A COMPARISON OF TWO GASTRIC FEEDING APPROACHES IN

MECHANICALLY VENTILATED PEDIATRIC PATIENTS

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Ann-Marie Brown

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A COMPARISON OF TWO GASTRIC FEEDING APPROACHES IN

MECHANICALLY VENTILATED PEDIATRIC PATIENTS

Ann-Marie Brown

Dissertation

Approved: Accepted:

_____   _____
Advisor   Department Chair
Dr. Elaine Fisher   Dr. Elaine Fisher

_____   _____
Committee Member   Interim Dean of the College
Dr. Michael L. Forbes   Dr. Roberta DePompeii

_____   _____
Committee Member   Dean of the Graduate School
Dr. Tracy Riley   Dr. George R. Newkome

_____   _____
Committee Member   Date
Dr. Richard P. Steiner

_____
Committee Member
Dr. Ratchneewan Ross

ABSTRACT

More than 30% of children admitted to the Pediatric Intensive Care Unit (PICU) are malnourished and are at risk to develop new or worsened malnutrition during their hospitalization. Delivery of enteral nutrition (EN) during hospitalization is associated with lower mortality and morbidity rates. Barriers to adequate delivery of EN include hemodynamic instability, feeding interruptions, feeding intolerance and lack of standardized feeding protocols.

Gastrointestinal (GI) dysmotility during critical illness increases the risk of feeding intolerance due to increased influence of the Sympathetic Nervous System. Critically ill children have traditionally been fed via continuous gastric infusion under the assumption that slow, continuous feeding decreases the risk of intolerance and aspiration. However, GI physiology suggests GI motility is enhanced when the gut is rested between feedings. The purpose of this comparative effectiveness study was to evaluate two enteral feeding delivery modes, continuous versus bolus, on the attainment of prescribed caloric and protein nutritional goals and the frequency and type of feeding intolerance events in mechanically ventilated infants and children 1 month corrected gestation age through 12 years of age.

Twenty-five children were randomized to a bolus (n = 11) or continuous (n = 14) feeding group. Group characteristics were similar for demographics and severity of

illness scores. Independent sample t-tests and Mixed Measures RM-ANOVA were used to test hypotheses.

The bolus group attained higher energy (p = .001) and protein (p = .006) intake in the first 24 hours of feeds compared to the continuous group. The bolus group also attained goal feeds faster than the continuous group (median of 15 hours versus 29.5 hours, respectively). There were few interruptions or intolerance events recorded in either group. No relationship was identified between emesis, gastric residual volume or abdominal girth as intolerance measures. No aspiration pneumonitis diagnosis was recorded in either group. No difference was found in Oxygen Saturation Index scores between groups. Bolus feeds enhance delivery of target energy and protein intake with an equivalent safety profile to continuous feeding. Further study is needed to compare delivery modes in critically ill patients on the delivery of target energy and protein goals and incidence of adverse events.

ACKNOWLEDGEMENTS

DEDICATION

This study is dedicated to the children and families who find themselves in the Pediatric

ICU. Their resilience and spirit in the face of difficult and often frightening

circumstances continue to humble and inspire me. It is my greatest hope, in some small

way, to contribute toward providing you the best possible care in your time of need.

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CHAPTER I

INTRODUCTION

Background and Significance

More than 30% of children admitted to the Pediatric Intensive Care Unit (PICU)

are malnourished and risk the development of worsened malnutrition during their

hospitalization (Mehta et al., 2012). Even previously healthy children experiencing

critical illness are at high risk for malnourishment because of increased protein and/or

caloric needs at a time when oral intake is not possible or is inadequate to support their

metabolic demand. Adequate nutritional support of critically ill children reduces

morbidity and mortality (Mehta et al., 2012). Inadequate delivery of nutrition during

hospitalization is a risk factor leading to poor healing, hospital acquired infections,

prolonged hospital length of stay, and increased health care costs (Khorasani &

Mansouri, 2010; Mehta et al., 2012; Mehta et al., 2010; Schindler et al., 2011).

Inadequate nutritional support results in a cumulative energy deficit; a deficit

whereby actual daily energy intake in kilocalories/kilogram/day (kcal/kg/day) is less than

prescribed nutrition based on calculated energy requirements. The previously held belief

was calories alone were key to the nutritional support of the critically ill patient, but the

importance of protein in the diet is highlighted by results from recent studies which

demonstrate when goal total kcals/kg/day are not delivered, improved outcomes may still

be accomplished if total prescribed protein is delivered (Larsen et al., 2012; Mehta et al., 2012). Cumulative protein deficit is similarly calculated as the actual grams of protein delivered to the patient divided by the daily protein prescribed. Thus, both energy and protein needs must be taken into account when caring for the critically ill child to prevent the development and/or progression of malnutrition.

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is a professional organization whose mission is to "improve patient care by advancing the science and practice of clinical nutrition and metabolism" (www.nutritioncare.org retrieved June 1, 2013). A.S.P.E.N. publishes population specific nutrition support guidelines. The most recent guidelines for nutrition support of the critically ill child were published in 2009. This document acknowledged a weak evidence base comprised of small, randomized trials with uncertain results or high risk of error, or non-randomized cohort studies, case series, or expert consensus. Consequently, a major recommendation by A.S.P.E.N. was the call for prospective, multi-site research studies to strengthen the evidence base to guide nutritional support in critically ill children (Mehta, Compher, & Directors, 2009).

A.S.P.E.N. guidelines recommend that in children without contraindications to feed, e.g., primary GI pathology, post GI surgery, enteral nutrition is the preferred nutrition delivery route (Mehta, Bechard, Leavitt, & Duggan, 2009). Enteral nutrition (EN) involves the delivery of formulaic nutrition (including breast milk) directly to the stomach (gastric) or intestines via a tube introduced into the body. Gastric EN may be prescribed via one of two delivery modes, continuous or bolus. Continuous delivery is the steady infusion of liquid nutrition delivered at an hourly volume via a feeding pump

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through a tube placed into the stomach. The second delivery mode is bolus, whereby liquid nutrition is intermittently delivered over a prescribed period of time, followed by a period of gut rest, e.g., 120 milliliters (mL) is delivered every 3 hours via a pump over 60 minutes. For the purpose of this investigation the two delivery modes will be referred to as continuous or bolus feeds.

The current standard for delivery of enteral nutrition in the Pediatric Intensive Care Unit (PICU) is continuous feeding (Brown, Forbes, Vitale, Tirodker, & Zeller, 2012). A gap in the literature exists regarding the most effective delivery mode for gastric nutrition in the PICU population, continuous versus bolus delivery. Historically, the pediatric critical care community has favored continuous EN, identifying this mode as being 'gentler', in that the stomach is not overloaded by a bolus of nutrition to digest and absorb. Anecdotal concerns regarding aspiration events and acute lung injury (ALI) have also been associated with bolus feeds because of the larger volume administered and the potential for dysfunction of the GI sphincters allowing feeds to reflux back up the esophagus and into the lungs. This study proposed to address the question of the safest, most efficacious delivery mode of gastric enteral nutrition that achieved the prescribed caloric/protein nutritional goals without the risk of clinical worsening; and avoided cumulative energy and protein deficits in the critically ill pediatric population (Mehta et al., 2009; Tume, Carter, & Latten, 2012).

Enteral Nutrition the PICU Setting

While enteral nutrition (EN) is the preferred route of delivery (Mehta et al., 2009), an alternate method of nutrient delivery is via the parenteral route whereby a sterile nutritive solution is infused via central venous access into the vascular system. Enteral

nutrition has several advantages over parenteral nutrition; enteral nutrition preserves gut integrity via maintenance of the intestinal epithelium (Dominguez & Coopersmith, 2010; Smith & Garcia, 2011) and eliminates the need for costly invasive central venous access and its associated risks of thrombosis, bleeding, extravasation and infection (Fuchs, 2011; Mehta, 2009). Furthermore, there is evidence to support EN as a modulator of cytokine release, thereby decreasing the inflammatory response which is common to the critically ill or injured infant or child (Fuchs, 2011). Thus, there is consensus among clinicians to use the enteral route to provide nutritional support when contraindications to feeding are absent.

Continuous versus bolus feeding. The two methods of gastric enteral nutrition delivery are continuous and bolus. While the standard mode of nutritional delivery to critically ill children has been continuous, from a physiologic perspective, bolus feeding into the stomach better mimics normal gut function. The major risk of enteral feeding in critically ill children is aspiration, the reflux of nutrition into the lungs. Under normal healthy conditions there is little risk for aspiration because gastric motility propels food and liquid unidirectionally by cephalocaudal muscular contraction called peristalsis. In addition, reflux is prevented by the coordinated opening and closing of sphincters along the gastrointestinal (GI) tract. Critical illness and its associated treatment, e.g., medications, immobility, increase the risk of GI dysmotility, the abnormal movement of nutrition through the GI tract producing feeding intolerance, hence increasing the risk of aspiration.

Dysmotility is linked to the disruption of homeostatic mechanisms of the Enteric Nervous System (ENS). Newer textbooks identify the ENS as an independent division of

the autonomic system comprised of the Sympathetic (SNS), Parasympathetic (PSNS), and Enteric Divisions (ENS). While the ENS can function independently, this system is influenced by the SNS, PSNS and higher brain centers as well as by the neuroendocrine stress response of critical illness and injury. Other hypotheses linked to dysmotility and the associated feeding intolerance include alterations in gut oxygenation from compensatory shifts in blood flow away from the gut to vital organs; the effect of inflammatory mediators released in response to critical illness; and the disruption in normal gut flora from critical illness and its treatments (Saps & Di Lorenzo, 2011; Smith & Garcia, 2011; Teitelbaum, 2011). This investigation focused on the theoretical framework of GI dysmotility in critical illness as it related to feeding intolerance when two different modes were used to deliver EN in critically ill mechanically ventilated children.

The theoretical basis for this study was GI dysmotility which results in feeding intolerance in critically ill children and contributed to energy and protein deficits. The current clinical assumption surrounding the use of continuous feeding is that delivery of smaller volumes would lessen the risk of feeding intolerance, particularly aspiration and would allow the delivery of adequate feeding volume to reach prescribed energy and protein goals. Continuous delivery while efficient from a staffing/resource perspective (e.g., reduced workload) may not serve as the best physiologic delivery mode, as gastric motility is better stimulated with the introduction of food after a period of rest (Mohr & Steffen, 2011). There is insufficient evidence to support which delivery mode is best suited to safely attain prescribed nutritional intake when children are critically ill.

Since caloric intake alone may be insufficient to define optimal nutrition in the PICU population, daily protein intake must also be considered (Larsen et al., 2012). Thus, nutritional goals for energy and protein goals are defined as kilocalories/kilogram/day (kcal/kg/day) and protein grams/kilogram/day (g/kg/day), respectively. The proposed study contributed evidence to guide the safe delivery of EN to attain prescribed nutritional goals and/or reduce cumulative energy and protein deficits.

Barriers to achieving prescribed nutritional goals. Due to the nature of critical illness and the PICU environment, there are several factors that may interfere with the attainment of prescribed nutritional goals. Barriers include hemodynamic instability, feeding intolerance, a lack of well-defined feeding protocols, and both avoidable and unavoidable feeding interruptions (Mehta, 2009; Mehta et al., 2010).

Hemodynamic instability. The first barrier, hemodynamic instability, may occur with or without changes in blood pressure. Critically ill pediatric patients can maintain a normotensive blood pressure due to compensatory mechanisms that allow peripheral vasoconstriction and shunting of blood from non-vital organs such as the gut, to vital organs such as the heart, brain and lung (Kleinman et al., 2010). The ENS, ANS, and higher brain centers modulate this compensatory shunting, resulting in altered motility, sphincter dysfunction, and imbalance of the GI hormones and secretory products. The use of exogenous catecholamines (e.g., epinephrine, norepinephrine) in patients who require blood pressure support affects organ function by shunting blood away from the gut, thereby reducing oxygen and nutrient delivery and waste removal from cells and tissues. Consequently, hemodynamic instability with or without blood pressure changes may result in gut dysfunction, particularly dysmotility.

Additionally, without the stimulus of food, normal GI tract secretory functions are altered and disrupt innate barrier function of the gut endothelium, further contributing to inflammatory processes that exacerbate critical illness (Fuchs, 2011). Thus, hemodynamic instability puts the critically ill pediatric patient at risk for cumulative energy and protein deficits by limiting the delivery of feeds due to disruption of normal gut secretory function, digestion, and absorption necessary to maintain the integrity of the intestinal lining (Mohr & Steffen, 2011). Feeding interventions that support normal GI function in the face of critical illness are needed to attain nutritional goals and support healing.

The physiology of critical illness suggests enteral feeding of the hemodynamically unstable patient could worsen outcomes and increase the risk of feeding intolerance. In a large retrospective, multi-center study of PICU patients ages 1 month – 17 years (n = 339) who received cardioactive and vasoactive medications, delivery of EN was associated with lower mortality when controlling for age, severity of illness, and study site (Panchal et al., 2013). Specific GI outcomes in this study were not reported. In this study, the administration of exogenous cardioactive or vasoactive medications, patient severity of illness, and their association with the attainment of prescribed nutritional goals and incidence of feeding intolerance between feeding approaches were collected. Evaluating this information may provide insight into treatment interventions that may promote "best feeding" practices in critically ill pediatric patients.

Feeding intolerance. Feeding intolerance is a second barrier to achieving prescribed nutrition goals. The literature defines feeding intolerance as the presence of one or more symptoms such as emesis, persistent high gastric residual volumes and/or

gastric distension (Fuchs, 2011; Mehta, 2009; Mehta et al., 2010; Moore & Wilson, 2011; Weckwerth, 2004). The presence of intolerance indicators has been linked to an increased risk of aspiration (Fuchs, 2011; Mehta et al., 2010). A.S.P.E.N. guidelines recommend gastric EN if there are no clinical contraindications; however, the optimal delivery feeding mode to minimize feeding intolerance has not been identified (Fuchs, 2011; Mehta et al., 2009). This study compared the incidence, effects, and types of feeding intolerance between the two delivery modes, continuous and bolus.

A lack of consensus in the literature and between practitioners regarding what constitutes GI feeding intolerance, and which parameters should be measured and thresholds tolerated (Horn & Chaboyer, 2003; Horn, Chaboyer, & Schluter, 2004; Hurt & McClave, 2010; Reignier et al., 2013; H. E. Skillman, 2010, 2011; Weckwerth, 2004). The three predominantly used clinical measures of gastric intolerance to feeding are emesis, elevated gastric residual volume (GRV), and abdominal girth as a measure of gastric distension.

Emesis, eructation of gastric contents, is the key factor ascribed to gastric intolerance. The risk of aspiration of emesis into the lung by the mechanically ventilated, intubated patient is of concern as it can lead to the development of chemical pneumonitis. Despite the endotracheal tube design of a balloon inflated around the outer aspect of the tube to create a sealed passage in the trachea, protection may be inadequate when gastric contents are forcefully propelled up the esophagus and may still be introduced into the trachea and lungs. Pulmonary aspiration of gastric contents is difficult to determine, yet when present, the resultant complication of pneumonitis leads to increased morbidity and mortality (Cooper & Haut, 2013).

To detect the incidence and consequence of pneumonitis and the associated acute lung injury, respiratory parameters such as the oxygen saturation index (OSI) have been used. This parameter is calculated via the following equation: $[(F_iO_2 \times MAWP)/S_pO_2]$, where F_iO_2 is the Fraction of Inspired Oxygen, MAWP is mean airway pressure, and S_pO_2 is the level of arterial oxygen saturation. Thomas and colleagues (2010) validated OSI as an equivalent measure to the traditionally used Oxygenation Index to assess acute lung injury severity without the need for invasive arterial monitoring (Thomas, Shaffer, Willson, Shih, & Curley, 2010). OSI was monitored as a parameter to follow the respiratory course of the study participants and as an indicator of possible aspiration.

The second indicator of gastric feeding intolerance is an elevated gastric residual volume (GRV), measured by the manual aspiration of the feeding tube for gastric contents at intervals. A single elevated measurement above a predefined threshold has been traditionally used as an indicator of feeding intolerance; however a validated threshold value to indicate the point of increased risk has not been identified. Recent studies in adults recommend a lessened emphasis or elimination of the use of GRV as an indicator of intolerance noting increased GRV was not associated with an increase in adverse clinical events (Poulard et al., 2010; Reignier et al., 2013). A single elevation of GRV may not adequately define intolerance, thus two consecutive elevated GRV measurements were used in this study. Also, a protocol defined the duration of feeding cessation for intolerance. It is of note that feeding protocols have been based on limited evidence even to define the length of time to hold feeds.

Abdominal distension, measured by the abdominal girth across the umbilicus has likewise been utilized as an indicator of feeding intolerance. The utility of this parameter

in predicting intolerance and adverse events in both children and adults in the ICU has been limited (Brown et al., 2012; Ukleja, 2010). To contribute evidence to the literature, the relationship between GRV, incidence of feeding intolerance, and abdominal girth was examined. Poorly defined clinical markers of feeding intolerance in critically ill children hamper the development of protocols which promote the safe and effective delivery of feeds. By examining signs of feeding intolerance including the presence of emesis, elevated GRV, and abdominal girth between continuous and bolus feeding delivery modes, decisions may be made on how best to feed the PICU population.

Feeding interruptions. A third barrier to attaining caloric and protein nutritional goals is the interruption of feeds. Feeding interruptions can be classified as unavoidable or avoidable. Unavoidable interruptions include: delay in feeding pending validation of feeding tube placement; unplanned dislocation of the feeding tube; patient procedures requiring NPO (nothing by mouth) status; feeding intolerance; and the need to stop feeds to correct an illness related issue, such as hyperglycemia (Fuchs, 2011). These unavoidable feeding interruptions reduce the amount of delivered nutrition and contribute to daily and cumulative nutritional deficits. While unavoidable interruptions cannot be altered, it is important to identify their frequency and their contribution to increasing nutritional deficits.

The second category of feeding interruptions is avoidable interruptions. Avoidable feeding interruptions include: stopping feeds longer than necessary before/after procedures; practice variability among practitioners; and failure to follow standardized protocols for cessation and continuance of feeds (Mehta et al., 2012). A bolus feeding protocol may reduce feeding interruptions as feedings are administered

intermittently during the 24-hour period, minimizing the loss of feeding volume and hence maximizing caloric and protein intake. The goal of nutritional support is to attain the prescribed nutritional goals, thereby reducing daily and cumulative energy/protein deficits. This study examined the frequency and type of feeding interruptions in relation to daily and cumulative energy/protein deficits between the two nutritional delivery modes, continuous vs. bolus. Information gained will contribute to protocol development for the safe, effective delivery of nutrition to the PICU population.

Lack of standardized feeding protocols. A fourth barrier to the delivery of prescribed nutrition is a lack of well supported and defined feeding protocols (Mehta et al., 2010; Skillman & Mehta, 2012). While use of a standardized protocol is shown to improve delivery of prescribed nutrition, a best practice protocol has yet to be identified (Braudis et al., 2009; Brown et al., 2012; Kiss, Byham-Gray, Denmark, Loetscher, & Brody, 2012). Evidence suggests calories alone fail to provide the necessary nutrients for healing, while the delivery of prescribed daily protein requirements may be critical to deriving the benefits of nutrition therapy (Larsen, 2012; Larsen et al., 2012). Inconsistencies in the delivery of feeds, variations in thresholds, and length of time to hold feeds post-intolerance event may result in nutritional deficits in critically ill pediatric patients and adversely affect patient outcomes. By examining factors that impact delivery during continuous and bolus feeds, this study contributed to the body of literature to validate the most effective delivery mode of enteral feeding resulting in the attainment of prescribed caloric and protein goals.

Theoretical Framework

The framework of gastrointestinal (GI) dysmotility in critical illness guided this study. While not a formalized theory, this framework links together the explained phenomena of critical illness, physiology of the ENS and how the ANS response influences GI motility under both normal and stress conditions (Fuchs, 2011; Mehta et al., 2010; Skillman & Mehta, 2012).

Both endogenous and exogenous factors influence motility along the GI tract contributing to the phenomenon of GI dysmotility in critical illness. Critical illness exerts adverse effects on GI motility via increased SNS activation resulting in reduced gut perfusion whereby blood is shunted to vital organs and hence impairs gut tissue oxygenation. In addition, sphincters along the GI tract normally promote the unidirectional movement of nutrition. SNS activation interferes with normal closure of these valve-like structures, causing sphincter incompetence and subsequent backflow of formula when pressure changes in the body occur, e.g., GI distension, retching and vomiting, or coughing during suctioning. The combined effect of PICU therapies, including effects of medications (vasoactive, opiates and others), immobility, and reduced nutritional intake into the gut also contribute to GI dysmotility. Dysmotility in critical illness is multifactorial, increasing the risk of feeding intolerance at a time when nutrition is critically needed for healing, restoration of health, growth and development of the child. The following sections present an overview of normal GI function, the effects of critical illness on dysmotility and critical care therapies that contribute to dysmotility, and their effect on feeding tolerance.

Normal GI motility and function. Commonly the ANS is described in texts to contain a PSNS and SNS arm. More recently this system is described to have a third arm, the ENS. Motility of the GI tract is directly regulated by the ENS. The ENS has approximately 100 million neurons, similar in number of neurons in the spinal cord. The ENS has both afferent and efferent branches which allow for sensing of changes and response via activation of motor and secretory functions. Under normal conditions the ENS functions via negative feedback loops controlling motile, secretory, absorptive, and digestive functions. Negative feedback loops respond to changes, returning the system to a steady state once the monitored variables return within normal range. These self-maintenance functions are influenced by the PSNS which is also known as the "wine and dine" response (Guyton & Hall, 1996; Mohr & Steffen, 2011).

From a motility perspective, the ENS innervates the gut via the myenteric or Auerbach's plexus and the submucosal or Meissner's plexus. It is the myenteric plexus that is primarily responsible for motor control of both the circular muscle segmentation and long muscle wave peristalsis processes. Both types of muscle activity are required to facilitate the unidirectional flow of contents from mouth to anus.

The ENS can function both independently and under the influence of the ANS-sympathetic and parasympathetic divisions. Neurohormonal mediators delivered via the bloodstream also impact gut function; their role in gut motility is less clear and was not the focus of this investigation. The primary neurotransmitter released by the ENS is acetylcholine. With parasympathetic nervous system stimulation of the vagus nerve associated with feeding occurs, release of acetylcholine occurs. This phase is termed the digestive phase. The multiple sphincters along the GI tract have a high level of muscle

tone under parasympathetic stimulation, thereby preventing the reflux of food. Motor function is stimulated by the ingestion of foods, beginning in the lower esophagus, and extending through the colon (Guyton & Hall, 1996; Mohr & Steffen, 2011).

There are two phases of digestion, the digestive and interdigestive phase. During the digestive phase, there is vasodilatation of the splanchnic circulation which supplies the GI tract and concomitant increased utilization of oxygen, providing the energy and substrate to carry out digestion, absorption and transport of nutrients from the gut lumen to the bloodstream (Guyton & Hall, 1996). The interdigestive phase is the rest period between meals, lasting 90-180 minutes in both adults and children (Saps & Di Lorenzo, 2011). During the interdigestive phase, the Migrating Motor Complex (MMC) serves to sweep contents from the stomach toward the intestine. One function of the MMC is to prevent movement of bacteria and undigested food particles in the intestine from migrating from the stomach up the esophagus to the lungs. The MMC is characterized by three phases: quiescence, slow, and high motor activity as it sweeps the GI tract from stomach through the ileum, clearing the lumen of food, dead enterocytes and excess GI flora (Guyton & Hall, 1996; Saps & Di Lorenzo, 2011).

GI dysmotility in critical illness. In critical illness SNS activation slows motility and loosens sphincter control in the GI tract. Under increased sympathetic stimulation, GI sphincter tone is relaxed in the critically ill, increasing the risk of reflux proximally (Fuchs, 2011). The dominant neurotransmitter in a state of stress, secreted from both from the ENS and from the ANS is norepinephrine. This results in vasoconstriction of the splanchnic bed (Ukleja, 2010). Hence, reduced perfusion results in impaired blood flow to the GI tract, altering motility, secretory, digestive and absorptive processes.

Additionally, ANS neurotransmitters such as epinephrine and cortisol delivered via adrenal stress response activation contribute to the severity and duration of GI dysmotility.

Hypoxia or inadequate oxygen delivery to tissues slows motility and is common in critically ill patients who are often on mechanical ventilation due to impaired gas exchange from disease processes such as pneumonia and bronchiolitis. The inflammatory response from trauma, infection and other causes is common in critical illness and exerts an inhibitory influence on GI motility (Shimizu et al., 2011). Hypoperfusion, hypoxia and inflammation, all processes common in the critically ill patient, place the PICU patient at risk for GI dysmotility and subsequent feeding intolerance (Solana et al., 2013; Ukleja, 2010).

Contributors to dysmotility in the PICU.

Medications. Commonly used PICU medications contribute to gut dysmotility. These medications include: opioid analgesics, neuromuscular blockers, catecholamines, vasopressors, and sedatives (Btaiche, Chan, Pleva, & Kraft, 2010; Ukleja, 2010).

Immobility. Immobility slows GI motility (Fuchs, 2011). In the PICU environment patients are typically confined to a bed for safety, to allow application of critical care therapies such as mechanical ventilation, and to minimize energy expenditure.

