IMPACT OF BLENDERIZED ENTERAL NUTRITION ON BOWEL FUNCTION IN CRITICALLY ILL PATIENTS ON EXTRA CORPOREAL MEMBRANE OXYGENATION

By

Emily F. Diana

A THESIS
Presented to the Department of Graduation Programs in Human Nutrition and
Oregon Health & Science University
School of Medicine
in partial fulfillment of the requirements for the degree of

Master of Science in Human Nutrition

June 2021

School of Medicine

Oregon Health & Science University

CERTIFICATE OF APPROVAL

_____

This is to certify that the Master's thesis of

Emily Diana

has been approved

_____
Julie McGuire, MS, RDN, LD

_____
Monica Buettner, MS, RD, LD

_____
Joanna Cummings, MS, RD-AP, CNSC

Table of Contents

Acknowledgments

Thank you to my committee members, Monica Buettner and Joanna Cummings, for supporting me through this process and showing me the steps to success. I appreciated your direction that allowed me to find my way through this project. Thank you to Monica Buettner, who harbored the expertise and clinical experience that manifested this project in the first place.

Thank you to Legacy Emanuel Medical Center and the Neurotrauma Intensive Care Unit for allowing me to conduct this research on a vulnerable patient population. A big thank you to Dr. Shaban Demirel for supporting me in my statistical analysis and having shared enthusiasm for the clinical data.

Thank you to my friends, family, and partner for supporting me through this arduous project. Thank you to Lacey, Sarah, and Corrin for the laughs and the shoulder to cry (and cry-laugh) on, as well as ears that would always listen. Thank you to my parents who cheered me on, gave unwavering support, and always encouraged me to persist. Finally, thank you to my partner, Jack, for the humor, the support and the unconditional love.

Finally, thank you to Julie McGuire for believing in me and giving me free reign on this project, you truly facilitated my growth and my knowledge. I remember my interview with you before being accepted into OHSU, and it is hard to believe that we are here now. I look forward for all the work we will continue to do on this project moving forward. Thank you for being my mentor.

Abstract

Background: Patients who are severely critically ill may require extra corporeal membrane oxygenation (ECMO) and nutrition support in the form of enteral nutrition (EN). Patients with critical illness may exhibit severe intolerance to EN, most prominently, diarrhea. Diarrhea challenges the clinical course and nursing workload, and the placement of rectal tubes is common to avoid diarrhea-associated complications. However, rectal tubes are not free from complications and pose a risk to the patient. Two factors that could be contributing to diarrhea in this patient population may be the provision of "as needed" bowel medication and/or the formulation of EN. Formulation of enteral feeds can contribute to diarrhea, and formulas given to patients who are critically ill often exclude fiber, which can bulk stool and regulate bowel movement frequency. Historically, while not well researched, the use of fiber in patients with critical illness has been cautioned due the potential of bowel ischemia. Thus, the use of blenderized EN is a novel practice in this patient population due to its inclusion of fiber.

Methods: To observe the effects of blenderized tube feeding (BTF) containing fiber and impact of bowel medications on diarrhea and rectal tube use, a retrospective chart review was conducted in the Neurotrauma Intensive Care Unit (NTICU) at Legacy Emanuel Medical Center (LEMC) from January 2018 to March 2020. Patients who were on ECMO and who reached goal EN were included. Patients were excluded if they had any confounding bowel diseases at baseline, if they received ECMO for treatment of COVID-19, and if they were on parenteral nutrition. Patients were then separated by formula type: blenderized formula (BTF) or non-blenderized formula (non-BTF).

Results: A total of 59 subjects were included for the analysis (33 in the BTF group and 26 in the non-BTF group). Wilson's rank sum test (Mann-Whitney U-test) was used to analyze continuous variables, while odds ratios, Fisher's Exact test, and Chi square analyzed categorical variables. The BTF group had more

frequent but more formed bowel movements with lower rectal tube placement. The non-BTF had a higher risk of developing diarrhea and requiring a rectal tube. Bowel medications did not have an effect on diarrhea incidence.

