.6)	1.9 (0.3, 3.3)	**0.045**
Small bowel length (cm)*[++]	45.0 (28.0, 85.0)	41.0 (17.0, 64.0)	0.248
Percent small bowel remaining*[+++]	23.5 (12.4, 93.8)	17.5 (8.0, 23.0)	0.159
Presence of ileocecal valve[++++] n (%)	8 (38)	10 (42)	0.664
Time to PN Wean from Initial Visit (months)	14.0 (9.5, 36.0)	21.5 (14.3, 41.0)	0.345
Intestinal Procedures n (%)			
Bianchi Bowel Split	2 (10)	1 (4)	0.592
STEP Procedure	5 (24)	4 (17)	0.713

cm – centimeters, PN – parenteral nutrition, STEP – serial transverse enteroplasty

*Median (Interquartile Range; 25%, 75%)

[+]n = 13 (tube feeding), 22 (oral diet)

[++]n = 15 (tube feeding), 23 (oral diet)

[+++]n = 18 (tube feeding), 23 (oral diet)

[++++]n = 19 (tube feeding), 24 (oral diet)

Table 3: Change in Height *z*-Score from Parenteral Nutrition Wean to 1 Year after Wean

	n	Height *z*-Score*			
		Wean	1 Year Post-Wean	Change in Height *z*-Score	P-Value
Tube Feeding	21	-1.85 ± 1.99	-2.28 ± 1.78	-0.43	0.108
Oral Diet	22	-1.68 ± 1.37	-1.73 ± 1.08	-0.05	0.804

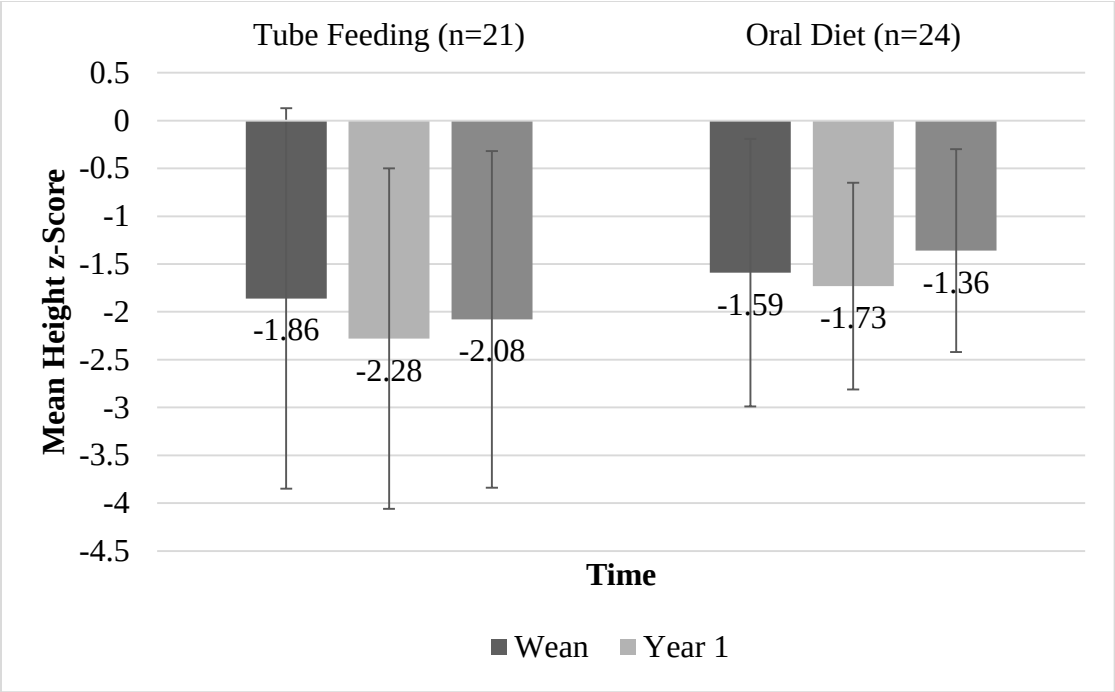
*Mean ± Standard Deviation

Table 4: Change in Height *z*-Score from 1 Year to 2 Years after Parenteral Nutrition Wean

	n	Height *z*-Score*			
		1 Year Post-Wean	2 Year Post-Wean	Change in Height *z*-Score	P-Value
Tube Feeding	17	-2.10 ± 1.89	-2.08 ± 1.76	+0.02	0.916
Oral Diet	20	-1.63 ± 1.08	-1.41 ± 1.07	+0.22	0.065