Feeding practices. Common practices in the critical care environment PICU such as periods of non-feeding during hemodynamic instability may exacerbate GI dysmotility. The use of hyperosmolar formulas, those with high caloric/protein and nutrient concentrations to enhance delivery of required energy in patients who are fluid

restricted, is common. Such formulas have been shown to alter GI motility by either slowing or accelerating motility (Fuchs, 2011). The administration of concentrated formulas can result in constipation or diarrhea, respectively. Lastly, use of continuous feeding methods and the resultant lack of an interdigestive period may impair the function of the Migrating Motor Complex and its housekeeping functions. The additive effects of critical illness and the effects of common PICU therapies heighten the risk of GI dysmotility, and subsequently feeding intolerance (Chapman et al., 2008; Solana et al., 2013). Gut dysfunction increases the risk for feeding intolerance and may lead to inadequate nutritional intake at a time when delivery of nutrition is crucial for restoration of health and optimal function in the critically ill child.

Summary

Nutrition is a critical therapy in the PICU population, not only to mitigate malnutrition present on admission, but to avoid further decline during the PICU stay. Gastric feeding is a commonly used route to delivery nutrition, but the best feeding mode to achieve daily prescribed energy/protein goals has not been investigated. While common practice is to deliver nutrition via continuous gastric feeding, evidence is lacking on how this practice contributes to feeding tolerance and the effect on morbidity and mortality. Continuous feeds may worsen the GI dysmotility of critical illness by eliminating the interdigestive phase and impairing natural function of the MMC. Thus, further study is needed.

To mimic the natural state by bolus feeding, even in critical illness, the MMC function may be preserved, and GI motility enhanced, hence limiting the incidence of feeding intolerance events. This study examined the impact of continuous and bolus

feeding modes of delivery on attainment of prescribed nutritional goals, the incidence of feeding intolerance, and provided a description of common PICU practices for monitoring and classifying intolerance events.

Purpose, Study Aims, and Research Hypotheses

The purpose of this comparative effectiveness study was to evaluate two enteral feeding delivery modes, continuous versus bolus, on the attainment of prescribed caloric and protein nutritional goals and the frequency and type of feeding intolerance events in mechanically ventilated infants and children 1 month corrected gestation age through 12 years of age. Prescribed caloric and protein nutrition intake is defined in terms of both energy in kilocalories/kg/day (kcal/kg/day) and protein in grams/kg/day (g/kg/day). There were two aims of this study:

> 1) To compare two gastric feeding delivery modes, continuous vs. bolus, on the percent of daily delivered/prescribed energy (kcal/kg/day) and protein (g/kg/day).
>
> 2) To describe and compare the frequency and type of feeding intolerance events between continuous and bolus fed mechanically ventilated infants and children 1 month corrected gestational age through 12 years of age.

Hypotheses

In mechanically ventilated PICU patients 1 month corrected gestation age through 12 years of age:

> 1. The 24-hour and 48-hour cumulative energy deficit is lower in the bolus compared to continuous fed group.

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2. Bolus fed subjects attain prescribed nutritional intake earlier than subjects in the continuous feeding group.

3. Bolus fed subjects have fewer feeding intolerance events compared to the continuous fed group.

4. There is a positive relationship between elevated gastric residual volume (GRV) and abdominal girth.

5. Bolus fed subjects have fewer unavoidable/avoidable feeding interruptions compared to the continuous feed group.

6. The duration of avoidable feeding interruptions is shorter in the bolus compared to continuous feed group.

7. There is no difference in the OSI or evidence of pulmonary complications between the two feeding modes

Definition of Terms (Theoretical; Operational)

1. Enteral feeding (EN) – liquid nutrition delivered via a tube introduced into the stomach; measured in milliliters (mL)

2. Continuous feeding (CF) – EN requirement delivered at a constant infusion rate via pump; measured as an infusion rate in mL/hour

3. Bolus feeding (BF) – EN requirement delivered in interval, finite volumes over a prescribed period of time; as measured in mL and delivered over one hour every 3 hours.

4. Prescribed Energy Intake – prescribed daily energy intake ordered to be given via formula; measured in kilocalories/kilogram/day (kcal/kg/day)

5. Prescribed Protein Intake – protein intake ordered to be given via formula; measured in prescribed grams of protein/kilogram/day (g/kg/day)

6. Delivered Energy Intake – daily EN energy actually administered; as measured in kilocalories/kilogram/day (kcal/kg/day)

7. Delivered Protein Intake – daily EN protein actually administered; as measured in grams of protein/kilogram/day (g/kg/day)

8. Ratio of Delivered/Prescribed Energy and Protein Intake – reported in percentages

9. Cumulative Energy Deficit – sum of serial daily percentages of energy and protein intake; measured in percentages

10. Feeding intolerance – disruption of EN delivery due to one or more of the following GI symptoms (see specific definitions below):

    a. Emesis – a single incidence, tussive or non-tussive

    b. Elevated GRV for two consecutive measurements

    c. Elevated GRV for one measurement and simultaneous abdominal distension

11. Emesis – gastric contents regurgitated from the mouth during tussive or non-tussive episodes; measured as yes or no

12. Gastric Residual Volume (GRV) – the volume of gastric contents aspirated from the stomach via syringe attached to the feeding tube; measured in milliliters (mL)

13. Elevated GRV – GRV that is greater than 50% of the delivered volume in the previous 3 hours; measured as present or absent

14. Abdominal girth – the circumference around the abdomen at the level of the umbilicus: measured in centimeters (cm)

15. Abdominal distension – 10% increase in abdominal girth calculated from the lowest girth measurement in the current 24-hour feeding period (based on the time feeding is initiated); measured in centimeters (cm)

16. PICU medications – Medications will be categorized for analysis in the following way:

    a. Prokinetic – a medication used to promote GI motility; prescription for metoclopramide per protocol or other medication prescribed by the healthcare team.

    b. Cardioactive agent – a medication that alters cardiac function and/or vasomotor tone; per protocol or medication prescribed by the health care team, e.g., dopamine, dobutamine, epinephrine, norepinephrine, milrinone, phenylephrine, vasopressin, nitroprusside, nitroglycerin

    c. Opioid – opiate derived or synthetically manufactured medication used for analgesia and/or sedation; per protocol or prescribed by the health care team, e.g., morphine, fentanyl, hydromorphone, methadone

    d. Sedative – non-opioid medication used for safety, (e.g, avoid self-extubation) amnesia, and/or comfort in the critically ill patient; per protocol or prescribed by the healthcare team, e.g., midazolam, lorazepam, diazepam, dexmedetomidine, propofol, ketamine, pentobarbital

e. Neuromuscular blocker – drug used to weaken and/or fully block skeletal muscle movement in the critically ill patient for therapeutic indications such as need for full ventilator control; per protocol or prescribed by the healthcare team, e.g., cisatracurium, vecuronium, rocuronium, succinylcholine

f. Laxative – medication used to increase lower GI motility to relieve constipation; as measured by a prescription for polyethylene glycol, senna, glycerin suppositories, or bisacodyl

g. Gastric acid suppressant – drug used to inhibit gastric acid secretion via histamine-2 blockade or proton pump inhibition; as measured by a prescription for famotidine, ranitidine, omeprazole, esomeprazole or lansoprazole

17. Attainment of prescribed feeds – delivery of prescribed nutritional intake; time in hours to reach the prescribed intake from time feeding is initiated.

18. Constipation – absence of stool for greater than 24-hours

19. Corrected Gestational Age – calculation of a premature infant's maturity based on chronologic age post-delivery and weeks of gestation completed at birth; as measured by post-menstrual age plus number of weeks after birth, e.g., an infant born at 33 weeks post-menstrual age who is 16 weeks old is 2 months corrected gestational age.

20 Oxygen Saturation Index (OSI) – A parameter which provides an index of respiratory acuity without the need for invasive monitoring, with higher numbers indicating worsening lung disease (5.3 = acute lung injury and 8.1 = acute respiratory

distress syndrome) (Thomas et al., 2010); as measured to 0.1 decimal places and derived

from the formula $[(F_iO_2 \times \text{Mean Airway Pressure})/S_pO_2]$.

CHAPTER II

REVIEW OF THE LITERATURE

Introduction

Adequate delivery of nutritional support to critically ill infants and children impacts important patient outcomes, including hospital length of stay and mortality. The purpose of this study was to identify the mode of delivery of nutrition support, continuous versus bolus, that supports the earliest attainment of energy and protein goals and has the least incidence of feeding intolerance.

This review of literature is presented in four sections. The first section discusses the incidence and impact of malnutrition in critically ill infants and children, both upon admission and during hospitalization, and current recommendations for nutritional support. The second section describes the modes of EN delivery, continuous versus bolus, their impact on clinical outcomes and gaps in the literature. The third section presents supporting literature to validate the guiding framework of gastrointestinal (GI) dysmotility in critical illness. The fourth and final section reviews barriers to the delivery of enteral nutrition in critically ill infants and children, namely avoidable and unavoidable interruptions caused by hemodynamic instability and feeding intolerance. Measures to evaluate feeding intolerance, e.g., emesis, gastric residual volumes, and abdominal distension , will be included as they relate to the two delivery modes being tested, continuous and bolus feeds.

Because of the limited studies in children, research from the adult ICU literature was included and evaluated as it relates to the PICU patient. The goal of this literature review was to identify gaps in the literature and how the proposed research addressed these gaps. The purpose of this study was to compare two delivery modes for enteral nutrition, continuous and bolus feeds, in critically ill infants and children and to identify which delivery mode results in the earliest attainment of energy and protein goals and produces the least feeding intolerance.

Epidemiology of Preadmission and Hospital Acquired Malnutrition in the PICU

Malnutrition as a presenting co-diagnosis and/or hospital acquired condition is a pervasive problem in infants and children admitted to the PICU (Mehta et al., 2012; Mehta et al., 2013; Mehta & Duggan, 2009). Malnutrition of critical illness results from the metabolic stress of illness, inaccurate estimation of energy requirements, and inadequate nutrient intake related to feeding delays stemming from avoidable and unavoidable factors (Mehta & Duggan, 2009; Mehta et al., 2010). The consequence of inadequate delivery of nutrition during hospitalization is cumulative energy (delivered/prescribed kcal/kg/day) and/or protein (delivered/prescribed grams/kg/day) deficits which contribute to delayed recovery (Mehta et al., 2012; Mikhailov et al., 2014). Proactive strategies that limit nutritional deficits are paramount when working with infants and children in the PICU to restore health.

Mehta and colleagues (2012) reported greater than 30% of children were malnourished on admission to the PICU (n = 500). This prospective observational study sampled children ages 1 month to 18 years who required mechanical ventilation for at least 48 hours. To obtain this sample, children from 31 PICUs in eight countries were

studied. Data regarding nutritional practices were collected for up to 10 days or to the point of PICU discharge, whichever came first. A multivariate analysis was conducted to assess the impact of nutritional variables and subject characteristics on 60-day mortality and the prevalence of hospital acquired infections. Inadequate delivery of nutrition to energy goals occurred and resulted in worsened or newly acquired malnutrition during the PICU stay. The percent of daily EN intake attained was 38% (n = 34) for energy and 43% (n = 44) for protein. Subjects attaining a higher percentage of goal energy intake (66.6% compared to 33.3%) via EN had a lower mortality rate (OR 0.27 [0.11-0.67], p = .002). A second comparison between subjects fed enterally and parenterally via IV revealed subjects receiving parenteral nutrition had a higher mortality rate (OR 2.61 [1.3 – 5.3], p = .008) when controlled for hospital site and severity of illness. Higher attainment of goal energy and protein via enteral nutrition resulted in a lower the mortality rate and decreased risk of health care acquired infections (Mehta et al., 2012).

The relationship between nutrition deficits and anthropometric measures was examined in a prospective, observational study of PICU patients (n = 262). Total daily energy for a maximum of 14 days was evaluated for nutritional deficits and compared to the anthropometric measures of; weight, arm circumference and calf circumference. Subjects were assigned to a study group by age: preterm neonates (gestational age < 37 weeks); term neonates (gestational age ≥ 37 weeks; age 0-30 days and older children (age > 30 days – 18 years). Average energy and protein deficits of 27, 20, 12 kcal/kg/day and 0.6, 0.3, and 0.2 grams protein/kg/day were reported, respectively. Energy and protein deficits correlated with declines in weight and arm circumference (r =.39), but not calf circumference (Hulst et al., 2003). Thus, the objective measures of weight and arm

circumference may be useful for guiding the effectiveness of nutrition support in critically ill children.

Hulst and investigators (2003) similarly used the anthropometric measures of weight, length, head circumference, mid upper arm and calf circumference, and skinfold thickness of biceps and triceps as outcome variables for PICU patients admitted to the PICU and neonatal ICU over a one-year period (2001). They examined the nutritional status of 293 children (104 preterm neonates, 96 term neonates and 93 older children up to age 18) upon admission, at discharge, at 6-weeks and 6-months post discharge. Twenty-four percent of subjects were malnourished on admission, defined as greater than 2 SD below the mean weight for age. On discharge preterm and term neonates had the poorest nutrition status [(weight for age-severity of disease state; (-0.92 SD, $p < 0.001$ and -0.67 SD, $p < 0.001$, respectively)]. At 6 months, 85% of subjects demonstrated a return to near PICU admission parameters. However, a significant number remained malnourished in each group, 15% preterm, 12% term and 10% older children (Hulst et al., 2003). A limitation of this study was a lack of data on cognitive, motor or other functional outcomes.

Similarly, in a prospective cohort study of children ages 3.9 to 63.3 months admitted to the PICU over a 2 year period (n = 385), de Souza Menezes and colleagues reported 46% of subjects (n = 175) were malnourished on admission, which was associated with longer duration of mechanical ventilation (6.30 ± 3.18 versus 5.14 ± 3.43 days; $p = 0.003$). PICU length of stay was not associated with malnutrition in this study when diagnosis and severity of illness were controlled for in a multivariate analysis. This study was underpowered to detect a difference in mortality between the groups. Thus,

malnutrition was an independent predictor of duration of mechanical ventilation in the PICU (de Souza Menezes, Leite, & Koch Nogueira, 2012).

Kyle, Akcan-Arikan, Orellana, and Coss-Bu (2013) evaluated the presence/absence of acute kidney injury (AKI) and nutritional intake in a retrospective chart review of patients admitted to a single PICU for greater than 72 hours between August 2007 and March 2008 (n = 167; median age 1.4 years). The distribution of AKI in this sample was: 61% had no AKI (n = 102); 26% were classified as at-risk for AKI (n = 44); 7% had AKI (n = 12); and 5% were diagnosed with renal failure (n = 9). For all subjects, 55% of energy needs and 19% of protein needs were met. However, only 35% of energy needs and 0% of protein needs were met for subjects classified with AKI and renal failure. These findings indicate subjects with AKI and renal failure were at risk for underfeeding. This finding may be explained as inadequate feeding practices due to fluid restrictions and reluctance to provide needed protein in patients with kidney injury. In addition, this study demonstrates the risk for hospital acquired cumulative energy and especially protein deficits in this PICU subpopulation, regardless of nutritional status on admission (Kyle et al., 2013).

As illustrated by the previous studies, one-third or more patients in the PICU are malnourished upon admission and at significant risk for worsened or acquired malnutrition during their PICU stay. Iatrogenic malnutrition of hospitalization from inadequate energy and/or protein nutrition during the PICU stay has been attributed to severity of illness, diagnostic subgroups, feeding protocol variations and barriers to adequate delivery of nutrition. Further exploration of the use of anthropometric measures may be useful guides to evaluate the adequacy of nutritional support in the PICU patient.

Enteral delivery of nutrition as an independent predictor of morbidity and mortality will

be further explored. Adequate enteral nutrition intervention has been demonstrated to

lessen mortality and hospital acquired mal-conditions, such as infections and skin

decubiti (Mikhailov et al., 2014; Schindler et al., 2011; Wakeham et al., 2013) .

Impact of Enteral Nutrition Therapy on Outcomes in the PICU

The early initiation of enteral nutrition limits nutritional deficits and possibly the

magnitude of hospital acquired malnutrition. Controversy remains however regarding

what constitutes safe, early feeding. Mikhailov and colleagues compared patient

outcomes in 12 PICUs (n = 5105) that did /did not achieve early enteral nutrition (EEN)

of subjects in the first 96-hours of admission. EEN was defined as the provision of at

least 25% of goal calories enterally during the first 48-hours of admission. Subjects

ranged in age from 1 month to 18 years (n = 5105, 53.8% male, median age 2.4 years,

IQR 0.5-9.8). Outcomes examined included: demographic data, weight, nutritional

intake, severity of illness, length of stay, duration of mechanical ventilation and

mortality. Early enteral feeding was achieved for an average of 27.1% of subjects (range

15.6%-45.1%). Overall mortality for this study was 5.3%. Subjects receiving EEN had a

lower mortality rate (odds ratio 0.51; 9% CI 0.34-0.76; p = .001) when the data were

adjusted for age, severity of illness, clinical site, and propensity score. The propensity

score was calculated by using logistic regression to derive the probability of receiving

EEN based on the patient's characteristics and was then added as a covariate in the

analysis of mortality to address the possibility that sicker patients were less likely to

receive EEN. No between group differences were found for length of stay or duration of

mechanical ventilation. While causality cannot be concluded from a retrospective study,

delivery of EEN was associated with a reduced risk of mortality in PICU patients (Mikhailov et al., 2014).

The impact of EN therapy and weekly anthropometric outcomes were described for a convenience sample of PICU patients less than 18 years of age (n = 90) admitted for a minimum of 7 days (median 11 days), excluding neonates (Zamberlan, Delgado, Leone, Feferbaum, & Okay, 2011). Nutrition therapy was initiated within an average of 72 hours of admission. Eighty percent (n = 72) of subjects received EN, 10% (n = 9) received parenteral nutrition (PN) and 10% (n = 9) received both EN and PN. Gastric complications occurred in 5% of subjects given EN resulting in the initiation of post-pyloric feeding. On average caloric and protein intake was 82 ± 47 kcal/kg/day and 2.7 ± 1.9 grams/kg/day (mean$\pm$SD), respectively. These energy and protein values were higher than those reported in other studies (Mehta et al., 2012). No changes in body mass index for age, weight for age, arm circumference or arm muscle area were noted between admission and day 7 of hospitalization ($p > .05$). Similar to the study by Hulst and colleagues (2004), there was a significant decrease in arm circumference for height (-1.37 to -1.89; $p < .001$) and triceps skinfold thickness (9.2 to 8.0; $p < .001$) between admission and day 7. This study supports the findings of Mehta et al. (2012) indicating improved outcomes are achieved with the delivery of more than 66% of prescribed daily.

A landmark paper published in 2013 was the result of an extensive literature review supported by American Society for Parenteral and Enteral Nutrition (A.S.P.E.N). The mission of the A.S.P.E.N. is to improve patient care by advancing the science and practice of nutrition support. This paper provided new definitions for pediatric malnutrition, with a shift toward identifying etiologic mechanisms. The pediatric

malnutrition literature was reviewed from 1955 to 2011 in 5 apriori identified domains: anthropometric parameters, growth, chronicity of malnutrition, etiology and pathogenesis, and developmental/functional outcomes. After completion of an iterative and multidisciplinary review process, a newly constructed definition of pediatric nutrition emerged. The new definition of pediatric malnutrition is "an imbalance between nutrient requirements and intake that results in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development and other relevant outcomes" (Mehta et al., 2013, p. 478).

In addition, a new set of classification domains was constructed to describe and treat pediatric malnutrition. These domains include chronicity, etiology, mechanisms of nutrient imbalance, severity of malnutrition and impact on outcomes. An emphasis on the etiology of malnutrition as a primary driver for nutrition support was among the key recommendations. In addition, further investigations to assess the relationships between inflammation and illness-related malnutrition are needed. Research to validate the clinical domains will add to the understanding of multiple causation as applied to the critically ill pediatric patient (Mehta et al., 2013).

Recommendations for Nutrition Support

Cumulative energy and protein deficits are expressed as a percentage or ratio of delivered to prescribed goals. For energy the unit of measurement is kilocalories/kilogram/day (kcal/kg/day). For protein the unit of measurement is grams/kilogram/day (g/kg/day). No consistent method of determining energy/protein needs is defined in the literature or adopted in practice. Challenges to the accurate measurement of protein and energy needs include the need for expensive equipment,

unreliable energy prediction equations, unstable patient condition and the inability of the patient to tolerate measurement procedures, particularly when patients are being mechanically ventilated (Irving, Simone, Hicks, & Verger, 2000; Mehta, Bechard, Dolan, Ariagno, Jiang, & Duggan, 2011; Mehta et al., 2009).

When faced with barriers limiting achievement of prescribed daily energy and protein, supplementation to target protein intake, even when unable to achieve target calorie intake, may still confer an outcome benefit for the patient (Larsen, 2012; Larsen et al., 2012). Further research targeted to optimizing delivery and eliminating barriers to delivery is crucial. This study will contribute to the literature by defining the time to zero energy deficit when comparing two modes of delivery and identifying avoidable and unavoidable interruptions and feeding intolerance.

A.S.P.E.N. is an interdisciplinary organization which provides expert consensus and guidance for assimilating literature findings into practice. Guidelines, typically revised every 5 years, provide team members with interventions likely to yield positive patient outcomes. In the most recent guidelines for critically ill children. Mehta, Compher, et al. (2009) emphasized the lack of well-designed and well powered studies as a major issue. There are six recommendations and four sub-recommendations, with only 2 of 10 rated "C" as the highest grade of evidence (C = supported by small, randomized trials with uncertain results). All other recommendations are rated D or F, meaning supported by non-randomized cohorts or non-cohort studies, respectively. Appendix A provides the guidelines for nutrition support for the critically ill child, and Appendix B summarizes the definitions of the levels of evidence for A.S.P.E.N. guidelines.

Well-controlled, multi-center, studies regarding nutrition support of critically ill children are needed. While there are studies in the literature for adult populations, extrapolation of recommendations from the adult literature may not be suitable for children (Mehta, Compher, & Directors, 2009). The weak evidence base for nutrition recommendations in children serves as an impetus for additional research targeted on best feeding protocols, elimination of avoidable barriers to achieve target nutrition, and clarity for consistent definitions and thresholds to define feeding intolerance.

A Cochrane Collaboration Review®, published in 2009 set out to "assess the impact of enteral and total parenteral nutrition on clinically important outcomes for critically ill children" (Joffe et al., 2009, p. 3). A search of seven databases, trial registries, reviewed reference lists from potentially relevant studies and conference proceedings, contacted experts in the field, and manufacturers of enteral nutrition and parenteral nutrition products was conducted. The search was not limited by language. Inclusion criteria were:

- randomized controlled trials

- patients ages 1-day to 18 years

- in a PICU setting and received nutrition within the first 7-days of admission, and

- reported data from at least one of 4 pre-specified outcomes.

  o 30-day or PICU mortality,

  o PICU or hospital length of stay

  o number of ventilator days and

  o morbid complications, such as hospital acquired infections.

Exclusion criteria were:

- only reported nutritional outcomes,

- quality of life assessments, or

- economic implications,

- specialty areas, e.g., immunonutrition.

An iterative process with cross checking by multiple team members was used. The initial search identified 3070 studies; however, the investigators noted only one trial as relevant. The researchers concluded limited evidence existed and like A.S.P.E.N., recommend further evidence from randomized controlled trials is needed to guide nutritional support in critically ill children (Joffe et al., 2009).

Summary

Nutritional support of the critically ill pediatric patient is key to healing and positive patient outcomes. Evidence supports the prevalence of greater than 30% of children are malnourished upon admission to the PICU. One strategy to prevent or limit malnutrition of hospitalization is the early initiation of enteral feedings. The use of validated anthropometric measures may provide an additional method to evaluate nutritional deficits. Some evidence exists suggesting if energy needs cannot be met, maximizing levels of protein intake may mitigate negative outcomes. Further consideration of supplementing both energy and protein needs of the patient are necessary to prevent cumulative nutritional deficits for PICU patients.

The importance of malnutrition in critically ill children and the need for evidence based nutrition support is noted in the literature. More recently an increase in the number of studies related to nutrition in the pediatric critically ill population is noted. These

studies have addressed the need for nutrition therapy, monitoring parameters and complications resulting from malnutrition (Prieto & Cid, 2011; Zamberlan et al., 2011); measurement of energy expenditure (Botrán et al., 2011; Irving et al., 2013; Kyle et al., 2011; Kyle et al., 2012); the effects on specific PICU associated morbidities such as pressure ulcers (Schindler et al., 2011); nutritional needs in special populations, e.g., patients with congenital heart disease and burn patients (Braudis et al., 2009; Khorasani & Mansouri, 2010; Larsen, 2012; Larsen et al., 2012); and specific modes of nutrition delivery to achieve target energy and/or protein goals (Bankhead et al., 2009; Brown et al., 2012; Corkins et al., 2013; Marshall et al., 2012).

Published standards for nutrition support in pediatric hospitalized patients (A.S.P.E.N., 2013) outline the hospital structure and processes necessary to deliver safe, competent care. Such guidelines, while helpful, require further evidence to guide nutrition support in the PICU population. In addition, studying subsets of the pediatric critically ill population may be needed for best practices and patient centered outcomes. The focus of this study was to identify cumulative energy and protein deficits and to pinpoint the time to zero energy deficit when two EN delivery modes are compared, continuous versus bolus. Examination of feeding intolerance events and avoidable/unavoidable interruptions will further help to identify barriers to attaining nutritional goals.

Continuous Versus Bolus Gastric Feeding

Two common modes of nutrition delivery used in clinical practice are continuous feeding and bolus feeding. Given the paucity of publications on these two delivery

approaches in the both adult and pediatric critical care literature, the question of safety

and efficacy between continuous and bolus gastric feeding remains unanswered.