Conclusion: In conclusion, the use of real food, BTF was advantageous for increasing tolerance to enteral feeds by reducing incidence of diarrhea and rectal tube placement. To improve patient outcomes and bowel function, the use of fiber in this patient population requires further research.

Introduction and Specific Aims

Critically ill patients often receive life-sustaining support such as oxygenation of the blood through mechanical ventilation or other methods. Extra-corporeal membrane oxygenation (ECMO) is a method of life support that allows for both cardiac and respiratory support.[1,2] Unlike mechanical ventilation, which supplies oxygen by inflation of the lungs, ECMO directly oxygenates the blood by removing the blood from circulation, oxygenating the blood externally through the machine, and delivering newly oxygenated blood to circulation through a central catheter.[3] ECMO bypasses the lungs and/or the heart, depending on the mode, allowing for additional rest and reducing chance of ventilator-related lung injury.[4]

Patients on ECMO can only be fed via nutrition support, the most common form being enteral nutrition (EN).[1] Enteral formulas differ in ingredients, macronutrients, micronutrients, and concentration, making them suitable for various medical conditions.[5] Most often, critically ill patients will be prescribed a fiber-free, non-blenderized tube feed (non-BTF) such as Peptamen© (Nestlé Health Science, Vevey, Switzerland) or Impact© (Nestlé Health Science, Vevey, Switzerland). Most commercially available formulas, including Peptamen© and Impact©, use highly processed ingredients for each macronutrient component. For example, corn syrup solids are used as a source of carbohydrate, whey protein isolate/casein are used as the protein source, and soybean oil is a source of fat. Blenderized tube feeds (BTFs), on the other hand, include ingredients from the whole form with minimal processing, such as blending. There are several formulas, both non-BTF and BTF that include fiber.[5,6] A fiber-containing formula may help achieve a better stool consistency and frequency, protecting the patient from diarrhea-associated complications, a common problem for patients with critical illness.[7,8,9]

Gastrointestinal (GI) issues can plague the critically ill patient population for a number of reasons including medications, such as antibiotics and opioids, sedation, immobility, administration of

enteral nutrition feeding and enteropathogenic colonization.[10,11] GI issues, such as diarrhea, constipation, among other adverse events, can result in adverse outcomes, affecting patients' length of stay (LOS), morbidity and mortality.[7] One of the most common GI complications is diarrhea, affecting 32-95% of critically ill patients.[10,12] Specifically, diarrhea can lead to interruptions to the provision of nutrition support, exacerbate electrolyte and fluid losses, lead to perianal wound infection and complicates clinical care by increasing nursing time at bedside, workload, and cost.[10,13,14] The volume of diarrhea can range from low/normal output (250-500 milliliters) to high output (≥500 milliliters).[7] Placement of rectal tubes are a frequent solution to high outputs of diarrhea.[9] Rectal tubes may lead to skin irritation, injury, and infection, which further complicates the clinical picture.[9] Rectal tubes are also an expensive intervention for diarrhea which can directly increase costs. Clinical tools to reduce the rate and incidence of diarrhea, thereby decreasing the use of rectal tubes, is important to improving patient outcomes. The type of formulation of the EN provided can be a tool that can decrease incidence and volume of diarrhea in the critically ill population.

Fiber is one ingredient that differentiates the types of enteral nutrition formulas prescribed in the critical care setting. The solubility of fiber affects its function and indication for use. Soluble fiber can be partially digested within the large intestine, while insoluble fiber cannot be broken down or digested in the large intestine.[7] Insoluble fiber decreases transit time by adding bulk, whereas soluble fiber allows for creation of more formed bowel movements.[7] Whole foods contain fiber in both soluble and insoluble forms. Other forms of fiber are used in commercial tube feeding formula, such as guar gum, inulin, fructo-oligosaccharides (FOS), soy polysaccharides, and more.[15] The amount of fiber in enteral nutrition can range from 0 grams per liter (low or no fiber) to greater than 20 grams of fiber per liter (high fiber).[5,7] Fiber provides bulk to stool and promotes optimal frequency of bowel movements, making it a viable treatment for diarrhea.[5,16] Due to the high prevalence of diarrhea in the critically ill, a fiber-containing formula is an often sought-after solution to help reduce frequency of bowel movements and