*Mean ± Standard Deviation

Figure 1: Mean Height *z*-Scores at the Time of Parenteral Nutrition Wean and One- and Two-Years Post-Wean by Feeding Method during Parenteral Nutrition Weaning



CHAPTER V

Discussion

In 2010, the ICARE Center adopted a change in nutrition management strategy for patients with SBS and IF that involved weaning from PN directly to an oral diet without the use of supplementary tube feedings. This change in treatment provided an opportunity to evaluate outcomes in patients who received a continuous enteral tube feeding vs. those that received bolus oral feedings. This observational retrospective cohort study examined the effects of weaning from PN using a supplemental continuous enteral tube feeding vs. progressing directly to an oral diet in 45 patients with SBS or IF.

The feeding groups were homogenous in their characteristics except for three variables: gender, age, and serum direct bilirubin level. The difference in gender distribution between the two feeding method groups are not likely to have influenced the study outcomes. Children in the oral diet group were significantly younger at the time of referral although there was no difference in mean gestational age. A primary management goal for children with SBS is to reduce the concentration of nutrients provided by PN while enteral nutrient intake is subsequently increased. The medical team would have been more likely to prescribe a continuous tube feeding with feeding therapy for a child with oral aversion vs. an oral diet alone in order to facilitate weaning from PN. Moreover, during the first 3 years of life, critical periods for feeding skill development occur.[59] Feeding and swallowing behaviors transition from reflexive to learned around 4-6 months of age.[60,61] Therefore, children whose oral intake is delayed often have diminished willingness to try unfamiliar foods and difficulty developing oral-

motor skills necessary for eating.[62,63] Children in the oral diet group were significantly younger; therefore, they were likely exposed to oral opportunities to eat sooner and started to develop necessary oral-motor skills during a critical development period. The ICARE registry does not include an assessment of oral aversion at the time of referral. Elevated serum direct bilirubin levels (normal range 0.0 to 0.5 mg/dL) in the oral diet group indicate that these patients may have had a greater degree of liver dysfunction at the time of referral. Prolonged cholestasis (>3 months) has been associated with an increased risk of mortality;[64] however, the mean serum direct bilirubin level in either group did not meet the definition of cholestasis (≥2 mg/dL) reported by the Pediatric Intestinal Failure Consortium.[55]

The current study focused on evaluating the impact of feeding method on three outcomes: time to complete weaning from PN, survival, and linear growth. In our sample, time to PN wean did not significantly differ between the group that received continuous enteral tube feedings and those who received an oral diet alone. Therefore, we fail to reject our null hypothesis that the time to achieve enteral autonomy would not differ by PN weaning approach. No previous studies have examined the difference in time to wean between patients by mode of feeding during PN weaning. The probability of survival did not significantly differ between feeding method groups; therefore, we fail to reject the null hypothesis that survival time will not differ by PN weaning approach. While one death occurred in a patient who received a continuous enteral tube feeding during weaning, this death was associated with liver tumor reoccurrence and not related to intestinal failure or mechanical issues from tube feeding. Previous studies have shown that enteral tolerance is significantly related to mortality, and enteral autonomy offers the

best chance of survival.[14,65] No other studies have examined survival between patients who weaned with an enteral tube feeding and those that weaned without enteral tube feeding.

Linear growth velocity did not significantly decline or increase within two years post PN wean. In addition, mean values of height *z*-score at the time of weaning, one year after weaning, and two years after weaning were not significantly different between the feeding method groups. Therefore, we fail to reject the null hypothesis that growth will not differ by PN weaning approach. Of clinical significance, both groups experienced a decrease in height *z*-score from the time of wean to one year after wean. The patients who received a continuous tube feeding experienced a larger mean decrease in z-score than the group that weaned directly to oral diet. From year one to year two after wean, both groups experienced a rebound in positive linear growth. The patients who weaned directly to oral diet had a larger increase than those who received a continuous oral tube feeding. Some degree of intestinal malabsorption may be an explanation for this observed decrease in linear growth velocity during the first year following wean from PN. Intestinal adaptation may take one to three years in children, which may explain the late increase in growth velocity after PN wean.[64]