Adult Studies

A literature search comparing bolus versus continuous feeding in the adult

population identified one study on healthy volunteers and five studies on adult acute or

critical care patients. Twelve healthy male volunteers each participated in three separate

study conditions, in random order, each three days apart. All subjects received the same

volume of formula with added contrast. The three conditions were: formula ingested

orally over 5 minutes; formula delivered via nasogastric tube (NG) as a bolus over 5

minutes; or formula delivered via a continuous pumped infusion via NG over 4 hours.

Scintigraphy and impedance recordings were performed every 15 minutes until the

stomach was empty to assess the rate of gastric emptying and the incidence of gastro-

esophageal reflux. The rate of gastric emptying was identical for the oral and bolus fed

groups. During the continuous feeding arm of the study, a steady state gastric emptying

was found equivalent to the rate of infusion. There was no difference in the number or

duration of reflux episodes between the bolus and continuous fed groups (Bowling et al.,

2008). It is important to note however, comparisons between healthy volunteers may not

be reflective of what occurs in situations of critical illness whereby stress and the

associated SNS activation alters GI motility and function.

Rhoney, Parker, Jr., Formea, Yap, and Coplin (2002) compared bolus versus

continuous gastric feeding in brain injured patients in a retrospective chart review of 152

consecutive patients admitted to a neurosurgical ICU. Brain injury is associated with

delayed gastric emptying and decreased tone of the lower esophageal sphincter, which if

incompetent may lead to gastric reflux, and subsequent risk of aspiration and pneumonitis. In addition to intolerance of feeding defined as GRV greater than 75 mL measured every four hours, abdominal distension, decreased auscultated bowel sounds, or diarrheal stools at least once per day; the researchers evaluated risk factors for feeding intolerance and the effects of prokinetic agents on achieving target nutrition goals. The study unit's current feeding protocol was applied to all subjects during the timeframe An important consideration to interpreting study findings is the choice to initiate bolus versus continuous feeds was at the discretion of the clinician. Fifty-three percent of patients received bolus feeds (n = 80), 43% received continuous feeds (n = 66), and 4% (n = 6) were not fed. Demographic and clinical characteristics were similar between groups except the continuous feeding group had a higher initial median Glasgow Coma Score (GCS) with a mean score and range of 9 (3-15) versus 6 (3-15), respectively. For reference, a higher GCS implies better neurological function. The bolus group experienced a higher rate of feeding intolerance than the continuous group (60.5% vs. 37.9%; p = 0.009). Interestingly, the mean caloric (28.3 vs. 24.9 kcal/kg/day, p = 0.01) and protein (1.4 vs. 1.2 grams/kg/day, p = 0.003) intake was higher for the bolus than continuous feed group. In addition, the continuous fed group achieved goal feeds earlier than the bolus group, but the bolus group achieved overall improved energy and protein intake. The incidence of pneumonia and other hospital acquired infections was similar between the groups. For patients with head injury, the bolus feeding mode resulted in improved energy and protein intake despite an increased incidence of feeding intolerance (Rhoney et al., 2002).

For patients experiencing diarrhea, a study was conducted to evaluate whether the feeding delivery mode was a contributing factor to the development and continuation of diarrhea. Subjects included in the study had diarrhea defined as three or more stools per day (n = 105). Subjects were recruited from an acute (not critical care) geriatric unit and were already receiving bolus tube feeds. Subjects were randomized to either continue bolus feeds or crossover to continuous feeds for the next 3-day period. Eighty-six subjects completed the study. An additional 12 subjects were excluded from data analysis for positive C. difficile assays, with 74 subjects remaining. Diarrhea scores and gastric residual volumes were similar between the groups, suggesting no difference related to the mode of nutrition delivery (Lee & Auyeung, 2003). However, neither formula dilution nor the use of anti-diarrheal medications was controlled between groups thus compromising conclusion validity. As both groups were already experiencing diarrhea on bolus feeds, the impact of feeding mode would have been better assessed if randomization occurred at the time feeds were initiated rather than after onset of diarrhea.

Bolus vs. continuous delivery mode was evaluated by Lee and colleagues (2010) related to the incidence of pneumonia in geriatric subjects receiving enteral nutrition (n = 175). Subjects were randomized to a continuous (n = 85) or bolus (n = 93) gastric feeding group for a 4-week period. The only between group difference was gender, whereby more women were in the continuous fed group. Neither the incidence of pneumonia (15 vs. 18; p >.05) or mortality rate (7 vs. 13; p =.226) differed between the groups. A limitation of this study was noted wherein clinicians were permitted to change feeding modes for intolerance events based on provider preference rather than by protocol (Lee et

37

al., 2010). Similar to the finding of the researchers previous study (Lee & Auyeung, 2003) the delivery mode did not impact the measured clinical outcomes.

Chen, Chou, Lin, and Wu (2006) compared the delivery mode on outcomes of gastric emptying index measured by gastric residual volume (GRV) and pulmonary aspiration index. A randomized, controlled study was conducted in adults in two ICU's (n = 107). Subjects were randomly assigned to a continuous feed group (n = 51) or bolus feed group (n = 56). No between group differences were found in demographic characteristics, severity of illness indicators, the gastric emptying index or pulmonary aspiration index on day 0 or 7. The incidence of aspiration pneumonia was less in the bolus group (odds ratio 0.146, 95% CI =.062-.423, p < .001) than the continuous group. The bolus group achieved higher nutritional delivery (>1000mL/day; p < .001) compared to the continuous group and had a shortened duration of mechanical ventilation as defined as less than or greater than 21 days (22 vs. 35; p = .002). The pharmacologic use of intravenous high dose dopamine was a predictor of increased GRV and aspiration in both groups. In this study bolus feeding improved delivery of EN and was associated with a shortened duration of mechanical ventilation (Chen et al., 2006).

Resting energy expenditure and respiratory quotients were compared between patients receiving bolus versus continuous feeds in 40 head-injured male patients on mechanical ventilation. Both groups had a 6 hour feeding break each night and had blood sugar levels analyzed every 4 hours. The continuous group had the total daily feed infused over 18 hours while the bolus group had the equivalent volume and composition of nutrition divided into 6 bolus feeds administered every 3 hours. Demographic and severity of illness scores (SOFA scores 20 vs. 20; p = .158) were similar between

continuous versus bolus groups. No between group differences were found for respiratory quotient, resting energy expenditure, total energy intake, or blood sugar. Increased GRV and use of prokinetic agents was noted in the bolus group. Unlike Chen and colleagues (2006), who noted an increased incidence of lung pathology with continuous feeds, no aspiration events, which may produce pneumonitis, occurred in either group. Of note females were excluded from the sample and hemodynamic stability was an inclusion criterion suggesting a difference between the sub- populations in the ICU (Maurya, Pawar, Garg, Kaur, & Sood, 2011).

In summary of these adult studies, no increased pulmonary risk occurred with bolus feeding (Chen et al., 2006) and there was a benefit of increased delivery of prescribed nutrition translating into higher energy and protein goals (Chen et al., 2006; Rhoney et al., 2002). No study reported an increased risk of aspiration with bolus feeding and in fact, some had a decreased risk for aspiration. The current study compared bolus versus continuous gastric feeds in critically ill children on the attainment of target nutritional intake and the incidence of feeding intolerance. Oxygen saturation index (OSI), an indicator of acute lung injury, was used in the current study as a marker of clinical worsening when comparing the delivery mode of feeds between the groups.

Pediatric Studies

Investigators examined protein synthesis in muscle based on the two delivery methods, bolus vs continuous. Using a porcine model, neonatal pigs received equivalent formulas and fluid volume as continuous (n = 6) or bolus feeds (n = 6). The investigators reported increased protein synthesis in muscles of different fiber types and visceral tissues in the bolus fed group compared to the continuously fed group (p < .05) (El-Kadi

et al., 2013). Further investigation comparing anthropometric measures related to muscle wasting may explain the changes noted by El-Kadi and colleagues (2013).

Only two publications were found in the pediatric literature comparing bolus versus continuous gastric feeding in the PICU population. In a randomized controlled trial, the relationship between continuous versus bolus gastric feeds and the prevalence of diarrhea and vomiting was examined in PICU patients (n = 45) (Horn & Chaboyer, 2003). Patients admitted to the PICU during a 9-month period were evaluated. Exclusion criteria included: history of vomiting or diarrhea in the 24-hour period preceding randomization; anticipated transfer from the PICU within 72 hours of starting feeds; and/or subjects on a specialized feeding protocol. Subjects enrolled in the continuous feeds arm of the study received formula at a steady delivery rate over a 24-hour period (n = 22). Subjects in the bolus group received the equivalent total volume with feeds divided into 12 equal periods given every 2 hours over 20-30 minutes (n = 23). Gastric residual volume (GRV) was measured every 4 hours in both groups. Groups were similar on the following parameters: demographics; volume of formula delivered/24 hours; and use of narcotics, prokinetic agents, antibiotics or gut protection agents. The age distribution in both groups was heavily skewed to the right, reflecting a preponderance of younger patients (range 0-153 months). There was no difference in the incidence of diarrhea (mean 1.5 vs. 1.6; p = .83) or vomiting events (mean 0.64 vs. 0.22; p = .19) between continuous and bolus fed groups (Horn & Chaboyer, 2003).

Using data from the previous study, Horn, Chaboyer, and Schluter (2004) conducted a secondary data analysis to examine differences in GRV between continuous and bolus feeding protocols. GRV was higher in the continuously fed group compared to

the bolus group as defined by a volume greater than 5 mL/kg. The median GRV was higher in the continuous (n = 15) compared to bolus (n = 18) group (83%) of the measured time points (p = 008). The clinical criterion used to define an elevated GRV was not associated with the outcome of vomiting and diarrhea.

The two pediatric studies evaluated diarrhea and GRV, both variables associated with dysmotility. Both the adult and pediatric literature strived to inform best practice related to delivery of nutrition. Further investigation is needed to evaluate other clinically significant parameters and the potential risks associated with feeding intolerance, such as aspiration.

Theoretical Framework

A proposed theory of gastrointestinal dysmotility in critical illness guided this study. This proposed midrange theory was based on combining the multiple mechanisms of normal GI function, how these mechanisms are influenced by the stress of critical illness, and the effects of common therapeutic interventions in the PICU. Dysmotility in the critically ill child is multifactorial and includes severity of illness, autonomic dysregulation from critical illness, effects of immobility, PICU medications and other therapies on gut function. Dysmotility increases the risk of feeding intolerance, and limits the delivery of nutrition to meet energy and protein needs at a time when nutrition is vitally needed for healing as well as growth and development. An expanded understanding of how critical illness and therapies alter gut function in the PICU population was offered as the current study provides insight into protocol development for the prevention of complications associated with feeding intolerance.

Normal GI Motility and Function

GI motility is directly regulated by the Enteric Nervous System (ENS), a branch

of the Autonomic Nervous System (ANS). The ENS has approximately 100 million

neurons running from esophagus to anus, a neuron number similar to that found in the

spinal cord. The ENS has both efferent and afferent branches that provide feedback loops

to control motility, secretion, absorption, digestion and other self-maintenance functions

associated with the gut lining. Two primary neuro-plexi of the ENS are responsible for

the control of motor and secretory functions. The outer plexus, known as the myenteric or

Auerbach's plexus, lies between the longitudinal and circular muscle layers and is

primarily responsible for the motor functions of segmentation and long wave peristalsis.

The innermost plexus, the submucosal or Meissner's plexus, lies in the submucosa, and

its primary functions are to modulate blood flow, secretion, and absorption (Guyton &

Hall, 1996; Mohr & Steffen, 2011).

The ENS is influenced by two other branches of the Autonomic Nervous Systems

(ANS), the parasympathetic (PSNS) and sympathetic (SNS) system, as well as the

Central Nervous System (CNS). Neuro-hormonal mediators delivered by the bloodstream

to the gut, such as epinephrine and cortisol also alter ENS function. Normally, the GI

tract is dominated by the PSNS which promotes digestion, secretion, absorption and GI

motility. The primary neurotransmitter of the ENS is acetylcholine, a key regulator of

muscle hence motor function. The purpose of the motile function of the GI tract is to mix

and break down food in the stomach, and promote unidirectional propulsion in a

cephalocaudal direction. In tandem, there are multiple sphincters along the GI tract e.g.,

gastroesophageal, pyloric, and ileocecal. Under PSNS stimulation sphincter tone is

maintained, preventing the reflux of food into the proximal gut. Conversely, with SNS stimulation, sphincter tone is relaxed, potentially allowing for reflux and motility is slowed (Guyton & Hall, 1996; Mohr & Steffen, 2011).

Motility and secretion vary between the two phases of digestion, the interdigestive and digestive phase. During the digestive phase, gut blood flow is enhanced via vasodilatation in the splanchnic circulation. This increased bloodflow provides the oxygen and other substrates necessary to carry out digestion, absorption and transport of nutrients from the gut lumen into the bloodstream (Guyton & Hall, 1996). "The basic rule of the gut is that food stimulates contraction above and behind the food bolus and relaxation below or distal to the bolus, forming the peristaltic wave" (Mohr & Steffen, 2011).

The interdigestive phase is the rest period between meals. During the interdigestive phase, the Migrating Motor Complex (MMC) becomes active. In the fasting state, the MMC has three phases. Phase I is a state of quiet motor or quiescence. Phase II is the occurrence of random, intermittent contractions similar to the fed state. Phase III has characteristic high amplitude, high frequency true contractions that sweep intestinal contents toward the ileum. Thus, residual food known as chyme in the gut lumen is swept forward, clearing the GI tract prior to the next meal. In children the MMC cycle occurs every 100-120 minutes during a fasting period. The initiation of feeding abolishes the MMC sequence, moving it back to Phase II, mixing (Mohr & Steffen, 2011). Bolus feeding mimics the normal feeding pattern while continuous feeding alters the interdigestive phase.

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GI Dysmotility in Critical Illness

In critical illness SNS tone dominates homeostatic mechanisms due to triggering of the stress response. Increased SNS tone reduces propulsive movement and alters sphincter tone; both effects are associated with an increased potential for reflux. The dominant neurotransmitter from the ENS in a state of stress is norepinephrine, which inhibits GI motility. The additional norepinephrine release from the SNS pathway results in an exaggerated effect on the gut. The measurement of pressures and motility via the insertion of a balloon into the stomach has demonstrated abnormal antro-duodenal pressures waves in critically ill adults. Chapman and colleagues (2008) compared motility patterns in 10 health and 15 mechanically ventilated critically ill adults. Subjects were fasted followed by a gastric then duodenal infusion of formula. Critical illness was associated with slower gastric emptying, fewer antegrade and more retrograde waves than found in normal healthy adults.

To evaluate the impact of slowed gastric emptying and possible reflux in PICU patients, intraluminal impedance testing has been used as a more sensitive test than pH testing for determining gastric reflux in mechanically ventilated children (n = 36). Solana and investigators reported a high incidence of reflux in the first 48-hours of PICU admission using intraluminal impedance testing (352 events compared to 171 events using a pH probe). They found no differences in the number or type of episodes of reflux when vasoactive or sedative agents were administered. There were fewer reflux events in subjects receiving neuromuscular blockade compared to those who did not. However, 97.5% of subjects were status post cardiac surgery and none of the study subjects were enterally fed thus, limiting practical application of study findings. Further studies using

antro-duodenal pressures may provide useful data to evaluate enteral feeding; however it is not a practical bedside tool (Solana et al., 2013).

The stress of critical illness produces dysmotility. Critical illness may also produce a response of gut hypoxia, ischemia, and/or inflammation.

Hypoxia. Decreased oxygen concentration in the gut wall can transiently increase intestinal blood flow by up to 50% in an otherwise healthy person (Guyton & Hall, 1996). Hypoxemia from conditions that alter gas exchange and/or delivery of oxygen to tissue may result in the need for mechanical ventilation either invasive or non-invasive. Significant hypoxemia often leads to tissue hypoxia. During tissue hypoxia, compensatory vasoconstriction occurs, shunting blood away from non-critical organ systems such as the gut and skin toward the heart, lungs and brain (Mentec et al., 2001). This leaves the gut vulnerable to alterations in motility, secretion, digestion, and absorption.

Ischemia. Whereas hypoxia occurs from inadequate oxygen delivery to the tissues, ischemia results from a decrease in blood flow. Both hypoxia and ischemia alter oxygen delivery to the gut. When critical oxygen delivery requirements are not met, dysoxia produces injury at the cellular, tissue and organ level, which may or may not be reversible. Ischemia results from any type of shock condition, and may occur in tandem with hypoxemia. Similar protective shunting of blood toward vital organs occurs in response to both ischemia and hypoxia (Felípez & Sentongo, 2009; Ukleja, 2010). In addition, the release of neurohormonal mediators by the ANS, e.g., cortisol and epinephrine, in response to the stress state, also slow gut motility (Mohr & Steffen, 2011).

Inflammation. In the 2013 pediatric malnutrition consensus definition there is an emphasis on inflammation and its role in the pathogenesis of malnutrition in the critically ill child. The role of inflammation has not been fully explored nor has the role of EN in the modulation of inflammation. While this study did not explore markers of inflammation, consideration is given here as it contributes to the proposed theory on gut dysmotility of critical illness. Inflammation results in a catabolic state. Catabolism associated with critical illness results in a critical need for protein early in the disease course, as well as a higher caloric need for healing. The goal of critical illness is to return the body to a balance between the catabolic and anabolic state (Mehta et al., 2013). Inflammation also has an inhibitory influence on GI motility and contributes to the vasoconstriction response in the splanchnic bed (Shimizu et al., 2011; Ukleja, 2010). Shimizu et al. (2011) found gut flora and organic acids were significantly altered in patients with severe Systemic Inflammatory Response Syndrome (SIRS) and patients with SIRS were also noted to have GI dysmotility and a higher mortality from sepsis.

GI sphincter tone is reduced in the stressed state of the critically ill as a result of SNS stimulation. GI dysmotility occurred in greater than 50% of mechanically ventilated patients (Btaiche et al., 2010; Montejo, 1999; Solana et al., 2013; Ukleja, 2010). The clinical significance of lower sphincter tone is increased risk of gastric reflux and the potential for pulmonary aspiration (Btaiche et al., 2010; Fuchs, 2011). Furthermore, critical illness is often associated with hypoxia, inflammation and/or hypoperfusion, which all affect GI function. Disruption of motility, secretion, digestion and absorption can further impact patient outcome by creating a state of malnutrition.

Contributors to Dysmotility in the PICU Care Environment

Medications. Commonly used PICU medications may alter GI motility. These medications include: opioid analgesics, sedatives, neuromuscular blockers, catecholamines, and other vasopressor agents. Opioids are known to slow GI motility, as are sedative agents, especially when used in higher doses as is often required in the PICU environment (*Drug Information Handbook For Advanced Practice Nursing*, 2010). Neuromuscular blockers affect skeletal muscle. While the gut is composed of smooth muscle, hence unaffected by the neuromuscular blockers, the resultant immobility of the patient may contribute to the GI dysmotility. Catecholamines and vasopressor agents stimulate alpha-1 receptors and produce vasoconstriction in the presence of hypotension. An unintended consequence of these therapies is a resultant decrease in blood flow to the splanchnic circulation, which further slows gut motility (Btaiche et al., 2010; Herbert & Holzer, 2008; Ukleja, 2010).

Immobility. Immobility slows motility in the GI tract (Fuchs, 2011; Meert & Metheny, 2004). PICU patients are typically restrained in bed for safety reasons and to allow for uninterrupted application of critical care therapies such as mechanical ventilation, nasogastric feeding, IV infusions, etc. Clinically, immobility introduces risk of GI dysmotility and poor propulsive movement which may lead to feeding intolerance and enhanced risk of aspiration.

Feeding status. Enteral feeding practices in the PICU may exacerbate GI dysmotility. Periods of non-feeding are common in the early stay of the ICU patient. Early feeding is proposed as one strategy to maintain motility and integrity of the gut lining to maintain secretion, digestion, absorption, and motility. The use of hyperosmolar

formulas, which are high caloric and nutrient dense are commonly utilized and have been shown to accelerate GI motility (Fuchs, 2011). The mechanism for this effect is thought to be the increased fluid drawn into the intestinal lumen from the high osmolar gradient of these formulas.

Continuous feeding deviates from normal feeding patterns and results in no interdigestive period. The impact of the disruption of the normal sweeping function of the MMC has yet to be fully evaluated and may impact the treatment decision to feed via continuous or bolus mode. The additive effects of critical illness and the effects of common PICU therapies create an increased risk for GI dysmotility (Chapman et al., 2008; Solana et al., 2013). Altered motility increases the occurrence of feeding intolerance, which is a contributing cause of inadequate energy and protein intake at a time when the delivery of nutrition is crucial for healing and the restoration of health in the critically ill child.

The proposed theory describes the interaction of the nervous system under conditions of critical illness. Current PICU therapies and patient characteristics alter GI motility and were the focus of this investigation. An initial study substruction model was developed (see Figure 1), based on methods described by Dulock and Holzemer (1991). Future studies will clarify the relationships of the numerous model concepts and measures (Dulock & Holzemer, 1991). It is assumed that the increased influence of the SNS would predispose the critically ill child to feeding intolerance, particularly when compounded by the commonly prescribed PICU therapies which are also known to risk slowed gut motility. However, continuous feeding may in fact increase the risk of dysmotility as there is no period of gut rest. An advantage in the delivery of EN without

increased risk of feeding intolerance may be conferred with feeding via bolus methods, as the gastric emptying may be improved. Combined with fewer interruptions with the bolus method (discussed elsewhere in this chapter), bolus feeding may provide superior nutritional intake by improving gastric motility and minimizing interruptions.
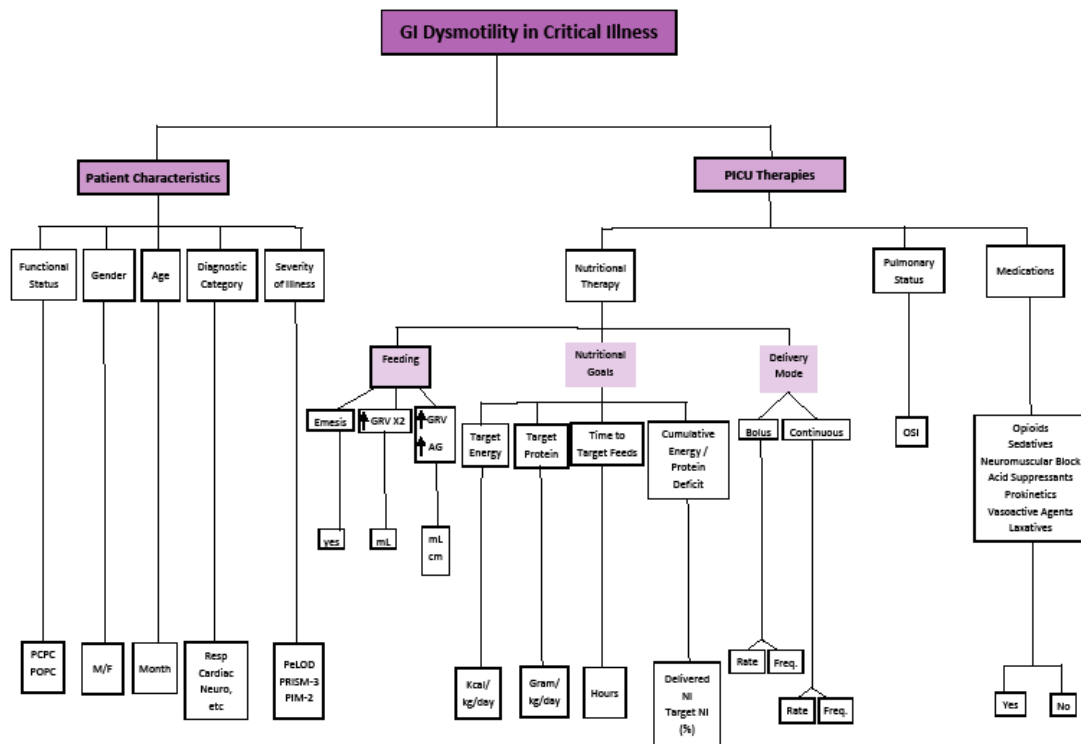
Figure 1. Initial study substruction model.

Barriers to Nutrition Delivery and Attainment of Nutritional Goals

Barriers to the successful attainment of prescribed enteral nutrition include hemodynamic instability of the patient, feeding intolerance, feeding interruptions, and lack of evidence based feeding protocols. Each of these factors contribute to delays in delivering feeding volume, hence caloric and protein intake to meet prescribed nutrition

goals (de Neef et al., 2008; McClave et al., 1999; Mehta, Compher, et al., 2009; Mehta et al., 2010; O'Leary-Kelley, Puntillo, Barr, Stotts, & Douglas, 2005; O'Meara et al., 2008; Souza de Menezes, Leite, & Koch Nogueira, 2012).

Hemodynamic Instability

Under physiologically normal conditions oxygen supply greatly exceeds oxygen demand. Dysoxia results when oxygen supply no longer meets demand. This may result from increased oxygen demand from the stress of illness, including fever; decreased supply which accompanies acute lung injury; or both conditions can occur simultaneously. The resultant oxygen debt results in a shift from aerobic to anaerobic metabolism with the production of lactate. Clinical indicators of adequate oxygen delivery include signs and symptoms evaluated by physical examination such as vital signs, work of breathing, skin color, blood gases, oxygen saturation, and end organ function (Guyton & Hall, 1996). This study used the oxygen saturation index (OSI) as an indicator of oxygen supply/demand balance. The OSI is calculated by multiplying the subject's fraction of inspired oxygen (FiO_2) times mean airway pressure (MAWP) recorded from the ventilator, then divided by the arterial oxygenation saturation measure via pulse oximetry (SpO_2). OSI represents the acuity of the subject's lung disease such that a higher numbers implies worsening acute lung injury (Thomas et al., 2010). Formula:

$$OSI = \frac{FiO_2 \times MAWP}{SaO_2}$$

During critical illness the body frequently has increased metabolic demands from fever, increased work of breathing, the stress response which produces increased heart

and respiratory rate, and illness driven conditions, e.g., sepsis. Physiologic changes to maintain or increase oxygen delivery to vital organs such as the heart and brain result in blood being shunted away from nonvital organs, e.g., gut and skin. Kleinman and colleagues (2010) noted hypoxia and/or hemodynamic instability, with or without hypotension resulted in the shunting of blood from the splanchnic vascular bed, thus putting the gut at risk for ischemia. Since the vital functions of the gut are secretion, digestion, absorption, and motility, reducing oxygen to the gut interferes with these functions and influences the ability to feed the critically ill patient.