bulk the stool.[5] However, while the critically ill have higher incidence of diarrhea, fiber-containing formulas may not always be suitable for the critically ill.[5,16] The Academy of Nutrition and Dietetics (Academy) states that it is inappropriate to provide fiber to patients that are positive for *Clostridium difficile*, are hemodynamically unstable, at high risk for bowel ischemia, and/or have severe dysmotility.[5] Conversely, the Academy supports the use of fiber for diarrhea, and the Society of Critical Care Medicine (SCCM) and the American Society of Parenteral and Enteral Nutrition (ASPEN) critical care guidelines supports the use of soluble fiber as adjunctive therapy to EN feedings in stable critically ill patients.[5,16,7]

Real food formula, or BTF, has traditionally been used in feeding non-critically ill patients for the long-term. Historically, BTF has not been used in patients who are critically ill. Some common enteral formulas are partially or fully hydrolyzed, but BTF formula is blenderized, which maintains the integrity of the ingredients and provides natural fiber content from the fruits and vegetables.[7] Other standard formulas may exclude fiber completely or add fiber in as a supplement in the form of soy polysaccharide (94% insoluble fiber) or guar gum (soluble fiber).[17]

The fiber found in standard EN products such as FiberSource HN © (Vevey, Switzerland), another commercially prepared enteral formula, is added in as a powdered forms of both soluble and insoluble fiber and the source may be different in composition (common fiber added in the form of guar gum and soy fiber).[7,10] In the only available literature, a randomized control trial examining BTF versus non-BTF formula for critically ill neurological patients, BTF improved diarrhea in the intervention arm with average stool consistency classified as Bristol type 4 (formed stool, soft and smooth).[10] The average stool consistency of the control group was Bristol type 7 (loose, watery).[10] It was unclear if these favorable changes in consistency were attributed to composition of fiber.[10] Due to the conflicting evidence and recommendations, it is important to explore how the inclusion of whole, natural fiber in formula affects the likelihood of bowel ischemia or bowel obstruction in this population.

Although fiber is known to improve gastrointestinal motility and diarrhea, there is a gap in research on the role of commercially prepared, fiber containing BTF formula for patients who are critically ill. Nutrition is understudied in the ECMO population, particularly the role of BTF formula in minimizing the incidence of diarrhea.[2,18] Providing critically ill patients with a BTF that could decrease diarrhea and reduce the use of rectal tubes may allow for more favorable outcomes such as: shorter LOS, reduced burden on nursing staff, and reduced costs. The overall goal of this study is to explore the relationship between commercially prepared BTF and GI complications, notably diarrhea. The results of this study will expand our knowledge to improve established feeding guidelines and protocols, provide evidence regarding the safety of the provision of fiber, and reinforce the positive impact of BTF has on critically ill patients receiving ECMO therapy. The specific aims for this project are:

Specific Aim 1: To determine the relationship between blenderized formula and the incidence of diarrhea and subsequent rectal tube use in critically ill patients on ECMO therapy.

- We hypothesize that the incidence of diarrhea and rectal tube use will be lower in critically ill patients receiving a blenderized enteral formula when compared to critically ill patients receiving a non-blenderized enteral formula.

Specific Aim 2: To understand how the provision of an enteral nutrition formula influences bowel medication use in ECMO patients.

- We hypothesize that patients on a blenderized enteral nutrition formula will require more laxatives compared to patients on a standard, non-blenderized, enteral formula; however, compared to patients on a standard, non-blenderized formula using laxatives patients receiving a blenderized formula will have more well-formed stools and less frequency and volume of diarrhea.

- We hypothesize patients receiving bowel medications to promote bowel movements and prescribed a blenderized enteral formula will have less incidence of diarrhea compared to patients receiving bowel medications and prescribed a non-blenderized formula.