There are some limitations to our study. Caloric intake of neither the tube feeding nor the oral diet was recorded. One possible explanation for the less favorable response by the tube-feeding group is that energy intake was insufficient to meet nutritional requirements for growth. Prior to referral to the ICARE center, some patients may have had a period of care at an outside facility. Some patients may also have already received enteral or parenteral nutrition prior to referral. The care received prior to first visit at the

ICARE center could impact clinical and anthropometric characteristics and time to PN wean. The addition of a bolus tube feeding group would help further explain the effects of feeding methods during weaning. While a continuous tube feeding may result in improved intestinal absorption due to the increased presence of nutrients, intermittent feedings are advantageous for intestinal adaptation because they produce cyclical changes in gastrointestinal hormones that more closely mimic normal gastrointestinal physiology.[15,21] This may result in more timely and successful weaning to oral diet.[15] Future studies including children who have received bolus tube feedings could expand upon the findings of this study by evaluating the difference in outcomes by continuous or intermittent feeding regardless of route. While the current study included a moderately-sized sample of patients with SBS or IF, the development of a multicenter registry would provide a larger sample size to assess the effect of feeding method or type of food or formula on nutrition related outcomes. Finally, patients were included in the tube feeding group if they received a continuous tube feeding at any point during the PN weaning process; therefore, the contribution of the tube feeding to nutritional intake varied between patients.

In conclusion, no association between weaning strategy and outcomes in children with IF was observed. Linear growth velocity declined during the first year after PN weaning but rebounded in year two. Children weaned directly to an oral diet exhibited a more favorable growth pattern after weaning than those supported by continuous tube feeding. Growth pattern changes between groups highlight the need for future studies that include an energy intake variable to assess the impact of nutritional intake on linear growth. Future studies should define the continuous tube feeding variable and include a

bolus tube feeding group to investigate the role of intermittent versus continuous feeding on time to PN weaning. Development of a multicenter prospective study to assess nutritional interventions in children with intestinal failure would provide further basis for strategies to shorten time on PN, reduce morbidity and mortality associated with PN use, and improve growth outcomes.

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Appendix A

Normal Functions of the Small Intestine

Duodenum	**Jejunum**	**Ileum**	**Ileocecal Valve**
Iron absorption Secretion • Cholecystokinin • Secretin	Nutrient absorption • Glucose • Amino Acids • Fat • Calcium • Magnesium • Folate • Iron • Thiamine • Vitamin C	Reabsorption • Fluid and electrolytes Absorption • Bile acids • Conjugated bile salts • Vitamin B12 • Vitamins A, D, E, K • Phosphorus • Zinc Secretion • Enteroglucagon	Slows intestinal transit time Prevents bacterial reflux into small intestine

*Adapted from Jakubik et al. (2000)[19]

Physiologic Response to Intestinal Resection

Loss of Jejunum	**Loss of Ileum**	**Loss of Ileocecal Valve**
Some nutrient malabsorption (ileum can adapt much of the nutrient absorption capacity of the jejunum) Malabsorption of • Calcium • Magnesium • Folate • Iron • Thiamine • Vitamin C Steatorrhea Cholestasis	Malabsorption of • Bile acids • Conjugated bile acids • Vitamin B12 • Fat • Vitamins A, D, E, K • Phosphorus • Zinc Steatorrhea Fluid and electrolyte abnormalities	Decreased intestinal transit time (increased malabsorption) Increased fluid and electrolyte losses Reflux of bacterial content into small intestine causes bacterial overgrowth leading to: Increased malabsorption (especially fat malabsorption)

*Adapted from Jakubik et al. (2000)[19]

Nutrition-Focused Physical Examination Findings

Area	**Normal Findings**	**Abnormal Findings**	**Related Nutrition Deficiencies**
Hair	Smooth and symmetrically distributed	Poor quality	Zinc, essential fatty acid, biotin, protein-calorie
Eyes	Bright, shiny, clear, pink moist membranes	Dull, dry membranes with Bitot spots	Vitamin A
Lips/Mouth	Pink, free of lesions	Dry, swollen Dry mucous membranes Dry mouth	Vitamin B6, folate, riboflavin, niacin, vitamin B12, iron Dehydration Zinc
Tongue	Moist pink with slightly rough texture	Magenta and edematous Enlarged in congenital anomalies Candidiasis lesions or thrush	Riboflavin, niacin, folate, B6, B12, iron May lead to feeding issues Vitamin C, iron
Gums	Pink without lesions	Bleeding and inflamed	Vitamin C
Teeth	Normal eruption begins at 4-12 months	Delayed eruption Dental caries	Severe malnutrition Vitamin D
Skin	Uniform color without rashes, tears, or flaking	Pallor	Iron, folate, vitamin B12
Nails	Symmetrical and smooth	Transverse lines Flaky Poorly blanched	Protein Magnesium Vitamins A and C