The body's response to the stress of illness is SNS activation and the release of bloodstream mediators such as epinephrine and cortisol. In addition, increased SNS efferent firing releases the neurotransmitter norepinephrine which results in alpha-1 vasoconstriction of gut blood vessels and an increased secretory and inflammatory response. Other neuroendocrine factors also serve as mediators that affect splanchnic blood flow leading to vasoconstriction and alterations in gut motility (Guyton & Hall, 1996; Saps & Di Lorenzo, 2011).

A condition resulting from gut dysoxia is necrotizing enterocolitis (NEC). This potentially lethal complication of critical illness describes the final pathway of ischemia/hypoxia resulting in reversible/irreversible gut injury, which if left unchecked results in tissue death, or necrosis. Factors which contribute to the development of NEC are multi-factorial and include gut immaturity; altered bacterial colonization; translocation of bacteria into the bloodstream; gut barrier dysfunction from disruption of the endothelium and/or abnormal intestinal vasoregulation (Iben & Rodriguez, 2011). Delayed feeding produces a reduction in the thickness of the mucosal barrier,

contributing to barrier dysfunction. The loss of gut mucosal integrity also contributes to a heightened inflammatory state and disruption in both amount and composition of intestinal flora, leading to an increased risk for bacterial translocation from the lumen of the gut into the bloodstream and sepsis (Teitelbaum, 2011; Wahbeh & Christie, 2011). Consequently, the challenge for the clinician is to identify when to feed to avoid additional metabolic stress on the compromised gut, a stress that may accelerate ischemia and lead to potentially life threatening complications such as NEC.

Both endogenously released and exogenously administered vasoactive substances have a positive inotropic, dromotropic, and/or chronotropic effect on the cardiovascular system, and increase oxygen demand. Medications such as epinephrine and norepinephrine administered as an intravenous continuous infusion to support blood pressure and hemodynamic stability reduce the production of endogenous mediators. The body must again endogenously manufacture these substances as the patient is weaned from the medication. As previously noted, the administration of exogenous vasopressors has been associated with increased GRV and risk of aspiration in some studies (Chen et al., 2006), but not in others (Mancl & Muzevich, 2013; Mikhailov et al., 2014; Panchal et al., 2013).

Khalid and associates (2010) compared the timing of early versus late initiation of feeds in patients receiving vasoactive drug therapy. Using a prospective study design, adult ICU patients (n = 1174) who required mechanical ventilation for ≥ 2 days and received vasopressor infusions were divided into two groups: those who received EN within 48 hours of starting ventilation (n = 707) and those who did not (n = 467). The primary measured outcomes were ICU and hospital mortality. For subjects receiving

early EN, both ICU and hospital mortality was lower (22.5% vs 28.3%; p = .03 and 34% vs 44%; p = < .001). The greatest benefit of early EN was seen in the sickest patients who received multiple vasopressor agents (Khalid, Doshi, & DiGiovine, 2010). Contrary to our understanding of the effect of vasoactive substances on gut bloodflow, feeding may have mitigated this effect by enhancing perfusion to support the functions of digestion/absorption. This is a clinically important finding that bears replication as clinicians treating the most critically ill patients are hesitant to initiate early feeding for fear of unduly stressing the gut, leading to NEC. Bench research to measure secretion, digestion, absorption, and motility, along with histological analysis of the gut layers may aid in understanding this phenomenon.

Similarly, Mancl and Muzevich (2013) evaluated feeding tolerance in a retrospective review of adult ICU patients (n = 259) who received both EN and IV vasopressors simultaneously for at least one hour. Feeding tolerance was defined as the absence of GRV ≥ 300mL, absence of emesis, and no positive pathologic finding on radiologic imaging or evidence of bowel ischemia/perforation. Overall tolerance of EN in subjects receiving vasopressors was 74.9%. An inverse relationship was reported between maximum equivalent norepinephrine and EN tolerance (12.5 mcg/min for subjects who tolerated EN vs 19.4 mcg/min for those not tolerating feeds; p = .0009). These authors concluded most patients can safely receive EN while on vasopressor support, but increasing vasopressor doses increased the risk of feeding intolerance (Mancl & Muzevich, 2013).

Panchal et al. (2013) evaluated feeding intolerance in PICU patients (n = 339) on vasoactive medications and fed/not fed by comparing the incidence of adverse GI events.

An increased incidence of adverse GI events, e.g. emesis, diarrhea, abdominal distension, GI bleeding but a lower risk of mortality was found in the fed versus unfed group [6.9% vs 15.9%; OR 0.39 (0.18-0.84;p < .01)] (Panchal et al., 2013). Consistent with the findings of Mancl et al. (2013), patients can tolerate EN while on vasopressor support with advantages conferred when EN is initiated.

What is yet to be defined is the level of vasopressor support that minimizes the risk of intolerance yet confers the benefits of EN to reduce morbidity and mortality. Furthermore, no study has examined the mode of delivery in patients receiving EN. This study collected data on the use of vasoactive medication; but without sufficient sample size, the data are useful only in the context of proposing explanations to study findings.

Feeding Intolerance

Challenges to defining feeding intolerance include not just what thresholds should be followed, but also what measures indicate intolerance. Commonly used signs and symptoms of GI intolerance are the presence of one or more GI findings: emesis, diarrhea, persistent high GRV and/or gastric distension. Limited evidence exists on the "best" measure(s) of feeding tolerance to limit the associated risks of aspiration and pulmonary complications. Moreover, study findings from the adult literature may not be transferrable to the pediatric population related to differences in physiology e.g., nervous system development and cardiovascular differences. Identifying the types, incidence and duration of feeding intolerance in this study are important to the beginning identification of appropriate thresholds and single or a constellation of signs and symptoms which would dictate the point at which feeding should be modified or discontinued (Horn &

Chaboyer, 2003; Horn et al., 2004; Hurt & McClave, 2010; Reignier et al., 2013; Skillman, 2010, 2011; Weckwerth, 2004).

The concept of feeding intolerance has been described for the premature infant (Moore & Wilson, 2011). The authors' purpose was to clarify the phenomenon of feeding intolerance and provide a universal conceptual and operational definition for researchers and clinicians to use in practice theory. In the preterm infant, feeding intolerance was conceptually defined as the "inability to digest enteral feedings presented as GRV more than 50%, abdominal distention or emesis or both, and the disruption of the patient's feeding plan" (Moore & Wilson, 2011; p. 153.) Their review of the literature did not identify any consensus regarding empirical indicators and thresholds which indicate feeding intolerance in the PICU population. The examined measures in this study indirectly measured motility by monitoring emesis, GRV, abdominal girth, and associated feeding interruptions.

This research study evaluated the empirical indicators and thresholds of feeding tolerance in the PICU population when two different delivery modes were used. It was the assumption of the investigator that the mode of delivery would provide an advantage for the optimal delivery of energy and protein nutrition if the number of intolerance events was limited. An understanding of differences when feeding continuous versus bolus may contribute to the standardization of protocols.

Emesis. There is literature consensus that emesis, the visible eruption of feedings from the mouth, constitutes intolerance (Fuchs, 2011; Guyton & Hall, 1996; Moore & Wilson, 2011; Skillman & Mehta, 2012). PICU clinicians from multiple hospitals were asked if emesis with coughing (tussive) and/or suctioning was a valid sign of intolerance

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in mechanically ventilated patients. These clinicians agreed that emesis was a valid indicator of feeding intolerance when it occurred spontaneously, but not with tussive events (personal communication during PICU Focus Group meeting, October, 2013). Data collection in this study included tracking of the type of events associated with emesis, e.g., coughing (tussive event), suctioning or spontaneous. Emesis correlated with other indicators of intolerance, such as elevated GRV and increased abdominal girth may contribute further evidence to what constitutes feeding intolerance.

Gastric residual volume. When gastric feeding is delivered in a state of reduced gut motility, feeding intolerance may result from overdistension of the stomach and reflux from incompetent GI sphincters. One measure of feeding intolerance is a rising GRV. GRV is determined by aspirating gastric contents via a nasogastric tube after which gastric contents are returned to the stomach. Clinically, GRV is measured at regular intervals, e.g., every 3 hours. Clinical decisions are made to continue, reduce or withhold feedings based on volume. Holding feeds may prohibit the delivery of volume and ultimately needed energy and protein nutrition. Additionally, the accumulation of feeds in the stomach may increase the risk of aspiration of feeds mixed with gastric juices into the lungs producing a chemical pneumonitis.

GRV is used by clinicians as a marker for delayed gastric emptying. While an increase in GRV has been associated with feeding intolerance and an increased risk of aspiration, consensus has not been reached on the amount of GRV predictive for the risk of pulmonary complications (Edwards & Metheny, 2000; Mentec et al., 2001; N. A. Metheny, Mills, & Stewart, 2012; Montejo, 1999; O'Meara et al., 2008; Pinilla,

Samphire, Arnold, Liu, & Thiessen, 2001). Most recent evidence deemphasizes the use of GRV as an indicator of feeding tolerance in adults (Hurt & McClave, 2010).

The literature focused on defining feeding intolerance has predominantly been in adult and pediatric ICU populations. Nurses by their proximity to the bedside often make practice decisions on what constitutes feeding intolerance. Metheny and colleagues (2012) conducted a national survey on methods used by adult critical care nurses to assess feeding tolerance. A total of 2,298 responses were received; most respondents reported using a combination of methods to define intolerance, including measuring GRV (97.1%), emesis (86%), nausea (79.6%), abdominal distension (88.5%) and abdominal discomfort (79.3%). The GRV threshold most commonly reported was 200-250 mL, with only 12.6% of respondents using GRV thresholds of 400 - 500mL. Survey findings indicate wide variation in clinical practice and protocols used to assess feeding intolerance. With a goal to optimize feeding delivery to reach nutritional goals and minimize risk to critically ill patients, additional research is needed (Metheny et al., 2012).

Additional studies provide strong evidence for the elimination or minimization of GRV as a primary indicator of feeding intolerance in critically ill adults. Montejo et al. (2010) compared the effects of increasing the GRV threshold in subjects receiving continuous EN. This prospective, multi-site study randomized subjects to two groups, those in which the threshold to stop feedings was set at 200 mL (control) and those in which the threshold to stop feeding was 500 mL (intervention). No difference in safety events was noted between groups. The control group had a higher number of feeding intolerance events (42.4% vs. 26.8%, p = .004). There were fewer feeding interruptions in

the higher threshold group and subjects received improved delivery of EN (88.2% vs. 84.5%, p = .003). The importance of this study is higher GRV values were not associated with an increase in adverse events and subjects had enhanced delivery of nutrition. The authors concluded a GRV of 500mL is a safe threshold and promoted improved delivery of EN (Montejo et al., 2010).

Similarly, Poulard et al. (2010) evaluated the use of GRV as a valid indicator of feeding intolerance. In a prospective pre-post study GRV as a measure to continue or stop feeding was compared to the incidence of vomiting and risk of nosocomial pneumonia. Subjects followed a standardized feeding protocol for 7 days. In the first group GRV was measured every 6 hours and feeds were held when the GRV exceeded 250mL (n = 102). A second group of subjects had no GRV measurement. Feeding intolerance was defined as emesis or elevated GRV in the first group, and emesis only in the second group. The non-GRV measured group received an increased volume of EN (Median daily volume 1489 mL vs. 1381mL, p = .002). A higher incidence of intolerance occurred in the control group where GRV was used as a key measure (46.1% vs. 26.2%, p = .004). The incidence of emesis and pneumonia was similar between groups (Poulard et al., 2010).

Reignier et al. (2013) tested the hypothesis that the risk of ventilator associated pneumonia is not increased when GRV is not monitored in a multicenter trial (9 sites) of adult ICU patients (n = 449). Subjects were randomized to a control group where feeding intolerance was defined as emesis and/or GRV greater than 250 mL (n = 222). In the intervention group intolerance was defined only as emesis (n = 227). Both groups were given a 25 kcal/kg/day daily EN prescription. A higher incidence of feeding intolerance occurred when GRV was measured. No difference in the incidence of ventilator

associated pneumonia, mortality, diarrhea or ICU-acquired infections were found despite an increased incidence of emesis in the non-GRV group (p = .003). The proportion of subjects reaching their daily calorie goal was higher in the non-GRV group (odds ratio 1.77; 90% CI 1.25-2.51; p = .008). An ideal threshold for GRV has yet to be defined. Studies of adult ICU patients suggest routine GRV measurements as an indicator of feeding intolerance may not be necessary and may in fact reduce delivery of needed calories to promote healing (Reignier et al., 2013).

Hurt and McClave (2010) published a review of the utilization and assumptions surrounding GRV in adult critical illness. After review of 32 studies on GRV measurement and management, they refute the following 6 assumptions regarding GRV.

- The practice of GRV is well standardized (Metheny et al., 2012).

- GRV accurately and reliably measure gastric contents(Metheny, Schallom, Oliver, & Clouse, 2008).

- GRV distinguish between normal and abnormal gastric emptying (McClave et al., 1992).

- GRV measurements are easy to interpret (Chang, McClave, & Chao, 2004)

- A tight correlation exists between GRV and aspiration (Metheny et al., 2008).

- Continuing EN after obtaining a high GRV leads to pneumonia and adverse outcomes (Poulard et al., 2010).

- GRV is an inexpensive "poor man's test" for gastric emptying and tolerance of enteral nutrition (McClave et al., 2005).

De-emphasis of the use of GRV as a primary determinant of feeding intolerance is recommended Hurt and McClave (2010). This study compared GRV to other indicators of feeding intolerance, namely abdominal girth.

Similarly, best practices have yet to be defined regarding GRV as a measure of intolerance in the critically ill pediatric patient population. Horn et al. (2004) compared continuous versus bolus gastric feeds and proposed 5mL/kg as the critical GRV threshold. Brown et al. (2012) used a less conservative threshold for GRV of greater than 50% of the amount of feed infused in the previous 4 hours. Decreased time to nutritional goals occurred for patients less than 10kg (p=.045) (Brown et al., 2012). This study completed as part of the dissertation evaluated feeding tolerance and set the same criteria for the GRV threshold, but required two consecutive elevations in GRV or the presence of an additional intolerance indicator, e.g., increased abdominal girth.

Inconsistent definitions of feeding intolerance limit the attainment of nutritional goals. The preponderance of evidence suggests no increased complications occur by either not measuring or raising the GRV threshold. A constellation of signs and symptoms may best describe feeding intolerance.

Abdominal girth. Abdominal distension as measured with the patient supine and the measure taken directly over the umbilicus is considered a marker of feeding tolerance. Abdominal girth is typically assessed in conjunction with one or more other parameters of feeding tolerance, e.g., GRV, emesis, diarrhea or abdominal pain (Brown et al., 2012; Fuchs, 2011; Urban, Splaingard, & Werlin, 1994). The limited evidence in the literature related abdominal girth may be feasibility related rather than evidential. For example, the PICU patient may have significant shifts in body weight, as much as 10-20% of

admission weight. Additionally, workload in the PICU, acuity of patients, and multiple interventions may limit the ease of measuring abdominal girth in the PICU population. This study took both of these factors into consideration. First, to minimize issues of weight shift, change was measured from the lowest measurement in each 24-hour feeding period. Second, comparison of GRV and changes in abdominal girth were evaluated to determine the best marker(s) of feeding intolerance to guide nutritional therapy.

Diarrhea. Diarrhea is another recognized sign of feeding intolerance. Variable operational definitions of diarrhea make the comparison of studies difficult to evaluate this sign as an indicator of feeding intolerance. The use of different formulas with varying levels of osmolality and protein content may alter stool composition. Varying treatment protocols may also affect the quantity and consistency of stool and limit this sign's predictive association with feeding intolerance. The continuum of definitions of diarrhea include varied frequency and/or consistency of stools (3 to greater than 6 episodes of liquid stools/24 hour period) to a complex, 3 phase diarrheal assessment (Brown et al., 2012; Fuchs, 2011; Horn & Chaboyer, 2003; Lee & Auyeung, 2003). Consequently, diarrhea was not used as a measure of feeding intolerance in this study, nor defined by current PICU nutrition support guidelines (Mehta, Compher, et al., 2009). The goal of nutrition in the PICU population is to reach target energy and protein nutrition with the assumption that these goals will meet the metabolic needs of the critically ill patient.

Abdominal pain. Abdominal pain has been associated with feeding intolerance in the adult population. This indicator is more difficult to assess and measure in the PICU because of patient age, state of acute illness, intubation, and concomitant sedation.

Because of these factors, measurement of this variable will be excluded in this study (Fuchs, 2011; Weckwerth, 2004).

Summary. Clinical markers of feeding intolerance include emesis, GRV, abdominal girth, diarrhea and abdominal pain. To date, no marker is predictive of increased risk of aspiration, pulmonary worsening or gut injury. There remains variability in practice for determining feeding intolerance. The adult literature has done little to inform pediatric best practices to limit feeding intolerance. Clinicians must also consider the underlying illness and co-morbidities e.g., pancreatitis, abdominal trauma, hepatosplenomegaly, or superior mesenteric artery syndrome, when defining feeding goals (Donnelly & Paterson, 2000; Smith & Garcia, 2011; Urban et al., 1994). The contribution of this study to the body of evidence is to evaluate signs and symptoms of feeding intolerance comparing two modes of feeding.

Feeding Interruptions

Interruptions are a significant barrier to delivery of target nutritional intake. Interruptions are categorized as avoidable and unavoidable (McClave et al., 1999; Mehta et al., 2010; Rogers, Gilbertson, Heine, & Henning, 2003; Taylor, Preedy, Baker, & Grimble, 2003). Avoidable interruptions may be safely eliminated or shortened by adherence to protocols. Examples are NPO for a procedure exceeding the minimum required time frame, or cessation of feeds for invalid markers of feeding intolerance. Examples of unavoidable interruptions are those mandated by procedures, such as extubation, or surgery.

Evidence of interruptions was obtained from two adult studies. In a prospective observational study of 59 consecutive adult patients on mechanical ventilation who

received EN, all feeding steps related to feeding were documented from admission to discharge. Two important findings from this study were: only 50% of subjects reached goal caloric nutrition, and EN was interrupted 27.3% of available feeding time. Most common causes for interruptions were problems with small bore feeding tubes (25.5%) and increased GRV (13.3%). Being able to identify the cause of interruptions is important when defining protocols in order to limit the frequency and duration of avoidable interruptions to ensure reaching targeted nutritional goals (O'Meara et al., 2008).

In a second study comparing nutritional intake to prescribed goals in adult ICU patients on mechanical ventilation (n = 60), most patients were underfed (68%). Based on indirect calorimetry or estimated by using energy equations, 38% of subjects received less than 50% of their prescribed nutrition. Feeding interruptions due to ICU tests and procedures accounted for the greatest amount of lost nutrition. A significant limitation of this study was that measurements began after target EN rates had been reached. Thus, evaluation of interruptions during the period after initiation of EN, when intolerance is most likely to occur was not assessed (O'Leary-Kelley et al., 2005). This research began data collection at the onset of EN and took into account the frequency and duration of feeding interruptions, noting whether they are avoidable or unavoidable when two delivery modes, continuous vs. bolus are compared.

In pediatric ICU patients, Mehta et al. (2010) recorded daily nutritional intake and monitored interruptions over a 28-day period (n = 88). Time to reach caloric goal, use of parenteral nutrition and clinical characteristics between patients with and without avoidable interruptions were recorded. Interruptions were classified by a multidisciplinary team as avoidable if they fell outside of institutional nutrition guidelines

for stoppage of feeds. Over half of feeding interruption events were deemed avoidable (58%). Subjects with avoidable interruptions were three times more likely to receive parenteral nutrition. For subjects receiving EN, feeding intolerance was the most common reason for interruption. In 48% of the cases deemed avoidable, best practice was not followed. An important conclusion is standardization of protocols is an important approach to minimize feeding interruptions (Mehta et al., 2010).

Controlling avoidable feeding interruptions is essential to meeting the energy and protein needs of critically ill children. The A.S.P.E.N. guidelines for nutrition support in critically ill children note the need for identification and prevention of avoidable interruptions (Mehta, Compher, et al., 2009). Standardizing criteria to minimize feeding interruptions has been echoed by other investigators and clinicians for the pediatric hospitalized patient (Corkins et al., 2013; Kyle et al., 2012). While consensus is strong, avoidable interruptions remain a problem. Efforts toward quality improvement within units are needed to ensure the implementation of best practices. This research provides for the classification of interruptions as avoidable/unavoidable, along with a measure of the frequency and duration of these events. Increased awareness by all health team members to avoid feeding interruptions will have a role in the recovery of critically ill children.

Lack of Evidence Based Feeding Protocols

The use of feeding protocols frequently involves standardization of advancing feeds, identification of intolerance and actions to take in the event of intolerance e.g., rate, volume, criteria for advancement and interruption of feeds. Implementation of feeding protocols has been identified as an area of needed study to ensure the delivery of

target feeds (Mehta, Compher, et al., 2009). This section compares studies related to the use of protocols from the adult and pediatric critically ill patient populations. Understanding best practices is necessary to limit hospital acquired malnutrition and contribute to a reduction of intolerance events and outcomes associated with morbidity and mortality. Literature describing the introduction of an EN feeding protocol and its impact on EN delivery and intolerance in both adult and pediatric ICUs is presented as additional to the continuous and bolus protocol studies previously described in this chapter.

Adult ICU feeding protocols. A pre-post study of adult ICU patients evaluating the caloric and protein delivery before (n = 100) and after (n = 103) implementation of a continuous feeding protocol. Percentage of goal intake served as the primary outcome measure. The intervention group demonstrated significant improvement in percent of both caloric (53.9 ± 2.3% vs. 64.5 ± 2.2%, p =.001) and protein intake (56.7± 2.6% vs. 67.4 ± 2.7%, p =.005) compared to the control (non-protocol) group. This difference persisted whether or not the subjects received a prokinetic agent. There were non-significant trends toward decreased GRV and the number of emesis events in the intervention group (Arabi, Haddad, Sakkijha, & Al Shimemeri, 2004). This dissertation compared caloric and protein intake, along with incidence, duration and types of feeding interruptions between bolus and continuous gastric feeding protocols.

A protocol by Petros and Engelmann (2006) increased daily EN by 500 mL/day to a goal of 2000 mL/day. Subjects were adult medical surgical ICU patients who were fed by EN 7 days or longer (n = 61). Outcome variables were energy expenditure measured by indirect calorimetry and delivery of EN with a target of at least 20 kcal/kg/day. In the

event of feeding intolerance, subjects were switched from feeding via the nasogastric route to the nasoduodenal site (22/61; 36.1%). Intolerance was defined as emesis, diarrhea, or elevated GRV (GRV threshold not identified). Despite the use of the post pyloric site when intolerance occurred, the overall daily percent of prescribed volume achieved was 86.2 ± 30.4%. The importance of this study is that patients remained significantly below goal, suggesting volume may not be the best variable to control in a feeding protocol and targeting the concentration of feeds or use of medications to promote motility may be key to meeting energy and protein requirements. Intolerance was also reported to be associated with a higher acuity of illness and mortality rate (Petros & Engelmann, 2006). This finding suggests protocols need to be tailored to meet subpopulation needs of ICU patients, focusing on acuity of illness as a likely variable to address.

A retrospective analysis on 2 cohorts of adult ICU patients, before (n = 56) and after (n = 56) instituting a nutrition algorithm, the mean delivery of nutrition based on energy (pre/post 909 ± 444 vs. 1097 ± 420 kcal/day; p = .023) and protein (35 ± 17.9 vs. 59.1 ± 27.3 grams; p < 0.001) for the intervention group. The cumulative energy deficit decreased from -5664 ± 3613 to -2972 ± 2420 kcal (p = 0.01) for subjects whose ICU length of stay was greater than 7 but less than 14 days. Developed by an interdisciplinary group, the protocol addressed timing of feeding initiation, target energy requirements, advancement of feeds, assessment of intolerance and indications for parenteral nutrition. Inclusion of a dietitian or a designated nutrition support team may have improved nutrition delivery (Kiss et al., 2012).

Pediatric ICU feeding protocols. Infants with complex congenital heart disease are at high risk group for pre-existing malnutrition upon admission to the PICU as well as worsening malnutrition during hospitalization. Investigators compared the use of higher versus normal formula caloric concentration advancement protocols for postoperative infants less than 1 year of age, post-transfer from the PICU to the regular cardiac unit. In subjects receiving the higher calorie formula, the median delivery of target energy prior to discharge was 98% vs. 78% in the group who received the standard formula concentration (p = .01). The rate of weight gain was improved as the intervention group achieved weight gain of 20 grams/day vs. loss of 35 grams/day in the standard group (p < .03) and their length of stay shorter (6 vs. 5 days; p < .05). Reduced LOS and weight gain suggest cautious, conservative feeding approaches in post-cardiac surgery infants may not be necessary, may increase cost of care, and negatively affect outcomes (Pillo-Blocka, Adatia, Sharieff, McCrindle, & Zlotkin, 2004).

Braudis et al. (2009) compared duration of parenteral nutrition (PN), time to achieve prescribed calories and incidence of necrotizing enterocolitis (NEC) for an 18 month period after implementing a continuous NG feeding protocol for infants post-Stage I palliative surgery with hypoplastic left heart syndrome. The median duration of PN (116 hours vs. 51 hours; p = .03) and time to achieve prescribed feeds (13 days vs. 9 days; p = .01) was shorter in the protocol group. There was no incidence of NEC in the protocol group compared to 11% in the control. The researchers concluded early and protocolized advancement of feeds in patients with hypoplastic left heart syndrome is safe and improves the attainment of nutritional goals (Braudis et al., 2009).

A protocol study by Petrillo-Albarano and colleagues (2006) reported a shortened time to achieve goal feeds after implementing a continuous gastric feeding protocol in a PICU (n = 184). Mean achievement of goal feeds in the post protocol group (n = 93) was 57.8 vs. 18.5 hours (p < .0001) compared to the non-protocol group (n = 91). Additionally, a decreased incidence of emesis from 20% to 11% and reduction in the incidence of constipation from 51% to 33% was noted. Neither severity of illness or concomitant therapies, e.g., sedation, analgesia, cardiovascular medications, were factors in this study (Petrillo-Albarano, Pettignano, Asfaw, & Easley, 2006).

Adherence to feeding guidelines was the focus of a British study. The researchers investigated adherence to unit feeding guidelines and whether compliance to guidelines improved nutritional intake in critically ill children (n = 47). This 1-month, prospective observational study reported 47% of subjects had EN initiated within the target first 6 hours of admission and 55% of those subjects received less than 50% of their target feeding requirements in calories. Adherence to feeding guidelines increased the percent of subjects who achieve target energy requirements to 75% vs. 38% (p = .004). Similar to the findings of Petrillo-Albarano et al. (2006), this study highlighted the fact that approximately a quarter of children (19%) admitted were malnourished on admission and the need to nutritionally support this population may be critical to outcome (Tume, Latten, & Darbyshire, 2010). To improve the attainment of energy and protein nutrition, the dissertation study compared two delivery modes to evaluate intolerance events and their effect on the optimal delivery of target energy and protein nutrition on the PICU patient.

A final study examining protocol implementation to reduce practice variability and assess the effectiveness of a continuous gastric feeding protocol to improve energy intake was conducted in PICU patients (n = 96). The outcome variable between pre-protocol (n = 48) and post-protocol group (n = 48) was time to goal feeds, with a secondary outcome variable the incidence of feeding intolerance. No difference was reported in the time to goal feeds between groups. However, for subjects less than 10 kg, a reduction in time to goal feeds was found (74/96 patients, 56.9 $\pm$ 22.7., 70.4 $\pm$ 32.5 hours, respectively, p = .045) (Brown et al., 2012). Feeding intolerance in the control group was not defined, thus eliminating the ability to measure rates of intolerance between groups.

A gap in both adult and pediatric literature exists in relation to defining an optimal feeding protocol. Based on research findings, implementation of a protocolized approach with specified algorithms to achieve target intake, and criteria for managing feeding intolerance, improves both energy and protein delivery. Adherence to feeding guidelines/protocols is needed as consistent implementation of these protocols is essential to reaching targeted nutritional goals. Further examination of the causes of feeding interruptions and elimination of avoidable interruptions is needed. Defining feeding intolerance events and duration of delays in feeding can help define the timeline for deviations from protocol and suggest reasonable time frames to resume feeds. While each child has unique nutritional needs, a protocolized approach will result in earlier goal feeds and minimize avoidable interruptions. Customized feeding protocols for different subpopulations of children may need to be developed with consideration given to the variables of age, primary diagnosis, acuity, nutritional status on admission and response

to enteral feeds. Studies such as the one conducted as part of this dissertation contribute to the growing body of evidence to define an optimal feeding protocol that both enhance EN delivery and minimize incidence of intolerance and feeding interruptions to attain targeted energy and protein nutritional goals.

Summary

This review of the literature presented research findings on the incidence of malnutrition, both as a presenting diagnosis and as a result of cumulative deficits of both protein and energy during PICU admission, as an independent predictor of increased mortality and other morbidities. EN as a therapeutic modality has been demonstrated to reduce mortality and other PICU associated morbidities, such as pressure ulcers and hospital acquired infections (Mehta et al., 2012; Mikhailov et al., 2014; Schindler et al., 2011). While EN via the gastric route is the preferred route of nutritional delivery, many gaps in the literature remain as to the optimal timing, route and tolerance thresholds (Mehta, Compher, et al., 2009). Both adult and pediatric ICU literature, while sparse, suggest no increased risk of pulmonary or GI adverse events when comparing bolus versus continuous gastric feeds. Importantly, some evidence reports improved delivery of target nutrition with bolus feeding methods.

The proposed theory of GI dysmotility in critical illness, which underpins this study, was presented. The increase in SNS activation during critical illness slows GI motility and alters GI sphincter function. Compounded by the effects of common PICU therapies, such as specific medications, immobility and altered feeding state creates a condition ripe for GI dysmotility and subsequent feeding intolerance. The dissertation study added evidence on the effects of bolus versus continuous feeding modes during

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critical illness and the effective delivery of target energy and protein to meet the needs in the PICU population.

Barriers have been identified that limit delivery of prescribed EN, e.g., hemodynamic instability, poorly defined feeding intolerance measures and thresholds, avoidable and unavoidable feeding interruptions and lack of standardized feeding protocols. By evaluating two feeding modes, continuous and bolus, the dissertation study identified the best method for a shortened time to achieve goal feeds in critically ill PICU patients, with a standardized approach to minimize feeding interruptions. In addition, less conservative feeding intolerance thresholds were evaluated between groups to help define best practices to safely deliver prescribed nutrition needed for healing and recovery in the PICU population.

CHAPTER III

STUDY DESIGN AND METHODS

Design

The purpose of this prospective, randomized, comparative effectiveness

intervention study was to compare continuous (CGF) and bolus (BGF) gastric feeding

protocols and their effect on attainment of prescribed nutritional goals and the incidence

and duration of feeding intolerance in mechanically ventilated critically ill children

during the first 96 hours of feeds. There were two aims of this study: 1) to compare two

gastric feeding delivery modes (continuous vs. bolus) on daily delivered/prescribed

energy (kcal/kg/day) ratio and protein (g/kg/day) requirements, and cumulative energy

deficits over 96 hours; and 2) to describe and compare the frequency and type of feeding

intolerance events and feeding interruptions between feeding groups in mechanically

ventilated infants and children. A CGF protocol was the standard feeding approach in the

study unit, the BGF protocol served as the intervention (Brown et al., 2012).

Institutional Review Board Approval and Consent

Approval from the Institutional Review Board (IRB) at the study hospital was

obtained prior to beginning this study, as there is an agreement of reciprocity between the

study hospital and The University of Akron (see Appendix C IRB approval letter and

Appendix D Agreement of Reciprocity).

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Setting/Sample

Subjects were recruited from a 23-bed PICU in a free standing pediatric teaching hospital that has both medical and surgical critically ill infants and children ages newborn to 18 years and beyond. Inclusion criteria for this study were patients: (a) 1 month corrected gestational age through 12 years; (b) mechanically ventilated within the first 24 hours of admission; and (c) with an anticipated duration of mechanical ventilation greater than 48 hours. Exclusion criteria included patients: (a) with a primary diagnosis of acute GI pathology or post-GI surgery; (b) clinically deemed unable to begin enteral nutrition within 48 hours post-admission; or (c) enteral nutrition initiated prior to admission to study PICU. The upper age limit of 12 years was chosen as those 13 years and older are given adult formulas and report energy needs in kcal/day rather than kcal/kg/day (Deborah Carpenter, RD, CNSC, personal communication June 24, 2013).

Eligibility was determined within 24 hours of admission to the PICU by a research team member. Written consent was obtained from the parents or guardians (see Appendix E). Assent was not sought as subjects were under the age of 10 years, critically ill, or mechanically ventilated and sedated, rendering them cognitively incapable of providing assent. The parent or legal guardian was informed of their right to withdraw from the study at any time. The Authorization for Research is provided in Appendix F. Appendix G provides the Health Care Portability and Accountability Act (HIPAA) forms.

An effect size was not identified in the literature for the primary outcomes of attainment of prescribed nutritional intake. Based on the principal investigator's (PI) original research on continuous gastric feeding, an effect size of 0.15 was used for this study (Brown et al., 2012). An *a priori* power analysis based on a power of 0.80, alpha ≤

0.05, effect size of 0.15 and anticipated minimum of 33 measurements of the feeding

intake and intolerance indicators, using Hierarchical Linear Modeling, a sample size of

30 subjects was needed per group for a total sample size of 60 subjects. The remaining

hypotheses were evaluated via independent t-tests and with an effect size of 0.5, a power

of 0.80, and alpha ≤ 0.05, 50 subjects in each group were needed. However, given the

small sample size, Mixed Measures RM-ANOVA was used for the repeated measures

data.

Procedure

      Training. Following IRB approval, training of the research team and PICU staff

began. Staff training focused on the study goals, recruitment of subjects with emphasis on

eligibility criteria, description of the protocols for the two arms of the study, and

reliability considerations for data collection. As an unblinded comparative effectiveness

study, the staff was asked not to share personal opinions with subjects and families

regarding the two feeding protocols. Targeted groups for training included the PICU

intensivists, Advanced Practice Registered Nurses, PICU Clinical Coordinators, PICU

and Float nursing staff, and Respiratory Therapists.

      A poster describing the role of the bedside nurse in data collection was posted in

the staff work area of the PICU. This poster remained on display throughout the data

collection period. A sample study packet for the continuous and bolus fed group which

contains the applicable protocol, sample completed data collection forms, and PI contact

information, was placed near the poster.

      Screening and reporting procedures. Subject eligibility, screening, consent,

study completion and data analysis was recorded and reported via CONSORT guidelines

(Schulz, Altman, & Moher, 2010). Eligibility was determined within 24 hours of admission by the PI or a research team member using the Screening and Eligibility Tool (see Appendix H). Parents or legal guardians of eligible patients were then approached to obtain consent. If consent was obtained, the subject data were entered on the Consent and Enrollment Form (see Appendix I) and a study identification (ID) number assigned. Subjects were randomly assigned to study groups in permutated blocks of six via a computer generated randomization program. Sealed envelopes with the random group assignment enclosed were selected according to the study ID number on the envelope. Enrollment commenced October 14, 2013 and continued through April 15, 2014.

A study notebook with the assigned study number on all collection sheets was placed at the bedside post-enrollment. Each folder contained protocol algorithms, feeding data collection forms, mock completed data forms, medication collection forms, contact information for the PI/research team and a study procedure information sheets. The notebook was collected and discarded after the study period was completed.

Time zero began when feedings were initiated. Initial and subsequent assessments were documented by the bedside nurse every 3 hours (3, 6, 9,…96) etc. If the initial feeding was started less than 30 minutes after the hour, the next data collection/feeding time commenced 3 hours from the prior whole hour. If the time the initial feeding was greater than or equal to 30 minutes after the hour, the next data collection/feeding time commenced 3 hours from the next hour. For example, if feeds began at 1715, the next data collection/feeding time was 2000; if feeds started at 1745, the next data collection/feeding time was 2100. Events altering the delivery of feedings, e.g., avoidable

and unavoidable interruptions were noted on the data collection form and time was adjusted to maintain 3-hour intervals for data collection/feeding.

Feeding Protocols. Initiation of feeds was at the discretion of the PICU care team. Team members include PICU intensivists, nurse practitioners, staff nurses and dietitians. This study did not prescribe the time feeds are initiated. Any patient not ordered feeds within 48 hours of admission became ineligible for the inclusion in the study.

If not already present, a nasogastric (NG) tube was inserted by the bedside nurse and radiographic confirmation of gastric placement was obtained prior to initiating feeds per standard PICU procedure. Initial formula orders were prescribed by the intensivist or nurse practitioner. A registered dietitian was consulted within 24 hours of the initiation of feeds to provide the prescribed energy and protein intake in kcal/kg/day and grams/kg/day, respectively, along with specific recommendations of the formula, volume, concentration and any needed supplements to attain the prescribed nutritional intake. Recommendations for energy and protein intake were derived utilizing Schofield's equation, which included modifications for stress and level of activity.

A standard protocol was used for both the gastric and bolus fed groups for advancing, holding and/or altering the rate of feeds (see Appendix J- continuous feeding protocol; Appendix K- bolus feeding protocol). Included within these protocols were prn medications for constipation (no stool passed for > 24 hours) and provider notification to add a prokinetic agent (metoclopramide) if a second feeding intolerance event occurred. All components of the protocols were the same except the mode of delivery, continuous or bolus as the independent variable from usual care provided by the PICU Care Team.

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For both groups, formula was delivered using either the Smith Medical Syringe Pump (Model 3500, Dublin, OH) or Zevex Enteralite Infinity pump (Moog, Inc., Salt Lake City, UT) as normally used in the PICU.

Continuous feeding. For subjects < 25 kg, feeds were started at 1 mL/kg/hr, then increased by 1 mL/kg/hour every 3 hours to the prescribed goal rate. For subjects ≥ 25 kg feeds were initiated at 25 mL/hr and increased by 25 mL/hr every 3 hours until prescribed goal volume was reached. After goal volume was reached, caloric concentration (kcal/ounce) and/or protein supplementation was increased every 12 hours until reaching the prescribed daily energy and protein goals (See Appendix J).

Bolus feeding. For subjects weighing < 25 kg, feeds were started at 3 mL/kg. For subjects weighing ≥ 25 kg feeds were initiated at 75mL. The feeding volume was increased by 3mL/kg or 75mL every 3 hours to the deliver the prescribed daily volume. Feeds were infused over 60 minutes by feeding pump at 3-hour intervals from the time the feed was initiated. After goal volume was reached caloric concentration (kcal/ounce) and/or protein supplementation was increased every 12 hours until the prescribed daily energy and protein requirements was reached (see Appendix K).

Feeding intolerance criteria. Feeding intolerance was defined in three ways: 1) any incidence of emesis (regardless of volume), noting whether associated with suctioning or a tussive (coughing) event as a yes/no or; 2) gastric residual volume (GRV) ≥ 50% of the infused volume for the previous 3 hours x 2 measurements (measured via manual aspiration of NG tube via syringe); and 3) GRV ≥ 50% infused in last 3 hours x 1 measurement <u>and</u> abdominal girth > 10% above baseline for the current 24-hour feeding period (measured over the umbilicus in cm with a tape measure). Episodes of intolerance

were documented on the feeding data collection form at the time of occurrence (See Appendix L for Continuous Feeding Data Collection Form and Appendix M for Bolus Feeding Data Collection Form). Tolerance of prescribed feeding was defined as no incidence of feeding intolerance for $\geq$ 12 hours after achieving prescribed nutritional intake.

   Feeding interruptions. Feeding interruptions were documented on the data collection form by the bedside nurse recording a stop and resume time. Time in hours was calculated by the research team and entered for analysis. When a feeding interruption occurred, the nurse documented the reason(s) the feeding was interrupted by category: intolerance, PICU therapies (e.g., planned extubation), general care procedures (e.g., repositioning, transfer), or other with an accompanying description of why the feed was halted.

   Oxygenation saturation index (OSI). The oxygenation saturation index was calculated every three hours by the bedside nurse as part of the ongoing assessment and entered on the feeding data collection form (Thomas et al., 2010). The OSI was calculated by multiplying the fraction of inspired oxygen (F_iO_2) x mean airway pressure (MAWP), then dividing by the arterial oxygenation saturation measure via pulse oximetry (S_pO_2) to achieve a score representing the acuity of acute lung injury. Higher numbers implied clinical worsening.

   Medications. Each subject was monitored daily for the use of commonly prescribed categories of medication in the PICU. Monitored medication groups included neuromuscular blockers, sedatives, opioids, catecholamines, laxatives, prokinetic agents, and gastric acid suppressants (see Appendix N).

Data Management and Protection

Study data were entered into a FileMaker Pro 11 Advanced (Copyright © 1994-2013, FileMaker, Inc) database by the principal investigator (PI) or a member of the research team. The PI reviewed every 10th subject's data for accuracy. The subject's medical record was reviewed to clarify any questions regarding data integrity. In addition, descriptive statistics were calculated after every 10th subject completed to assess for outliers and any unusual data were double checked for validity and data entry accuracy. The original data collection forms linking the subject's name, medical record number and study number were housed in a separate folder and stored in a locked file cabinet in the PI's office. This step was taken to ensure anonymity and confidentiality during the study.

Data were reviewed with a faculty mentor after the first10 subjects to assure data outputs allowed for use of the planned analyses. Data were evaluated for patterns of missing data or the need to revise data collection forms or processes. These data were also used to update members of the healthcare team.

Data Analysis

Demographic and descriptive data. Post-discharge from the PICU, data for each subject were obtained from the Virtual PICU Performance System © (VPS, LLC), a national PICU outcomes database. These VPS data included: age, gender, primary diagnostic category, severity of illness scores (see Table 1 for PIM 2, PRISM 3, and PeLOD score descriptions), PICU length of stay, and duration of mechanical ventilation in hours. In addition to VPS data, hospital length of stay, prescribed nutrition in kcal/kg/day and prescribed protein in g/kg/day was collected on each subject from the

medical record. Enteral nutrition data were collected up to 96 hours after initiation of

feeds. No major data integrity or procedural issues were identified that would interfere

with data integrity, thus the data from all subjects were included in the final analysis.

Table 1

Description of Severity of Illness (SOI) Scores Adapted From the Virtual PICU
Performance System © (VPS, LLC), a National PICU Outcomes Database

SOI Scoring Tool	Purpose	Measures Utilized
Pediatric Index of Mortality-2 (PIM-2)	Predict risk of mortality based on data collected With 1st hour of admission to the PICU. Allows PICUs to evaluate groups of patients or compare groups of patients between PICUs, not to describe individual patients. Is used for risk-adjusted comparisons	Data from multiple body systems, diagnostic group and whether patient is post-operative, especially from cardiac bypass
PRISM-3	Predict risk of mortality based on data collected With 1st 12 hours of admission to the PICU. Allows PICUs to evaluate groups of patients or compare groups of patients between PICUs, not to describe individual patients. Is used for risk-adjusted comparisons	Data from cardiac, respiratory, hematological, neurologic systems and numerous lab values, certain diagnostic group criteria, operative status, transfer from another ICU, need for cardiac massage.
Pediatric Logistic Organ Dysfunction (PeLOD) Score	Uses daily data for up to the first 10 days of the PICU admission to calculate a risk score. A daily score is obtained using the worst values of that day.	Data from cardiovascular, respiratory hematological, neurological, renal and hepatic systems are used along with other factors such as transfer from another ICU.

Descriptive data were analyzed and reported as means ± standard deviation (SD)

using SPSS 22 (SPSS, Inc©, International Business Machines, Inc.). Depending on the

type of missing data, data were imputed with the last known value (Last Value carried

Forward, LVCF). Other missing data were critically assessed for the best imputation

management.

Analysis by hypotheses: 1) a-b The daily 24-hour ratio and 48-hour proportion of delivered/prescribed energy intake and protein intake is higher in a bolus compared to continuous gastric feeding protocol; the prescribed nutrition delivery ratio (defined as delivered kcal/kg/day divided by prescribed kcal/kg/day and delivered grams protein/kg/day divided by prescribed grams/kg/day) was measured each 24-hour feeding period and 48-hour feeding period and compared between groups via independent t-test. Time to attain prescribed feeds for the continuous versus bolus fed group was analyzed via an independent t-test.

2 a) There are fewer feeding intolerance events in a bolus compared to continuous gastric feeding protocol; the number of events in each group by day per every 3 hour measurement utilizing Mixed Measures RM-ANOVA. The total number of feeding intolerance events between groups was analyzed via independent t-test; b) There is a positive relationship between elevated GRV and abdominal distention was evaluated using Mixed Measures RM-ANOVA; the incidence of elevated GRV as a yes/no nominal variable with and without increased abdominal girth as a yes/no nominal variable was analyzed via Chi Square.

3) There is a lower incidence and duration of total and avoidable feeding interruptions in a bolus compared to continuous gastric feeding protocol; the total number of feeding interruptions and avoidable feeding interruptions was measured in each group and analyzed via independent t-test or Chi Square based on number of data points. The time to first feeding intolerance and duration of total and avoidable feeding interruptions was measured in hours in both groups and analyzed via independent t-test.

CHAPTER IV

RESULTS

Data were collected in the study PICU beginning October 14, 2013 through April 15, 2014. A total of 842 patients were admitted to the PICU during this time. The study flowchart in Figure 2 identifies how subjects were screened for inclusion. A total of 28 subjects were enrolled; 25 are included in the final analysis (bolus group n = 11; continuous group n = 14). Subjects were excluded from analysis due to extubation prior to initiation of feeds (n = 1), and lost data (n = 2).

Only six subjects completed at least 90 of the target 96-hour study period, whereas 15 completed at least 40 hours of data collection and were included in the inferential analyses. Table 2 describes the attrition rates, and Table 3 describes the reasons for study attrition by group.

Table 2

Time in Study by Group

Hours Completed	Bolus (n=11)	Continuous (n=14)
96-hours	2	1
48-hours	6	5
< 48 hours	3	8
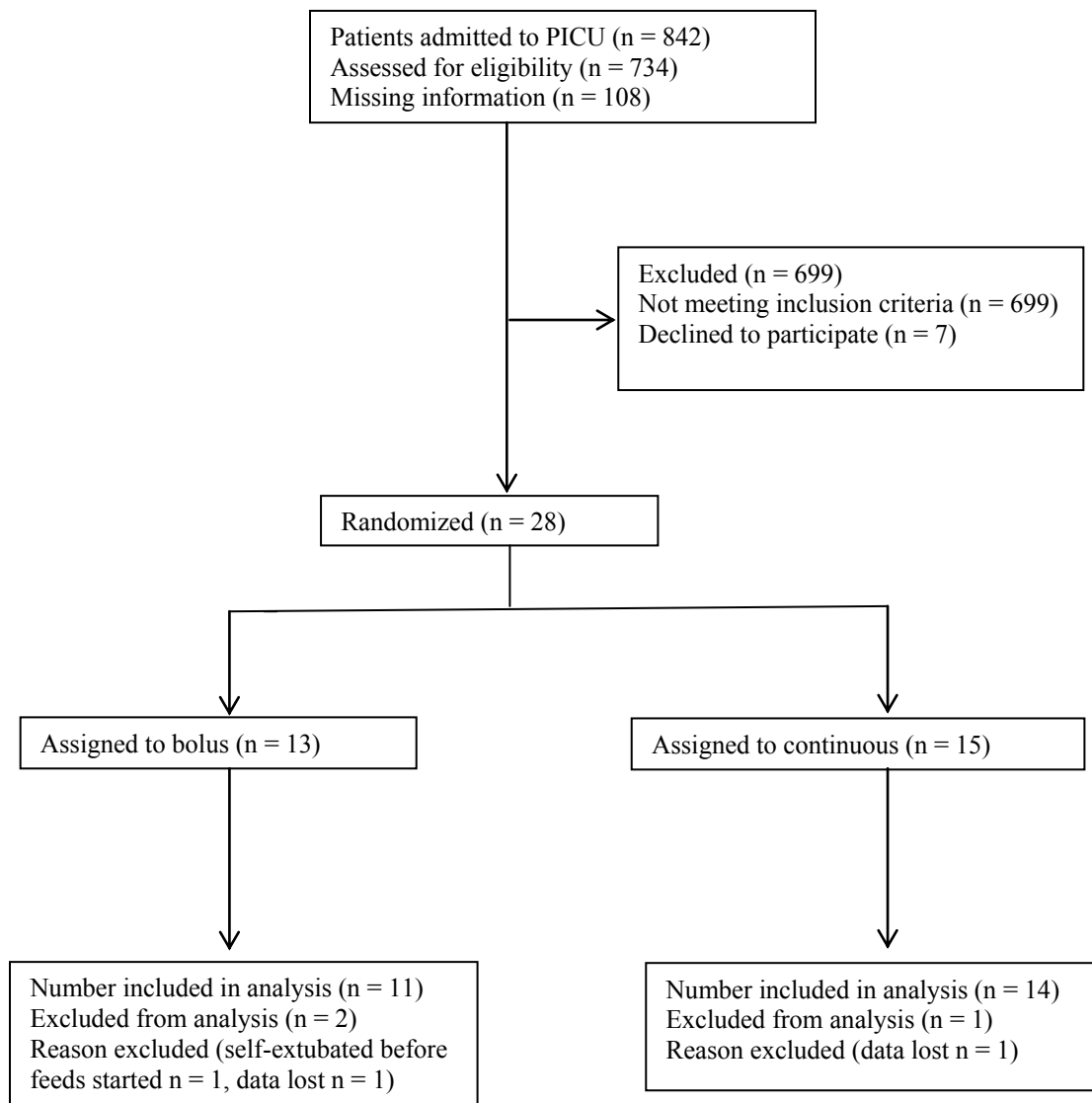
Figure 2. Study flowchart, adapted from Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *J Pharmacol Pharmacother, 1*(2), 100-107.

Table 3

Reasons for Study Attrition by Group

Reason for Attrition	Bolus (n=11)	Continuous (n=14)
Completed Study (≥ 90 hrs)	4	2
Extubated/Procedure	5	8
Feeding Intolerance/ Transition to ND* feeding, Worsening Acuity	2	4

*ND = nasoduodenal feeding

Descriptive analyses were used to characterize the entire study cohort as noted. A higher than expected rate of attrition occurred within the study period, thus only the first 48 hours of data were used for inferential analyses. This approach was used to avoid data imputation, as this would affect conclusion validity.