*Adapted from Corkins et al. 2017[35]

Appendix B

Primary Indicators of Malnutrition When Single Data Point Available

Indicator	**Mild Malnutrition**	**Moderate Malnutrition**	**Severe Malnutrition**
Weight-for-length *z* score	-1 to -1.9 *z* score	-2 to -2.9 *z* score	Below -3 *z* score
BMI-for-age *z* score	-1 to -1.9 *z* score	-2 to -2.9 *z* score	Below -3 *z* score
Length/height-for-age *z* score	No data	No data	Below -3 *z* score
Mid-upper arm circumference	-1 to -1.9 *z* score	-2 to -2.9 *z* score	Below -3 *z* score

*Adapted from Corkins et al. 2017[35]

Primary Indicators of Malnutrition When 2 or More Data Points Available

Indicator	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Weight gain velocity (<2 years of age)	Less than 75% of the norm for expected weight gain	Less than 50% of the norm for expected weight gain	Less than 25% of the norm for expected weight gain
Weight loss (2-20 years of age)	5% usual body weight	7.5% usual body weight	10% usual body weight
Deceleration in weight-for-length/height (BMI) *z* score	Decline of 1 *z* score	Decline of 2 *z* score	Decline of 3 *z* score
Inadequate nutrient intake	51%-75% estimated energy/protein need	26%-50% estimated energy/protein need	<25% estimated energy/protein need

*Adapted from Corkins et al. 2017[35]

Appendix C

Calculating Energy Needs for Pediatric Critically Ill Patients[42]

Name of Equation or Formula and Source	Formula
Energy Requirements	
Schofield[66]	**Males** 0 to 3 y: (0.17 x weight [kg]) + (15.17 x height [cm]) – 617.6 3 to 10 y: (19.6 x weight [kg]) + (1.303 x height [cm]) + 414.9 10 to 18 y: (16.25 x weight [kg]) + (1.372 x height [cm]) + 515.5 **Females** 0 to 3 y: (16.25 x weight [kg]) + (10.232 x height [cm]) – 413.5 3 to 10 y: (16.97 x weight [kg]) + (1.618 x height [cm]) + 371.2 10 to 18 y: (8.365 x weight [kg]) + (4.65 x height [cm]) + 200
Food and Agriculture Organization/World Health Organization[66]	**Males** 0 to 3 y: (60.7 x weight [kg]) – 54 3 to 10 y: (22.7 x weight [kg]} + 495 10 to 18 y: (17.5 x weight [kg]) + 651 **Females** 0 to 3 y: (61 x weight [kg]) – 51 3 to 10 y: (22.5 x weight [kg]} + 499 10 to 18 y: (12.2 x weight [kg]) + 746
Protein Requirements	
ASPEN Clinical Guidelines Nutrition Support for the Critically Ill Child[67]	i. 0 to 2 y: 2 to 3 g/kg/day ii. 2 to 13 y: 1.5 to 2 g/kg/day iii. Adolescents: 1.5 g/kg/day

cm – centimeters, g – grams, kg - kilograms

Enteral and Parenteral Requirements of the Very Low-Birthweight Premature Infant

Nutrient	**Parenteral (unit/kg/day)**	**Enteral (unit/kg/day)**
Energy (kcal/kg)	110-120	110-135
Protein (g/kg)	1.5-4.0	3.5-4.0
Carbohydrate (g/kg)	13-18	11.6-13.2
Fat (g/kg)	3-4	4.8-6.6
Na (mmol/kg)	3.5-5.0	3.0-5.0
K (mmol/kg)	2.5-5.0	1.7-3.4
Cl (mmol/kg)	2.0-3.0	3.0-5.0
Ca (mmol/kg)	1.5-2.0	3.0-3.5

*Table adapted from Rossouw et al. 2016

Ca – calcium, Cl – chlorine, g – gram, K – potassium, kcal – kilocalorie, kg – kilogram, mmol – millimole, Na - sodium