Sample Characteristics

Descriptive statistics were used to present subject characteristics. Categorical variables are reported as counts and percentages and continuous variables are summarized by their means ± SD. A p value of < .05 was considered significant for all analyses.

The characteristics of the two groups were similar (see Table 4). Subject age ranged from 1 to 80.3 months, with a mean of 12.4 ± 20.2 months (n = 25). The median age was 5 months, suggesting most subjects were infants. The two major diagnostic categories were respiratory [72% (n = 18) and cardiac (20% (n = 5)]. Only 16% of subjects were post-operative (n = 4). The mean duration of mechanical ventilation was 139.4 ± 164.9 hours with a median of 97.6 hours. The mean PICU length of stay (LOS)

was 8.3 ± 5.6 days, with a median of 7.1 days. Hospital LOS was 12.5 ± 9.1 days, with a

median LOS of 10.0 days. No differences were noted between groups in any of the

severity of illness or functional outcome scores; PIM-2, PRISM-3, PeLOD, PCPC or

POPC.

Table 4

Subject Characteristics - Continuous Variables Reported as Mean (±SD; range)

Group		Bolus	Continuous	P
Gender	Male	8 (73%)	8 (57%)	NS
	Female	3 (27%)	6 (43%)	NS
Age: months		15.5 (±20.5; 1.9-72.5)	10.0 (±20.5; 1.0-80.3)	NS
Weight: kg		9.7 (±4.7; 2.9-18.5)	7.2 (±6.5; 2.9-29.0)	NS
Race	African American	4 (36%)	1 (7%)	NS
	Caucasian	7 (64%)	12 (86%)	NS
	Hispanic	0	1 (7%)	NS
Diagnostic Category	Respiratory	10 (91%)	8 (57%)	NS
	Cardiac	0	5 (36%)	NS
	Oncologic	1 (9%)	0	NS
	Neurologic	0	1 (7%)	NS
Post-operative		0	4 (29%)	NS
Admission/Discharge PCPC		1.6 (±1.6; 1-4) no change pre/post	Pre 1.9 (±1.9; 1-4) to post (1.8±1.8)	NS
Admission/Discharge POPC		Pre 1.7 (±1.7;1-4) to post (1.6±1.6)	1.9 (±1.9; 1-4) no change pre/post	NS
PICU LOS days		7.9 (±5.0;2.3-17.0)	8.8 (±6.3;2-24)	NS
Hospital LOS days		13.1 (±8.8; 3-24)	12.1 (±9.6; 3-33)	NS
Duration MV days		5.3 (±3.4; 1.9-12.1)	6.3 (±8.8;1.5-36)	NS
PIM2 Predicted Death Rate		1.5 (±1.5;0.18-3.81)	3.8 (±3.8;0.23-19.1)	NS
PRISM3 Predicted Death Rate		1.3 (±1.3;0.3-3.51)	1.4 (±1.9;0.3-6.19)	NS
PRISM3 Predicted PICU LOS Days		4.5 (±4.5;2.29-6.98)	4.5 (±4.5; 2.0-8.82)	NS
PELOD Day 1 Score (Higher is sicker)		11.9 (±11.9; 2-21)	11.9 (±11.9; 2-22)	NS
PELOD Day 2 Score		11.9 (±11.9; 2-21)	12.5 (±12.5; 2-22)	NS
PELOD Day 3 Score		13.7 (±13.7; 12-21)	13.9 (±13.9; 12-22)	NS
PELOD Day 4 Score		13.7 (±13.7; 12-21)	14.4 (±14.4; 12-22)	NS

PCPC-Pediatric Cerebral Performance Category; POPC-Pediatric Overall Performance Category; LOS-Length of Stay; MV-Mechanical Ventilation; PIM2-Pediatric Index of Mortality 2; PRISM3-Pediatric Risk of Mortality 3; PELOD-Pediatric Logistic Organ Dysfunction Score
NS-no difference between groups (Chi Square for categorical, Levene's test for continuous variables)

Analysis by Hypotheses

The purpose of this comparative effectiveness study was to evaluate two enteral feeding delivery modes, continuous versus bolus, on the attainment of prescribed caloric and protein nutritional goals and the frequency and type of feeding intolerance events in mechanically ventilated infants and children 1 month corrected gestation age through 12 years of age. Data analysis is next presented according to study hypotheses. The hypotheses were:

H_1: The 24-hour and 48-hour cumulative energy deficits will be lower in the bolus compared to continuous feeding group.

H_2: The 24-hour and 48-hour cumulative protein deficits will be lower in the bolus compared to continuous feeding group.

H_3: Bolus fed subjects attain prescribed nutritional intake earlier than subjects in the continuous feeding group.

H_4: Bolus fed subjects have fewer feeding intolerance events compared to the continuous fed group.

H_5: There is a positive relationship between elevated gastric residual volume (GRV) and abdominal girth

H_6: Bolus fed subjects have fewer avoidable/unavoidable feeding interruptions compared to the continuous feed group.

H_7: The duration of avoidable feeding interruptions is shorter in the bolus compared to continuous feed group.

H_8: There is no difference in the OSI or evidence of pulmonary complications between the two feeding modes.

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Delivery of Prescribed Nutritional Intake

H_1: The 24-hour and 48-hour cumulative energy deficits will be lower in the bolus compared to continuous feeding group.

The bolus group achieved significantly higher energy intake at 24 hours than the continuous group (p = .001). This finding did not hold true for 48 hours where no statistical difference in mean energy delivery was found (p = .190). Approximately 2/3 of target energy intake was delivered for the bolus group whereas only 1/3 energy intake was delivered in those subjects receiving continuous feeds. The mean deficit ± SD for each group was .38 ± .14 and .67 ± .20 for bolus and continuous, respectively. Deficits ranged from 14% to 57% for the bolus group and 41% to 96% for the continuous fed group at 24 hours. Table 5 presents results from the Independent Samples t-test analysis of mean energy intake, measured in kcal/kg/day, at 24 and 48 hours. Figure 3 is a graphical depiction of the group means by time.

Table 5

Difference in 24- and 48-hour Energy Intake in kcal/kg/day

	Levene's Test for Equality of Variances		t-test for Equality of Means		
	F	Sig.	t	df	p
24-Hour kcal/kg/day	1.996	.171	3.943	23	.001*
48-Hour kcal/kg/day	.465	.504	1.361	18	.190

The bolus group received significantly more energy at 24 hours than the continuous group, but not at 48 hrs. *p < .05. There is a clinically significant increase in delivery by the bolus group at 48 hrs.
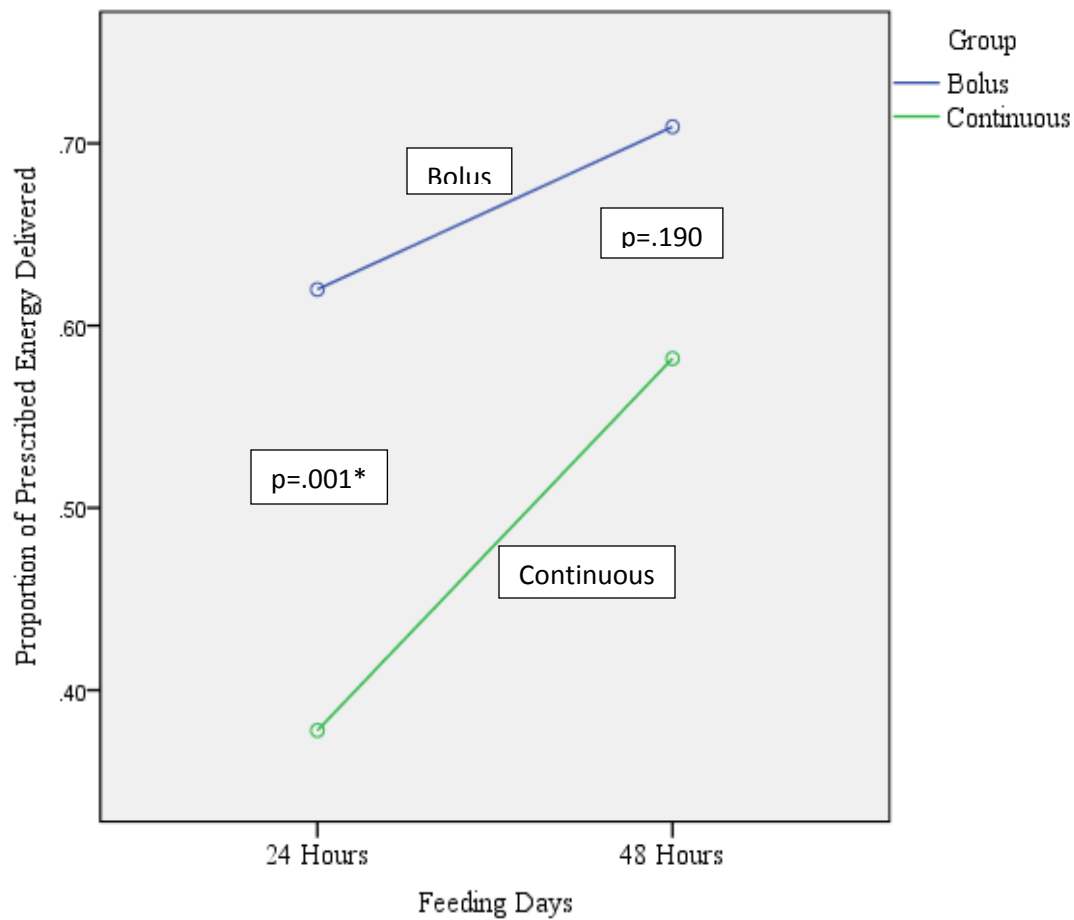
Figure 3. Average proportional intake of prescribed energy in kcal/kg/day at 24 and 48 hours between groups. The bolus more intake at 24 hours, but not 48 hours, but still a clinically significant difference.

H_2: The 24-hour and 48-hour cumulative protein deficits will be lower in the bolus compared to continuous feeding group.

Subjects who were bolus fed achieved significantly higher protein intake at 24 hours than the continuous group (p = .006). No group difference in protein deficit was identified at 48 hours (p = .205). The mean deficit ± SD for each group was .44 ± .13 and .66 ± .21 for bolus and continuous, respectively. Deficits ranged from 16% to 59% for the bolus group and 36% to 96% for the continuous fed group at 24 hours. Table 6 represents

the analysis of mean between group differences in protein intake at 24 and 48 hours.

Figure 4 presents these data graphically.

Table 6

Difference in 24- and 48-hour Protein Intake in grams/kg/day

	Levene's Test for Equality of Variances		t-test for Equality of Means		
	F	Sig.	t	df	P
24-Hour Protein g/kg/day	2.765	.110	3.033	23	.006*
48-Hour Protein g/kg/day	.008	.930	1.315	18	.205

The bolus group received more protein at 24 hours than the continuous group, but this difference was not significant at 48 hours. *p < .05
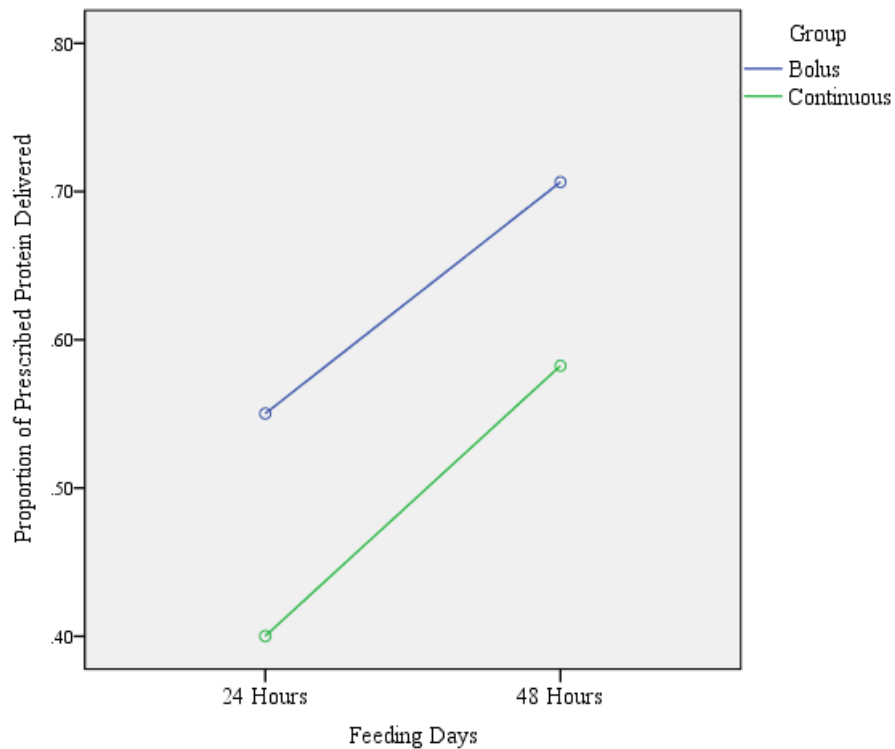
Figure 4. Average proportional intake of prescribed protein in grams/kg/day at 24 and 48 hours between groups. Similar to energy intake, the bolus group was significantly higher at 24, but not 48 hours, but the increased intake is clinically important.

H$_3$: Bolus fed subjects attain prescribed nutritional intake earlier than subjects in the continuous feeding group.

The mode of delivery did not result in a difference in time to goal feeds (hours) between groups as analyzed via Independent Samples t-test (p = .915). The mean ± SD time to goal feed for the bolus group was 34.7 ± 33.0 hours and for the continuous group was 36.3 ± 18.7 hours. For the bolus fed group time to goal feeds ranged from 9.0 to 87 hours and for the continuous fed group 18.0 to 67.5 hours. Of note, data for both groups were positively skewed (see Appendix O, Time to Goal Feeds Descriptives Between Feeding Groups). Thus Independent Sample median times between the bolus group (15 hours) and continuous group (29.5 hours) were analyzed, and were not significant (p = 1.00, see Appendix O, Time to Goal Feeds Descriptives). This may be attributed to study sample attrition resulting in a smaller number of subjects in the 48-hour analysis. The shorter time to goal feeds in the bolus group was positively related to increased energy and protein delivery in the bolus group at both 24 and 48 hours.

Intolerance Events Between Groups

H$_4$: Bolus fed subjects have fewer feeding intolerance events compared to the continuous fed group.

Feeding intolerance events by study protocol were: emesis, elevated GRV x 2, or elevated GRV x 1 and increased abdominal girth > 10% of the daily baseline. Few feeding intolerance events occurred in either group (bolus n = 4; continuous n = 5), excluding protocol violations. A protocol violation is defined as interruption of feeds for a single elevated GRV. This violation occurred because the previous standard of care was to hold feeds for a single elevated GRV. Emesis was the only intolerance event recorded

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in the bolus group, whereas all three types of intolerance events occurred in the continuous group (see Table 9, Avoidable and Unavoidable Feeding Interruptions by Group). Emesis events in both groups were associated with coughing or suctioning. No spontaneous emesis events occurred in subjects in either group.

While not intolerance according to study criteria, one subject in the bolus group and two in the continuous group had feeds halted or transitioned to post-pyloric feeding by the study unit clinical team due to worsened acuity. While the number of subjects is small, the incidence of intolerance events between bolus and continuous feeding groups was low.

H_5: There is a positive relationship between elevated gastric residual volume (GRV) and abdominal girth.

Only one subject in the study sample had a single increased abdominal girth greater than 10% over the baseline measurement. This girth was associated with an elevated GRV greater than 50% of the volume infused in the last three hours. For this subject feeds were held according to protocol. No other subject experienced an elevated abdominal girth. Thus there was no relationship between abdominal girth and GRV.

All five recorded emesis events (bolus n = 4, continuous n = 1) were associated with suctioning or coughing. Emesis events had no relationship to increased GRV for four subjects. One subject, in the continuous group, did have a single elevated GRV recorded both before and after the emesis occurred. No relationship was identified between emesis and GRV, as defined by this study protocol.

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Feeding Interruptions

H_6: Bolus fed subjects have fewer avoidable/unavoidable feeding interruptions compared to the continuous feed group.

Feeding interruptions were identified as avoidable and unavoidable in both groups. Both types of interruptions were included since both impede delivery of target nutritional intake. Overall there were 10 interruptions in the bolus group compared to 15 in the continuous group. Some subjects experienced no interruptions and others had multiple interruptions, up to three or four. Four subjects in the bolus group (n = 11) and seven subjects in the continuous feed group (n = 15) experienced at least one interruption, excluding protocol violations. Extubation, while causing cessation of feeds, was not considered an interruption as it defined the end of the study period. Only feeding stoppages where resumption of feeds was possible under study criteria were considered an interruption. Table 7 presents a summary of the number and type of interruptions by group. In addition, feeding interruptions were examined for each 24-hour study period. These data are presented in Table 8 and excludes avoidable interruptions. Most feeding interruptions occurred during the first 48 hours. The high study attrition rate on days 3 and 4 of feeding limit statistical conclusions and thus statements made are anecdotal.

Table 7

Avoidable and Unavoidable Feeding Interruptions by Group

	Reason Feeds Held	Interrupt 1	Interrupt 2	Interrupt 3	Interrupt 4
Bolus n=11					
Unavoidable	Intolerance				
	Emesis	2	2		
	Elevated GRVx2				
	Elev GRVx1+Inc AG				
	Procedures	1	1		
	Other*	1			1
Avoidable	Elevated GRV x1	1		1	
	Total Interruptions	5	3	1	1
Continuous n=14					
Unavoidable	Intolerance				
	Emesis	1			
	Elevated GRVx2	2	1		
	Elev GRVx1+Inc AG	1			
	Procedures	1	1	1	
	Other*	2		1	
Avoidable	Elevated GRV x1	2	2		
	Total Interruptions	9	4	2	0

GRV-gastric residual volume; AG-abdominal girth
*Held due to increased acuity/severity of illness, or transition from nasogastric to post-pyloric feeds.
There were few interruptions or intolerance events in either group. The only avoidable interruption recorded in both groups were feedings held for a single elevated GRV, which reflects the study unit's standard feeding protocol.

Table 8

Feeding Interruptions by 24-Hour Feeding Periods

	Reason Feeds Held	24 Hrs	48 Hrs	72 Hrs	96 Hrs
Bolus n=11					
Unavoidable	Intolerance				
	Emesis	2	1		
	Elevated GRVx2		1		
	Elevated GRVx1+Inc AG				
	Procedures	1		1	
	Other*		1		1
	Total Interruptions	3	3	1	1
Continuous n=14					
Unavoidable	Intolerance				
	Emesis	1			
	Elevated GRVx2	2	1		
	Elevated GRVx1+Inc AG	1			
	Procedures		2		1
	Other*	1	1	1	
	Total Interruptions	5	4	1	1

GRV-gastric residual volume; AG-abdominal girth
*Held due to increased acuity/severity of illness, or transitioned from nasogastric to post-pyloric feeds. Incidents of protocol violations are excluded.
Most interruptions and intolerance events occurred in the first 48 hours. Given the attrition rate, it cannot be determined if this would stand with a larger sample size.

H_7: The duration of avoidable feeding interruptions is shorter in the bolus compared to continuous feed group.

Table 9 presents the Independent Samples t-test analyses demonstrating no difference between groups in either the time to first interruptions ($p = .623$) or the number of hours feeds were held between groups ($p = .777$). The average time to first feeding

interruption in the bolus group was 24.1 ± 18.5 hours (n = 5), whereas the average time to first feeding interruption in the continuous group was 16.8 ± 15.0 hours (n = 9).

Table 9

Comparison of Mean Time to First Feeding Interruption and Mean Duration of Feeding Interruptions Between Groups

	Levene's Test for Equality of Variances		t-test for Equality of Means		
	F	Sig.	t	df	p
Mean Time to 1st Interruption	.940	.351	-.505	12	.623
Mean Hours Feeds Held	.472	.505	.289	12	.777

Avoidable interruptions. The only avoidable interruptions noted were those for feeding protocol violations (holding feeds for an elevated GRV x 1 episode), which were identified in both groups (bolus n = 2; continuous n = 4). The total number of interruptions remained similar in the bolus (n = 8) and the continuous group (n = 11) after excluding protocol violations.

Unavoidable interruptions. Unavoidable interruptions included feeding intolerance as defined by the study protocols, or PICU procedures, such as surgery or a diagnostic test requiring NPO status. In addition, subjects in both the bolus (n = 1) and continuous (n = 2) groups had feeds halted and/or changed to postpyloric feeding by the study PICU clinical team. These were included as unavoidable interruptions. NPO status in preparation for extubation was not included as subjects no longer met study criteria.

The mean (±SD) duration of feeding cessation in the bolus group was 4.58 (±6.89) hours compared to 3.67 (±4.93) hours for the continuous group and was not significant via Independent Samples T-test (p = .505). The mean duration for subjects

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experiencing up to two interruptions is displayed in Figure 5. The mean (±SD) time to the

first occurrence of feeding interruptions in the bolus group was 14.25 (±12.16) hours

compared to 18.12 (±15.46) hours for the continuous group and was not significant via

Independent Samples t-test (p = .351). Figure 6 then presents the mean time from

initiation of feeds to each interruption by group. All interruptions, including protocol

violations are included in these two charts, given that each impacted the delivery of target

energy and protein.

Duration of Feeding Interruptions

Mean ± SD
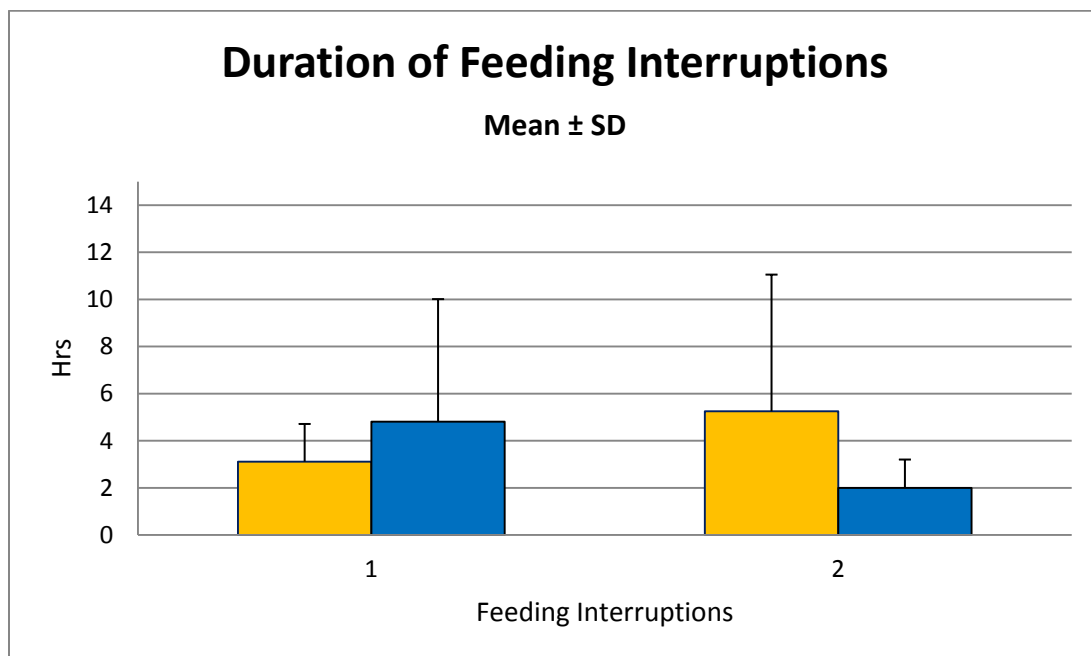
Figure 5. Duration of first and second feeding interruptions by group. There was no difference in overall duration of interruptions between group (p = .351). While the duration was shorter in the bolus group for first interruptions, for those who experienced a second interruption, the duration was longer in the continuous group.
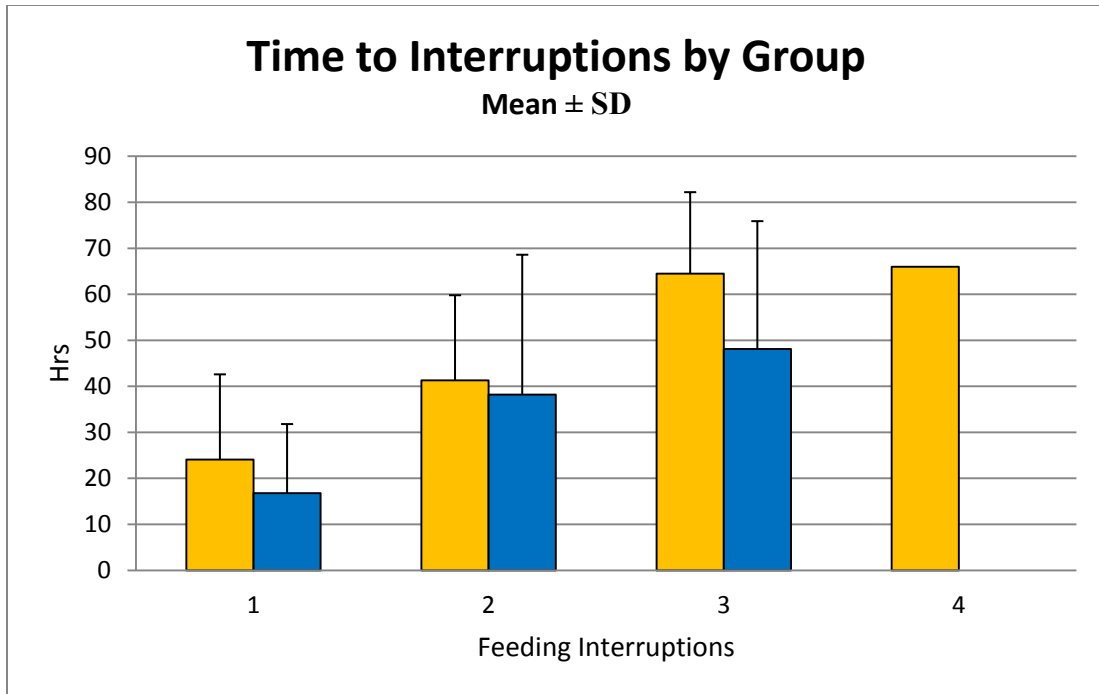
Figure 6. Time to each feeding interruption event by study group. Although not statistically significant, there was a longer time to each feeding interruption in the bolus group, allowing increased delivery of feeds.

Pulmonary Complications/Oxygen Saturation Index

H_8: There is no difference in the OSI or evidence of pulmonary complications between the two feeding modes.

No aspiration pneumonitis was noted in either group. The OSI was calculated by multiplying the fraction of inspired oxygen (F_iO_2) x mean airway pressure (MAWP), then dividing by the arterial oxygenation saturation measured via pulse oximetry (S_pO_2) to achieve a score representing the acuity of lung injury. Higher numbers implied clinical worsening.

The mean OSI for the sample on day one was 4.4 ± 2.11, with a range of $1.7 - 9.5$; the mean OSI on day 2 was 4.0 ± 1.87, range $1.6 - 8.0$. Table 10 presents the average OSI between groups by day. The OSI was monitored in both groups as a marker of acute

lung injury over the course of each subject's study duration. Figure 7 presents the mean

OSI scores by group for up to 48 hours, or 16 time points. Seventy-three percent (8/11)

subjects in the bolus group completed 16 time points versus 50% (7/14) in the continuous

group completed 16 time points.

Table 10

Average OSI Between Groups by Day

	Bolus			Continuous	
	Day 1	Day 2	Day 1	Day 2	
OSI Mean±SC	4.2±2.19	4.0±1.96	4.5±2.03	4.1±1/76	
(range)	(1.7 – 5.1)	(1.6 – 8.0)	(2.2 – 9.2)	(1.8 – 7.6)	

As anticipated, as most subjects' health improved from interventions in the PICU,

the scores for both groups decreased similarly over time. Analysis by RM-ANOVA

demonstrated no difference between groups (p = .866).
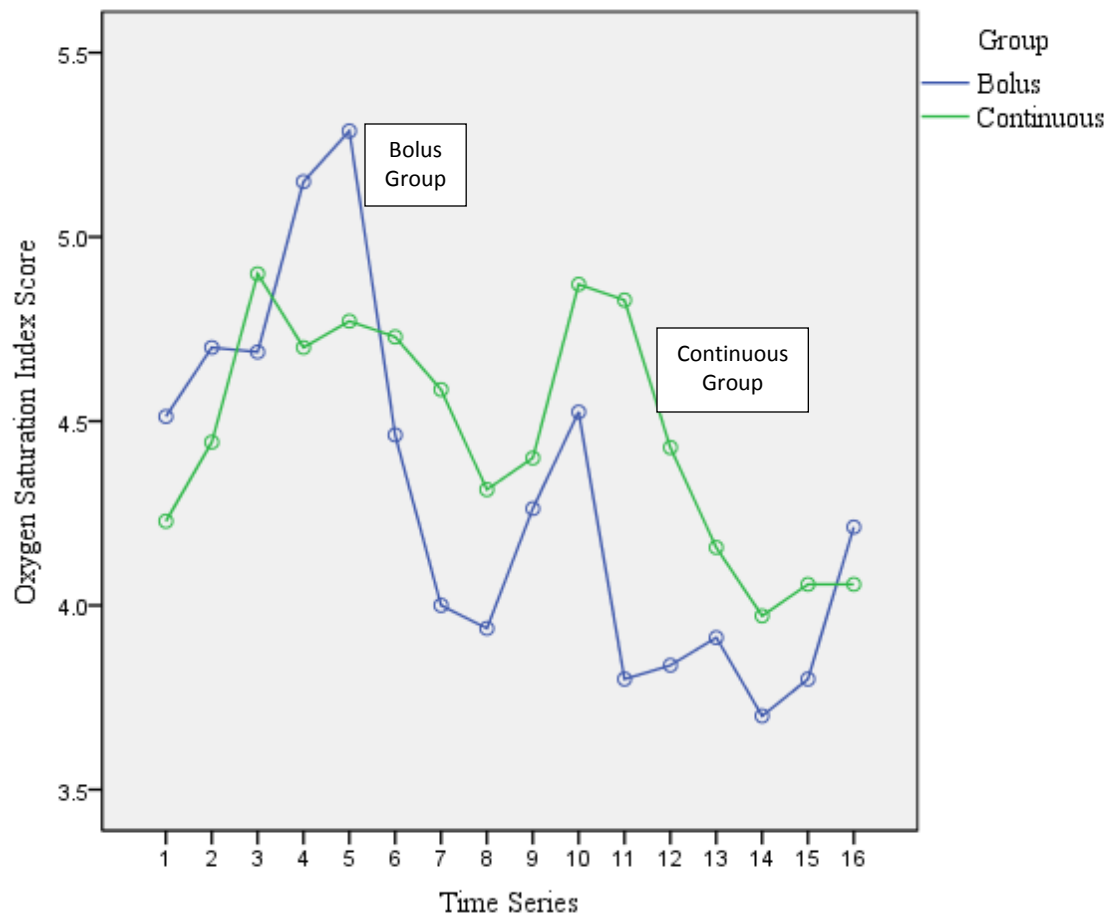
Figure 7. Mean OSI over time by group.
OSI between groups – there was no difference between groups (p=0.866) in this repeated measures analysis (sphericity assumed).

Medication Administration

Medication data are reported in a categorical fashion. Only medications administered, versus ordered and not administered, were reported in this study.

Medication use by group is presented in Table 11.

Table 11

Administration of Medications Between Groups by Day

Medication Category	Group	Day			
		1	2	3	4
Neuromuscular Blocker	Bolus	4	5	6	4
	Continuous	8	4	3	1
Sedatives	Bolus	11	10	8	6
	Continuous	14	10	6	4
Opiates	Bolus	6	6	7	6
	Continuous	7	7	4	3
Catecholamines	Bolus	0	0	0	0
	Continuous	3	3	1	0
Prokinetic Agents	Bolus	0	2	2	1
	Continuous	1	2	1	0
Laxatives	Bolus	3	3	5	3
	Continuous	3	4	3	2
Gastric Acid Suppressants	Bolus	5	2	1	1
	Continuous	6	3	1	1

Number of subjects in each group who received at least one dose in that medication category. The 2 groups were similar except increased used of neuromuscular blockade in the bolus group and catecholamines were only administered in the continuous group.

The two groups were similar in the administration of sedatives, opiates, prokinetic

agents, laxatives, and gastric acid suppressants. Increased use of neuromuscular blockade

on Days 1 and 2 was noted in the bolus group which coincided with a higher OSI score on Days 1 and 2, although not statistically significant. Catecholamine use was observed only in subjects in the continuous group, particularly those with a primary cardiac diagnosis. Table 12 presents medication administration by day for the two highest dosing categories for neuromuscular blockade, sedatives, opiates, and catecholamines.

Table 12

Subjects Receiving Infusion or Infusion + Intermittent Dosing by Days

		Bolus				Continuous		
Medication Category	Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Day 4
Neuromuscular Blockade	3	4	5	2	8	4	2	1
Sedatives	11	10	8	6	13	9	6	4
Opiates	6	6	6	6	7	7	4	3
Catecholamines	0	0	0	0	3	3	1	0

Summary of Findings

The sample in this study consisted of 25 subjects randomized to two groups, 11 in the bolus group, and 14 in the continuous feeding group. The two groups were homogeneous with respect to all recorded subject characteristics. Of particular import to study outcomes was the equivalence in severity of illness scores, diagnostic groups, and duration of mechanical ventilation. Aspiration pneumonitis was not recorded in either group. OSI scores between groups were similar.

The bolus group demonstrated improved delivery of both prescribed energy and protein at 24-hours post-initiation of feeding. The mean delivery of energy and protein intake remained higher in the bolus group at 48 hours, but was not statistically

significant. The mean time to delivery of prescribed feeds, or zero energy deficit, did not differ between groups. However, the data were skewed. When comparing median times to achieve goal feeds, the bolus group attained goal feeds 15 hours earlier than the continuous group. While not statistically significant, this is a clinically significant finding and further study to identify the relationship between groups in the time to achieve goal feeds is necessary.

The number of interruptions, time to first interruption and duration of feeding interruptions between groups was similar. The only avoidable feeding interruptions identified in either group were related to violations in protocol, e.g., feedings were held after a single elevated GRV event. Unavoidable interruptions fell under two categories: feeding intolerance events and feeds held under the direction of the study unit clinical team. The rationale for these latter interruptions was perceived worsened acuity and/or perceived increased risk of intolerance or adverse events.

There were few intolerance events in either group, with emesis being the most frequent event. All emesis events in both groups were associated with coughing or suctioning; none were spontaneous. Thus no emesis event could be directly attributed to feeding intolerance. No relationship was identified between elevated GRV, increasing abdominal girths, or emesis events.

Both feeding approaches, bolus and continuous, demonstrated an excellent safety profile. Bolus feeding attained goal feeding faster and increased delivery of target energy and protein intake in the first 24 and 48-hours of feeding.

CHAPTER V

DISCUSSION

The purpose of this comparative effectiveness study was to evaluate two feeding methods, bolus and continuous, in mechanically ventilated children for three primary outcomes: delivery of prescribed feeds, incidence and types of feeding interruptions, and types of feeding intolerance events. In addition, any difference in respiratory course and adverse events between groups was evaluated. This chapter is divided into three main sections: review and discussion of the main study findings, recommendations for future research, and implications for clinical practice.

Group Characteristics and Pulmonary Complications

This study proposed a 96-hour feeding measurement and data collection period for each subject. Upon examination of the study unit population, two primary events accounted for the lower sample size. The first reason for the lower than expected sample size was the increased use of non-invasive ventilation in pediatric patients with respiratory failure. This study evaluated bolus and continuous gastric feeding methods in intubated and mechanically ventilated patients; thus the pool of eligible subjects was significantly diminished for the study proposal. Additionally, the rate of early exit from

the study was explained by early extubation and some subjects did not make the required minimum of 48 hours.

The second cause of low enrollment was the criterion that subjects must be one-month corrected gestational age. During development of the study proposal, the study PICU outcomes database (VPS, LLC) was queried. Based on the query, it was projected an adequate numbers of subjects would meet the study eligibility requirements in a single "respiratory season". However, VPS records only chronologic age, and not corrected gestational age. Over the course of study data collection, it became clear there were a significant number of patients admitted to the PICU who are one-month chronologic age, but not yet one-month corrected gestational age, thus excluding at minimum, 20 subjects from the study. Corrected gestational age has not been used historically in the literature to define the PICU infant population. However, this researcher felt it was important to consider corrected gestational age because maturity of the ANS and GI system may be a confounding factor when evaluating delivery mode related to the framework of GI dysmotility.

The two groups were statistically similar on all study characteristics. The study period was selected to obtain the majority of patients who would be mechanically ventilated. While the proportion of cardiac patients in the study PICU is higher, only five were included as many were not fed within the requisite 48-hours of admission. Five subjects had a primary cardiac diagnosis, with the majority of these subjects being post-operative (n = 4). Despite randomized, these subjects were enrolled in the continuous feed group. In addition, these four subjects received catecholamines to support blood

pressure and two of these subjects experienced an intolerance event. Four of the five cardiac subjects exited the study due to early extubation and not to intolerance.

The reason for presenting this information on the cardiac subjects is that PICU patients with a primary cardiac diagnosis have been identified as a difficult to feed subpopulation. This group is found to be at high risk to develop a new or exacerbate state of malnutrition while in the PICU (Irving et al., 2013; Larsen, 2012; Larsen et al., 2012; Leong, Field, & Larsen, 2013; Mehta et al., 2013). Consequently, several investigators have conducted studies targeted to improve delivery of nutrition to cardiac patients (Braudis et al., 2009; Khalid et al., 2010; Pillo-Blocka et al., 2004). Further study to compare bolus versus continuous feeding protocols in this subpopulation is needed to evaluate whether the benefits of improved nutrition delivery have an impact on outcome.

The severity of illness scores were similar between groups. The PIM2 and PRISM3 scores are tools used routinely to stratify patients by risk based on data within the first hour of admission in the PICU and first 12 hours of admission in the PICU, respectively. Variation in these scores is often related to the point of entry into the healthcare system. For example, patients may present within hours of symptom onset, or several days post-onset of symptoms. The PeLOD scores which are derived from multi-organ system data on each of the study days were similar between groups. The PeLOD score provides the strongest evidence of homogeneity between groups of all the acuity of illness indicators. The majority of studies in which severity of illness is reported utilize the PIM2 and/or PRISM3. In part the reliance on these two scoring systems by PICU teams may be related to the ease of use of these scoring tools. More recently the PeLOD

has been utilized as it more accurately reflects the patient's course of illness (Raj, Killinger, Gonzalez, & Lopez, 2014).

Delivery of Prescribed Feeds

Based on normal physiological functioning of the gut, the researcher proposed there would be improved gastric motility following a period of non-feeding. For this reason, the directional hypothesis posed cumulative energy and protein deficits would be lower in the bolus compared to the continuous feeding group. This was assessed in two ways: effective delivery of prescribed feeds, and the time to reach the target feeding prescription. Delivery of both energy (62% vs. 34% prescribed kcal/kg/day) and protein (56% vs. 34% prescribed grams/kg/day) was higher in the bolus group in the first 24 hours of feeding. However, at 48 hours, both groups had statistically similar energy and protein delivery. Because of the small sample size, significance may not have been reached because there were fewer subjects in the 48-hour compared to the 24-hour analysis. While not statistically significant, the clinical significance of reaching goal feeding outcomes in the bolus fed group versus continuous fed group (71% vs. 58%) for both prescribed kcal/kg/day and grams/kg/day may affect outcome. Mehta and colleagues (2012) demonstrated reduced mortality when EN delivery was increased from the first to second tertile (33.3% to 66.6%). Mikhailov et al. (2014) reported a significantly lower mortality rate when delivery of 25% of target feeds occurred within the first 48 hours. While both groups achieved the 25% goal feed target, only the bolus group achieved the second tertile for target energy delivery.

The mean time to zero energy deficit was not statistically different between groups. Small sample size may be a key factor for this finding. The data were positively

skewed in both groups. When comparing the median time to goal feeds, the bolus group

achieved zero energy deficit in half the time when compared to the continuous group (15

hours vs. 29.5 hours). This shortened time to goal feeds translated to a higher proportion

of prescribed energy and protein delivered in the first 24 and 48 hours of feeding. In a

population where malnutrition increases risk of mortality and hospital associated

morbidities, this is clinically significant.

Protocols are used to ensure the consistent advancement of feedings to reach

energy and protein goals. In the study unit, the bedside nurses require an order to advance

caloric concentration every 12 hours. In this study the advancement protocol was not

consistently followed and likely resulted in the delayed attainment of target feeds. For

example, the bolus group's range of time to goal feeds was 9-87 hours and 18-67 hours in

the continuous group. Given the growing body of evidence that early delivery of enteral

nutrition conveys a critical protective effect to PICU patient, including reduction in

mortality, these findings are clinically important (Mehta et al., 2012; Mikhailov et al.,

2014; Panchal et al., 2013). The importance of protocol adherence must be emphasized in

order to achieve consistent attainment of target feeds. The use of change theory (Mitchell,

2013) when implementing new protocols is an important consideration in best practice.

Feeding Interruptions

Avoidable and unavoidable feeding interruptions were identified across feeding

groups. Protocol violations were the only avoidable reason for feeding interruptions.

Study protocol varied from the standard unit protocol in which a single elevated GRV

was considered feeding intolerance and dictated feeds be held. However, the study

protocol defined feeding intolerance as two episodes of elevated GRV. Therefore, when

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protocol errors occurred, they were done under the premise of the standard unit protocol. While these interruptions are not considered feeding intolerance, they were included in analysis of time to feeding interruptions and duration of feeding interruptions as they directly impeded delivery of target nutrition. Elimination of avoidable interruptions is necessary to ensure the maximum delivery of target nutritional intake.

Unavoidable interruptions included procedures, such as radiologic studies or surgery. In addition, each group had subjects for whom feeds were interrupted for worsening acuity and/or transition to post-pyloric feeds. However, as these subjects could potentially have had feeds continued, they were included as interruption events.

NPO (nil per os, or nothing by mouth) status in preparation for extubation was not considered an interruption. Extubation indicated the end of time in study. While most interruptions occurred within the first 24 hours, it is difficult to interpret these data and derive conclusions given the high rate of early attrition and small sample size.

The duration of feeding interruptions was hypothesized to be lower in the bolus group. This directional hypothesis was made based on the occurrence of unavoidable feeding interruptions for common PICU procedures which may be conducted within the rest period inherent in the bolus feeding group. A larger sample is needed to further evaluate this hypothesis.

Similarly, no difference in the time from initiation of feeds to the first or subsequent interruptions in the bolus compared to continuous group was found. The mean time to first interruption in the bolus group was 24.1 hours compared to 16.8 hours in the continuous feed group. Given the 3 hour feeding regimen, this time difference allowed the bolus group to receive at least two additional feeds prior to first interruption.

Thus, increased delivery of EN to the bolus feed group was attained, despite the presence of interruptions. With a goal to prevent malnutrition or worsening of pre-existing malnutrition in the PICU population, bolus feeding may be of clinical significance. Further study to evaluate the cost benefit ratio is necessary to support the use of bolus versus continuous feeding.

Feeding Intolerance

There were few feeding intolerance events as defined by the study protocol for either group. It could be argued that feeds halted due to worsening patient condition or changed to post-pyloric by the PICU staff were due to a perceived risk of intolerance or other adverse events. However, these events were not intolerance events as defined by the study protocol. A growing body of evidence supports PICU patients tolerate enteral feeding during vasopressor administration, a critical point in the illness trajectory, and may be of increased benefit to outcome (Mancl & Muzevich, 2013; Panchal et al., 2013). Protocols are intended to define best practice for patient populations; however, individual patient responses dictate the need for clinician appraisal and modification to support each child.

Emesis events in both feeding groups were associated with coughing or suctioning. While this observation does not change the potential risk of aspiration, it suggests these events may not represent actual feeding intolerance. Consequently, the decision must be made regarding how long feeds should be held after emesis associated with coughing or suctioning versus spontaneous emesis. The findings of this study suggest perhaps feeds should be held briefly, e.g., 10-15 minutes, after a coughing/suctioning associated emesis if there are no other signs of respiratory distress.

Conversely, any spontaneous emesis should be treated as intolerance and per protocol feeds held for two hours. A considerable gap in the literature exists regarding the duration feeds should be held in the event of intolerance.

The association between emesis and GRV has not been fully described in relationship to cough or suctioning. Similar to the adult ICU literature regarding feeding intolerance, the findings of this study suggest there is limited if any value to use either GRV or abdominal girth as predictors of emesis, whether spontaneous or coughing associated (Poulard et al., 2010; Reignier et al., 2013). While a larger sample is needed to support or refute this finding, this study contributes to the body of evidence defining feeding intolerance in critically ill children and suggests spontaneous emesis is the single best indicator of feeding intolerance.

This study hypothesized there would be a positive relationship between elevated GRV and increased abdominal girth. Upon examination of the data, a single episode occurred whereby an increased abdominal girth greater than 10% over the baseline measurement for that study day was recorded, and was positively associated with an elevated GRV greater than 50% of the volume infused within the prior 3-hour period. Thus no relationship between GRV and abdominal girth was identified. The implications for practice around these intolerance indicators require further evaluation.

Data related to the categories of medications administered to PICU patients were collected to aid in explaining study findings as they related to GI motility. PICU patients frequently receive sedatives, opiates, catecholamines, prokinetic agents, laxatives, and gastric acid suppressants. These categories of medications were frequently administered to the study sample. The bolus group received the highest dosing regimens of

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neuromuscular blockade (NMB) medications compared to the continuous group. Subjects receiving NMBs had the highest OSI scores in both groups. This finding is consistent with the fact that patients with a high degree of lung disease may require complete control of ventilation for safety and to avoid ventilator induced lung injury and thus receive NMB medications.

Neuromuscular blocking agents affect skeletal muscle. While the bowel is comprised of a preponderance of smooth muscle, anecdotally there is concern neuromuscular blockade adversely affects GI motility. However, it is likely the immobility created by NMB medication administration is the key factor affecting GI motility.

This study utilized the Oxygen Saturation Index (OSI) in repeated measurements in both study groups as a surrogate marker of overall respiratory course as well as an indicator of acute respiratory events. Aspiration of feeds may produce pneumonitis. Neither group showed evidence of aspiration pneumonitis in this study. OSI was chosen as a validated scoring tool that obviates the need for further invasive monitoring, such as placement of an arterial catheter (Thomas et al., 2010). Both feeding methods demonstrated an excellent safety profile in this critically ill, mechanically ventilated population. In summary, there was no increased risk of pulmonary complication whether feeds were delivered via bolus or continuous mode.

Recommendations for Future Research

Both bolus and continuous gastric feeding had an equivalent safety profile when administered to critically ill children in the PICU. In this study, feeding by bolus showed the greatest potential to reach zero energy deficit early and thereby deliver the goal

energy and protein prescription. The small sample size, a major limitation of the study, was related to two reasons: a change in ventilator management therapies toward a use of noninvasive devices and imposing a correction for gestational age as a criteria for inclusion.

The reason for ending this study before sampling goals were reached was to avoid a threat to internal validity, namely history. Each "respiratory season" has its own characteristic viruses and pathologies. Continuing to collect data into the next year may have produced illnesses with different trajectories and complications, thus affecting conclusion validity. Furthermore, emerging noninvasive therapies would have reduced the availability of patients for recruitment and likely those patients who were mechanically ventilated would be sicker.

To adequately evaluate feeding protocols in the PICU population and expand sample size there are two recommendations. First, broaden inclusion criteria to omit correction for gestational age and second, recruit from multiple sites.

The decision to end this study prior to reaching the original sample size was also driven by our observation on the consistent use of protocols. With the unit protocol varying from the study protocol in the area of the definition of feeding intolerance and whether feeds should be held or not, continuing the study may have been disruptive to unit routine. Disruption to routine in fast paced, high stress environments may contribute to safety concerns creating distraction at a time when the nurse needs to be focused on the critical needs of the child. While there were very few missing data points and few errors in implementing protocols, the use of two feeding protocols created an additional workload burden on the staff.

Early on, the staff coined a name for this study, COBO (COntinuous vs. BOlus). Adoption of the name appeared to increase ownership of the study and adherence to study protocol. Future studies would benefit from adoption of acronyms by the staff to increase "ownership" and adherence to protocol.

The inclusion criteria related to correction for gestational age resulted in a significant loss for recruitment. Studies by Mikhailov et al. (2014) and Mehta et al. (2012) used non-age corrected infants. While these children were omitted in the current study for concerns that their physiology would not be sufficiently matured and would interfere with conclusions related to the framework of GI dysmotility of critical illness, one way to manage this would have been to analyze this subset of subjects in relation to "developmentally mature" infants. It will be important to determine whether inclusion of these younger patients yields different results related to the mode of nutritional delivery as this age group of patients comprises a significant portion of the PICU population. Thus, to ensure external validity when making feeding decisions, uncorrected gestational age infants should be included and data analyzed as part of the whole with sufficient numbers to allow for comparisons as a subpopulation.

The incidence of critical illness is lower in children compared to adults. Thus, obtaining an adequate sample size is a common challenge in PICU clinical research necessitating pediatric hospitals to be linked together via nationwide networks. A key recommendation for future research to determine "best practice" as it pertains to gastric enteral feeding is a multi-center replication of the current study. In addition, post-pyloric feeding, often prescribed when there is increased concern for aspiration, should be added

as a third study arm. Further study of the feeding mode and delivery site are needed to evaluate the efficacy of feeding safety in PICU patients.

The growing use of noninvasive ventilation modes requires study for feeding practices. Current feeding practice is highly variable, with no literature to guide nutrition delivery in these children. Noninvasive ventilation is delivered via mask or specialized cannulae and requires gases be delivered under positive pressure. The concern is that these gases will be forced into the stomach, causing distension and increasing the likelihood of spontaneous emesis, a defined condition of feeding intolerance. Designing a feeding study for subjects receiving noninvasive ventilation would provide evidence regarding the safety of feeding this population of patients and assist in defining best feeding practices. For this subgroup the use of abdominal girth measurement may be important when defining feeding intolerance. Likewise this variable could be considered in conjunction with GRV, determining if intolerance should be defined by a single or multiple elevations GRV, and the amount of tolerance for GRV volume. Study considerations in the subpopulation of children receiving noninvasive respiratory support will assist in defining practices for the early and safe delivery of EN.

The literature suggests attaining protein goals despite not attaining energy goals may have a significant impact on outcome (Larsen, 2012). Additional studies to assess the benefit of supplementation to achieve protein goals in the first 24 to 48 hours of feeding, regardless of energy delivery, would add to the body of evidence regarding the importance of early feeding on patient outcome. Patient outcomes to be examined for all studies should include mortality, incidence and type of hospital acquired infections, duration of ventilation, PICU and hospital length of stay, and associated hospital costs.

While time to attain nutritional goals is important, a focus on best practices which achieve safe and effective patient outcomes is key. This is particularly important given the growing body of evidence that supports the early delivery of EN and its protective GI benefits in lowering the risk of mortality (Mehta et al., 2012; Mikhailov et al., 2014).

Implications for Clinical Practice

Results from this study have important practice implications. Bolus feeds demonstrated an equivalent safety profile to continuous feeds while simultaneously improving delivery of target energy and protein and earlier attainment of zero deficit for both energy and protein. Bolus feeding can be considered as a primary approach to EN in the mechanically ventilated pediatric patient. With further study to include a larger sample, other practice change recommendations may include elimination of abdominal girth as a measure of feeding intolerance; protocol stipulations for at least two elevated GRV measurements or spontaneous emesis as criteria for defining feeding intolerance; and protocol changes to define the GRV volume that would constitute a concern for aspiration and subsequent development of pneumonitis. Reconsideration of what constitutes feeding intolerance is needed, particularly with defining emesis associated with coughing or suctioning as an intolerance event if there is no prior elevation of GRV.

Careful consideration and planning are necessary when implementing protocol change in a fast paced unit such as the PICU. Optimizing ways to bring the interprofessional healthcare team together to promote change is essential. Practice change must focus on the safety and outcome for the patient. For this study, some subjects were delayed in their attainment of goal energy due to procedural missteps, e.g., caloric density was not increased every 12 hours as defined by protocol. Attention to this component of

the protocol was needed. In the current unit, a provider order, written by a physician or nurse practitioner, was necessary for each change in formula concentration. The bedside nurse who is in close proximity to the patient is ideally the person who can keep track of this progression. Implementation of a pathway or order set that would allow the bedside nurse to enter a communication order to increase the caloric concentration as provided in an initial order set would keep control of feeding protocol advancement in the hands of those nurses at the bedside who are monitoring patients for feeding intolerance.

The benefit of having order sets empowering bedside caregivers to proceed along a clinical pathway has been demonstrated in the literature. Such a pathway for patients with status asthmatics in the PICU demonstrated reduced PICU and hospital LOS by 24.8% and 33.3%, respectively (Kahlenberg, Forbes, Enrione, et al., 2012). These investigators also demonstrated an 11% reduction in hospital costs, another area for possible investigation in the nutritional therapy research venue. In summary, several practice changes are warranted in the study PICU based on the findings of this study to improve the delivery of critical nutritional intake to the mechanically ventilated child.

Conclusion

This study sought to compare two feeding approaches, bolus versus continuous gastric feeds, on the delivery of prescribed nutrition intake. In addition, the incidence and type of both feeding interruptions and feeding intolerance events were compared between groups.

Findings of this study supported the hypothesis that bolus feeds improved both the proportion of prescribed feeds delivered as well as shortening the time to attain goal feeds. Both groups attained a minimum 25% of goal feeds within the first 48 hours. This

finding supports the recommendations of the 2009 A.S.P.E.N. guidelines suggesting protocolization of feeds may improve EN delivery (Brown et al., 2012; Mehta et al., 2012; Mikhailov et al., 2014; Tume et al., 2012).

The incidence of feeding interruptions and intolerance was small in both groups and corroborates findings in the adult ICU literature recommending emesis as the primary indicator of feeding intolerance. The use of abdominal girth and GRV was not supported in this study as indicators of feeding intolerance. No conclusions can be reached on the volume of GRV that may be associated with feeding intolerance.

Nutrition is a key therapy to reduce morbidity and mortality in the PICU population. Adequate nutrition at a time of high metabolic need is important to preserve lean body mass, decrease inflammation, and modulate the metabolic response. Despite the GI dysmotility of critical illness and common PICU therapies which are also known to slow GI motility, bolus feeding was found to provide an equivalent safety profile in this study sample. Contrary to common practice, but consistent with our current understanding of gastric physiology (e.g., improved gastric motility and emptying after a period of gut rest), the most effective mode of delivery to achieve target nutritional goals and attain zero energy deficit for this study was bolus feeding. Further study to confirm this finding and optimize end user functionality of this protocol is recommended to define best practice.

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APPENDICES

APPENDIX A

A.S.P.E.N. GUIDELINES FOR NUTRITION SUPPORT IN THE

CRITICALLY ILL CHILD

The recommendations are listed followed by their evidence grade in parentheses **Bold inserted by this author as those recommendations addressed by this study**:

1. A) Children admitted with critical illnesses should undergo nutrition screening to identify those with existing malnutrition and for those who are at risk (Grade D) and B) a formal nutrition assessment with the development of a nutrition care plan should be required, especially in these children with premorbid malnutrition (Grade E).
2. A) Energy expenditure should be assessed throughout the course of illness to determine the energy needs of critically ill children. Estimates of energy expenditure using available standard equations are often unreliable (Grade D) and B) in a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using indirect calorimetry (IC) is desirable. If IC is not feasible or available, initial energy provision may be based on published formulas or nomograms. Attention to imbalance between energy intake and expenditure will help to prevent overfeeding and underfeeding in this population (Grade E).
3. There are insufficient data to make evidence-based recommendations for macronutrient intake in critically ill children. After determination of energy needs for the critically ill child, the rational partitioning of the major substrates should be based upon understanding of protein metabolism and carbohydrate and lipid handling during critical illness (Grade E).
4. In critically ill children with a functioning gastrointestinal tract, A) enteral nutrition should be the preferred mode of nutrient provision, if tolerated (Grade C), and B) a variety of barriers to EN exist in the PICU. **Clinicians must identify and prevent avoidable interruptions to EN in critically ill children (Grade D) and C)** *there are insufficient data to recommend the appropriate site (gastric or post-pyloric) for enteral feeding in critically ill children.* **Post-pyloric feeding may improve caloric intake when compared to gastric feeds. Post-pyloric feeding may be considered in children at high risk of aspiration or those who have failed a trial of gastric feeding (Grade C).**
5. Based on the available pediatric data, the routine use of immunonutrition or immune-enhancing diets/nutrients in critically ill children is not recommended (Grade D).

6. A specialized nutrition support team in the PICU an aggressive feeding protocols may enhance the overall delivery of nutrition, with shorter time to goal nutrition, increased delivery of EN, and decreased use of parenteral nutrition. The effect of these strategies on patient outcomes has not been demonstrated (Grade E) (Mehta, Compher, et al., 2009).

APPENDIX B

A.S.P.E.N. CLINICAL GUIDELINES: NUTRITION SUPPORT OF THE

CRITICALLY ILL CHILD

Table 1

Grading of Guidelines and Levels of Evidence

Grading of Guidelines

A   Supported by at least two level I investigations
B   Supported by one level I investigation
C   Supported by level II investigations
D   Supported by level III investigations
E   Supported by level IV or V evidence

Levels of Evidence

I   Large randomized trials with clear-cut results; low risk of false-positive (alpha) and/or false-negative (beta) error
II   Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error
III   Nonrandomized cohort with contemporaneous controls
IV   Nonrandomized cohort with historical controls
V   Case series, uncontrolled studies, and expert opinion

Reproduced from Dellinger RP, Carlet JM, Masur H. Introduction. *Crit Care Med*. 2004;32(11)(suppl):S446 with permission of the publisher. Copyright 2004 Society of Critical Care Medicine.

APPENDIX C

HOSPITAL IRB APPROVAL

Akron Children's Hospital

Akron Children's Hospital - FWA #00000917 - Expiration Date 1/10/17
IORG #0001125 - Expiration Date 1/10/15

July 15, 2013

Ann-Marie Brown, MSN, CNP
Critical Care
Akron Children's Hospital

Re: Comparison of Two Gastric Feeding Approaches in Mechanically Ventilated Pediatric
      Patients

      IRB No: 130709

Dear Ms. Brown:

The IRB Chair has reviewed the application, protocol and consent relating to the above referenced
study. It is a comparison of two standard methods of enteral feeding in ventilated patients in
PICUs to determine if one is more advantageous. The extra risk posed by the study involves the
collection of PHI. Appropriate consent and HIPAA will be obtained. Intubated patients are sedated
and cannot give appropriate assent.

The study is minimal risk. It is granted expedited approval under Subpart D 46.404 (21 CFR
50.51) subject to the following:

1.   Approval is for one year 12 July 2013 to 11 July 2014 and ends unless appropriately
     renewed.

2.   Any serious incidents or events associated with the study be promptly reported to
     the IRB.

3.   No changes will be made to the conduct of the study unless they are first reviewed
     and approved by the IRB.

4.   That IRB approval does not preclude the need for other institutional approval.

5.   All individuals participating in this study must provide the IRB evidence of
     completion of the Protecting Human Research Participants on-line training course
     prior to any involvement in the study. This can be found at
     http://phrp.nihtraining.com/users/login.php

Robert W. Novak, M.D.
Chairman, Institutional Review Board

RWN/hs

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APPENDIX D

UA-ACH IRB RECIPROCITY AGREEMENT

INSTITUTIONAL REVIEW BOARD
Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution/Organization A):

Children's Hospital Medical Center of Akron (CHMCA)   FWA #: 00000917

Name of Institution Relying on Designated IRB (Institution B):

The University of Akron (UA)   FWA #: 00002160
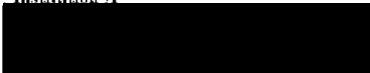
The Officials signing below agree that UA may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (check one)

☐ This agreement applies to all human subjects research covered by Institution B's FWA.

☒ This agreement applies to research conducted by UA faculty, staff and students that will take place at CHMCA and/or involve CHMCA staff, physicians and/or patients. The Principal Investigators will submit a copy of the CHMCA IRB approval letter and consent form to the UA IRB.

In situations where research is taking place both at CHMCA and UA, the signatory officials at both institutions shall agree on which IRB has review and oversight. If UA IRB will review, a separate Authorization Agreement will be put in place for the individual protocol.

The Officials signing below agree that Institution B may rely on the IRB review, approval, and continuing oversight provided under Institution A's Assurance for the protocols identified above.

Signatures:

Institution A	Institution B
Date Grace K. Wakulchik, RN, MSN, MBA, CNS VP for Patient Services Chief Nursing Officer	Sharon McWhorter, V.A. Date IRB Administrator
Robert W. Novak, M.D. Date 10-6-09 Chairman, Institutional Review Board	Stephanie Woods, Ph.D. Date IRB Chair

APPENDIX E

BOLUS CONT-FEED CONSENT

Study **Directors:** Ann-Marie Brown, PhD(c) , CPNP-AC/PC, CCRN, FCCM(or her designee)
                Michael Forbes, MD, FCCM

Contact **Telephone** **Numbers:** ▮▮▮▮▮▮▮ or through the hospital page operator at ▮▮▮▮▮▮▮ (24 hours a day, 7 days a week)

CONSENT - To Participate In A Clinical Research Study

Subject Name: _____   **Date   of   Birth:** _____/_____/____

> **Note:** *Reference to "You" stands for the parents or legal guardians of the research study subject.*

1) **INTRODUCTION:**
   You have been asked to allow your child to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without any changes to the care your child would otherwise receive.

   A copy of this consent form will be included in your medical research record.

2) **WHY IS THIS RESEARCH BEING DONE?**
   The purpose of this research study is to identify the best way to feed children who are on a ventilator, a machine that helps your child breathe. Providing nutrition is important to help them heal and get better. For children on a ventilator a tube is put in the nose and goes down into the stomach. We would like to know if children have less feeding problems if their nutrition is continuously given or if giving the feeding every 3 hours is best. Both ways are used to feed children on ventilators around the world. This study will help us identify the best way to feed children on ventilators.

APPENDIX F

HIPAA AUTHORIZATION

Akron Children's Hospital	**AUTHORIZATION for RELEASE of MEDICAL INFORMATION for RESEARCH**

Protocol Title/Number

A Patient Name _____
(Please Print)   Last   First   Middle

Date of Birth _____   Phone _____   MR# _____

Address _____
Street   City   State   Zip

B The undersigned authorizes the use or disclosure of the above named individual's health information by Akron Children's Hospital or its subsidiaries (Children's) as described below:

C 1. *Use/Disclose Information to the Person(s) and/or Organization(s) listed below and on the attached Information Sheet*:*

Name _____   Phone/Fax _____ / _____

Address _____
Street   City   State   Zip
*See attached Information Sheet for a complete listing of the entities with whom information will be shared.

D 2. *Purpose of Use of Disclosure:*
☐ At request of patient   ☐ Research Database or Repository   ☐ Billing/Payment   ☐ Other

3. *Treatment during clinical trial is CONDITIONED UPON THE SIGNING OF THIS AUTHORIZATION::* Check One: ☐Yes ☐No

E 4. *Type of information to be used or disclosed:*
☐ Complete Medical Record   ☐ Consultation Reports   ☐ Pathology Reports
☐ History & Physical   ☐ Diagnostic Imaging Reports   ☐ Photographs/videotapes
☐ Progress Notes   ☐ Lab Reports   ☐ Diagnosis & Treatment Codes
☐ Discharge Summary   ☐ Radiology Reports/Films ☐ Other

5. *Treatment date(s)* _____

F Unless revoked, this authorization will expire at the end of the research study or on the following date or event: <u>no expiration date</u>

I understand that the information in my health record may include information relating to sexually transmitted disease, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV). It may also include information about behavioral or mental health services, and treatment for alcohol and drug abuse.

I understand that if the person(s) or class(es) of persons in Sections B 1 are not health care providers, health plans or health care clearing houses covered by the Federal privacy regulations, the protected health information they receive may be further used or disclosed by them and may not be protected any longer by the Federal privacy regulations.

I understand that this Authorization may be revoked at any time, except to the extent that Children's has taken action in reliance on this Authorization. Notify in writing, the Privacy Officer, Akron Children's Hospital, One Perkins Square, Akron, OH 44308. I understand that Children's can use and disclose health information obtained prior to the effective date of such revocation to maintain the integrity of the research data.

I understand that access to my health information may be restricted for the duration of the research study. However, once the study has concluded at all sites, I can inspect and obtain a copy of this information.

_____   _____
Signature of Patient or Parent/Legal Guardian   Date

If this Authorization is signed by the Parent/Legal Guardian, please specify
the relationship to the patient/authority to sign on behalf of the individual

_____   _____
Signature of Witness   Date

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APPENDIX G

HIPAA INFORMATION SHEET

AKRON CHILDREN'S HOSPITAL
One Perkins Square • Akron, Ohio 44308-1062

Information Sheet for "Authorization for Release of Medical Information for Research"
(Use and/or Disclosure of Protected Health Information for Research Study)

What is the purpose of this form?

You/your child has been asked to participate in a research study and you have agreed.

Study title:

Person in Charge of the Study:

Purpose: In order to perform the study, the researchers need to use and share some of your/your child's personal health information. Starting on April 14, 2003, federal privacy laws require that the study doctor explain to you/your child in detail what information will be obtained during the study, how that information will be used and with whom it will be shared. Please carefully review the information below. If you agree that researchers can use your/your child's personal health information for the study, you must sign and date the last page of this form.

Organization/Study Sponsor:

What personal health information do the researchers want to use?

The study doctors or staff will collect information for the study from medical records, examinations, observations and forms or questions that you/your child may have completed. This information may identify you/your child by name, social security number, date of birth or other identifying information. The information used for the purposes of the study that may be released may include:

- History and diagnosis of the condition to be studied
- Current and previous treatments that you/your child received
- Other medical conditions that may affect the management of the condition to be studied
- Laboratory, radiology and any test results that have been used to determine if you/your child may participate in the study
- Results used to assess response to and the safety of study
- Physical findings, vital signs and clinical notes from your/your child's care during the study
- Follow-up information about your/your child's health, course of the condition and any late effects from the study

Who will receive and be able to use your/your child's personal health information?

As part of the research, your/your child's personal health information may be given to the following entities. These entities may also review your/your child's original records to assure that the information submitted is accurate. Entities (list):

_____, including representatives who work on behalf of _____ to conduct the study
Other companies owned by or associated with the Sponsor
Akron Children's Hospital and its representatives
Outside laboratories working on this study
Any company that buys the sponsor, or a company owned by or associated with the Sponsor, that is involved in development, regulatory, manufacturing, or marketing activities relating to the study medication
Any company that takes over the development, production, marketing, or sale of the _____. study medication
People or companies working for any of these parties.
Institutional Review Board and government regulatory agencies such as the US Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), the European Medicines Evaluation Agency (EMEA) or other regulatory agencies within and outside the United States

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AKRON CHILDREN'S HOSPITAL
One Perkins Square • Akron, Ohio 44308-1062

Information Sheet for "Authorization for Release of Medical Information for Research"
(Use and/or Disclosure of Protected Health Information for Research Study)

The researchers and sponsors will keep all patient information private in accordance with applicable law. Only those working with the researchers and sponsors will have access to your/your child's information. Personal health information will not be given to others except as authorized or required by law. However, once your/your child's information is given to other organizations that are not required to follow federal privacy law, the researchers and sponsors cannot assure that the information remains protected.

What happens if you do not sign this form?
If you do not sign this form, you/your child will not be able to take part in the research study. Your refusal to allow your/your child's personal health information to be shared for research now or at any time in the future will not cause you/your child to lose any benefits, medical treatment or legal rights to which you/your child is otherwise entitled.

If you sign this form, does it mean you have been entered in the research study?
No, you enter the research study only when you have had the study completely explained to you and you have signed a separate informed consent/permission. This form is only intended to inform you about research-related use and disclosure of your/your child's health information.

What happens if you refuse to continue or let your child continue in the study or want to revoke (withdraw) your authorization?
You can change your mind about the study at any time and revoke your authorization. If this happens, you must revoke your authorization in writing. Beginning on the date that you revoke your authorization, no new protected health information will be used for research. However, researchers may continue to use the health information that was provided before you revoked your authorization. If you signed this form and enter the research study, but change your mind and revoke your authorization, you will also be removed from the research study at that time.

To revoke your authorization, please contact the person below. He/she will make sure your written request to revoke your authorization is processed correctly.
Name of Contact Person (Study Doctor or designee):
Address: **Akron Children's Hospital**
One Perkins Square
Akron, Ohio 44308-1062
Phone: ▮▮▮▮▮▮- Fax: (▮▮▮▮▮▮▮▮
How long does this authorization last?
This authorization has no expiration date. However, as stated above, you can change your mind and revoke this authorization at any time.

What are your/your child's rights regarding your protected health information?
You have the right to refuse to sign this authorization.
You have the right to review and/or copy records of your protected health information.
You do **not** have the right to review and/or copy records kept by the sponsor or other researchers associated with this research study.

APPENDIX H

ELIGIBILITY TOOL

Admission Date	Patient Sticker	1month CGA – 12yrs?	If yes, intubated ? If yes, and <mark>no exclusion**</mark>, date parents approached for consent, and yes/no consent?	If no, reassess 24 hrs post admission and note date/ outcome

<mark>**Exclusion Criteria: primary GI diagnosis, post GI surgery, has a G-tube, or already being tube fed upon admission to the PICU.</mark>

APPENDIX I

ENROLLMENT AND RANDOMIZATION LIST

Admission Date	Patient Sticker	Subject Study#	Group Assignment	Consent and HIPPA release form signed and placed behind this page	Copy of consent placed in patient chart by AM Brown

APPENDIX J

CGF PROTOCOL

APPENDIX K

BGF PROTOCOL

Bolus Gastric Feeding Protocol

Radiologic confirmation of NG placement

Initial orders written for formula, dietitian consulted

Folder given to bedside nurse with baseline subject data entered

Patient < 25 kg?

YES

NO

Begin feeds at 3ml/kg, run over 60 minutes every 3 hours, advance by 3ml/kg every 3 hours to goal volume. Decrease IV rate accordingly

Begin feeds at 75ml, advance by 75ml every 3 hours to goal volume. Decrease IV rate accordingly.

Feeding Intolerance?

1. Emesis OR
2. GRV > 50% volume infused last 3 hours for 2 consecutive measurements (or >400ml for subjects > 80kg) OR
3. GRV > 50% volume infused last 3 hours x 1 measurement AND increased abd girth > 10% from baseline in current 24 hour feeding period

NO

YES

After goal volume tolerated for 12 hours, adjust caloric concentration and protein supplements q12h until at target prescription

Glycolax and/or stimulant suppositories ordered for all subjects to be given daily prn if no bowel movement > 24 hours

Hold feeds for 2 hours and resume at one half rate feeds stopped and advance per protocol

YES

Feeding Intolerance?

Hold feeds for 2 hours and initiate metoclopramide. Restarted feeds at rate they were stopped and advance per protocol.

Feeding Intolerance?

NO

NO

YES

After goal volume tolerated for 12 hours, adjust caloric concentration and protein supplements q12h until at target prescription

Attending physician/NP to evaluate need for formula change, post-pyloric feeding or discontinuation of enteral nutrition.

After goal volume tolerated for 12 hours, adjust caloric concentration and protein supplements q12h until at target prescription

APPENDIX L

CGF DATA FORM

Data Collection Tool Continuous Feeding

Subject Study #_____ "Dry Weight" _____kg Study Day # _____ Date/Time Feeds Initiated _____Target/Formula/Strength/Rate_____

Assessment Every 3 Hours and at Time of Events, Continued Through 96 hours after Initiation of Feeds

Date	Time	Feeding rate/ *Volume delivered* the past 3 hours, not ordered)	Formula Name	Formula Strength (cal per ounce)	Gastric Residual Volume (GRV)	Abd Girth (cm)	Emesis (with suctioning or coughing?)	Feeds Held with Reason /Comments Time Held: Time Restarted:	OSI [(FiO2 x Mean Airway Pressure)/ SpO2]	Initials

Definition of Intolerance: emesis x 1(document whether with sxing/coughing or not), OR GRV > 50% volume infused past 3 hrs for 2 consecutive measurements OR GRV > 50% volume given past 3 hours x 1 with increased abdominal girth > 10% lowest baseline in current 24 hour feeding period.

Reasons feeds held: 1 – intolerance   2 – therapies (planned extubation,etc)   3 – general care procedures (transfers, repositioning, etc)   4 – other (describe)

Nurse Printed Name _____Signature_____ Initials _____

Nurse Printed Name _____Signature_____ Initials _____

Nurse Printed Name _____Signature_____ Initials _____

CONTACT NP OR ATTENDING IF ANY OTHER CONCERNS AT ANY TIME

APPENDIX M

BGF DATA FORM

Data Collection Tool Bolus Feeding

Subject Study #_____ "Dry Weight" _____kg Study Day # ____ Date/Time Feeds Initiated _____Target Formula/Strength/Rate_____

Assessment Every 3 Hours and at Time of Events, Continued Through 96 Hours after initiation of Feeding

Date	Time	Feed Volume (amount delivered that hour, not ordered)	Formula Name	Formula Strength (cal per ounce)	Gastric Residual Volume (GRV)	Abd Girth (cm)	Emesis (with suctioning or coughing?)	Feeds Held with Reason /Comments Time Held: Time Restarted:	OSI [(FiO2 x Mean Airway Pressure)/ SpO2]	Initials

Definition of Intolerance: emesis x 1 (document whether associated with sxing/coughing or not), OR GRV > 50% volume infused past 3 hrs for 2 consecutive measurements OR GRV > 50% volume infused past 3 hours x 1 with increased abdominal girth > 10% lowest baseline in current 24 hour feeding period.

Reasons feeds held: 1 – intolerance   2 – therapies (planned extubation,etc)   3 – general care procedures (transfers, repositioning, etc) 4 – other (describe)

Nurse Printed Name _____Signature_____ Initials _____

Nurse Printed Name _____Signature_____ Initials _____

Nurse Printed Name _____Signature_____ Initials _____

GASTRIC FEEDS STUDY MEDICATIONS DATA COLLECTION FORM

Subject # _____Date/Time Feeds Started _____
Feeding Study Date/Day ____

Medication Categories/ Included Meds	Administered Yes/No *If yes, must fill out next 2 columns*	If yes, infusion Yes/No	If yes, Intermittent incl prn, scheduled, one time Yes/No
Neuromuscular Blockers – cisatracurium, vecuronium, rocuronium, succinylcholine			
Sedatives – midazolam, lorazepam, diazepam, dexmedetomidine, propofol, ketamine, pentobarbital			
Opioid analgesics – morphine, fentanyl, hydromorphone, methadone			
Catecholamines/Intropic/ Vasoactive Agents – dopamine, dobutamine, epinephrine, norepinephrine, milrinone, phenylephrine, vasopressin, nipride, nitroglycerin			
Prokinetic agents – metoclopramide			
Laxatives – polyethylene glycol/Miralax, senna, glycerin supp, bisacodyl supp			
Gastric acid suppressants – famotidine, ranitidine, omeprazole, esomeprazole, lansoprazole			

APPENDIX O

TIME TO GOAL FEEDS DESCRIPTIVE DATA BETWEEN FEEDING GROUPS

	Group			Statistic	Std. Error
Goal Feeds (hours)	Bolus	Mean		34.7	12.48
		95% Confidence Interval for Mean	Lower Bound	4.2	
			Upper Bound	65.3	
		5% Trimmed Mean		33.2	
		Median		15.0	
		Variance		1091.6	
		Std. Deviation		33.49	
		Minimum		9.0	
		Maximum		87.0	
		Range		78.0	
		Interquartile Range		63.0	
		Skewness		.88	.79
		Kurtosis		-1.14	1.59
	Continuous	Mean		36.286	7.07
		95% Confidence Interval for Mean	Lower Bound	18.99	
			Upper Bound	53.58	
		5% Trimmed Mean		35.57	
		Median		29.50	
		Variance		349.49	
		Std. Deviation		18.69	
		Minimum		18.0	
		Maximum		67.5	
		Range		49.5	
		Interquartile Range		34.0	
		Skewness		.89	.79
		Kurtosis		-.57	1.58