  Specific Aim 3: To assess if fiber in standard and blenderized tube-feeding enteral formulas increases the odds of adverse gastrointestinal events, such as bowel ischemia or bowel obstruction, in critically ill patients.
- We hypothesize that enteral formulas with intact fiber will improve diarrhea without inducing bowel ischemia or causing bowel obstructions in critically ill patients.

Exploratory Aim 1: To gauge how blenderized formula influences feeding adequacy in patients receiving ECMO therapy.

Exploratory Aim 2: To explore how rectal tubes influence skin integrity.

This project aims to expand clinical feeding guidelines for patients receiving ECMO in critical care units, and this research is increasingly needed as ECMO becomes a leading critical care measure during the COVID-19 pandemic. It is expected that by learning how to manage diarrhea, clinicians can consequently ameliorate related complications and improve feeding tolerance and nutrient provision, ultimately improving outcomes in the highest risk patients.

Background

Extra Corporeal Membrane Oxygenation (ECMO) Support

Patients in the critical care unit are at the highest risk of malnutrition (and mortality) in the hospital.[5,7] Patients who are under respiratory distress require supplemental oxygen, and these patients may require circulatory support so oxygen can be delivered by the blood to maintain vital organ function.[18] Extra corporeal membrane oxygenation (ECMO) offers life sustaining therapy to critically ill patients when they are unable to breathe or adequately use their circulatory system.[18] ECMO support may be used under certain circumstances and clinical conditions by using cannulation thereby bypassing the lungs and/or the heart. In contrast, mechanical ventilation mechanically inflates the lungs with fresh oxygen, forcing the body to rely on the cardiovascular system to deliver the oxygenated blood to vital organs.[19] ECMO can be used as circulatory support, meaning the heart does not have to be used to deliver blood to the rest of the body.[19]

ECMO therapy externally oxygenates the blood through a catheter and offers two modes of function: Venovenous oxygenation (VV ECMO) or venoarterial oxygenation (VA ECMO).[19] The mode of ECMO dictates how much support the machine gives.[20] In VV ECMO, the machine oxygenates the blood externally, but the body's own cardiac function is responsible for circulating the blood to other tissues.[7] ECMO deposits the newly oxygenated blood into the jugular vein or inferior vena cava.[20] In VA ECMO, the machine assumes responsibility for both the respiratory function and systemic circulation, delivering the oxygenated blood into a carotid artery to enter central arterial circulation.[21] In both cases, the machine oxygenates the blood, allowing for the lungs to rest and recover.[22] Critical illness alters many of the body's vital organ functions, and one of the major changes that occur due to critical illness is alteration of metabolic function.

Metabolic Disturbances During Critical Illness

Critical illness alters natural physiologic and metabolic processes.[7] During critical illness, the body enters into two periods: an acute response and a systemic response.[7] During the acute phase, the body aims to conserve the body's physical stores, and it begins the breakdown of fat mass and mobilize glucose from the liver to support the catabolic response.[7] As the body begins to shift into the systemic response, there is a large shift in energy usage, as the body becomes hypercatabolic and has higher nutrient needs to avoid depletion of adipose tissue and lean body mass.[7,23]

Patients with critical illness are hemodynamically unstable, characterized by fluctuations in mean arterial pressure (MAP). Altered GI function occurs during critical illness, resulting from hypoperfusion of the gut splanchnic circulation, electrolyte disturbances, mechanical factors such as positioning and movement, variations in the gut microbiome, neurohormonal shifts, and diet.[24,25] ECMO patients often receive high doses of vasopressors to help minimize fluctuations in MAP, which can interfere with provision of nutrition.[18] For patients on high doses of vasopressor medication, there is significant risk for bowel ischemia as blood is shunted from the GI to the heart and the brain.[7] However, bowel rest also can result in negative consequences, as the absence of nutrition atrophies the gut-associated lymphoid tissue (GALT) and the mucosa-associated lymphoid tissue (MALT), thereby resulting in gastrointestinal (GI) dysfunction, lowered immune response, and increased morbidity and mortality.[7]

Due to this drastic metabolic response, ASPEN recommends initiating feeds in a patient who is critically ill within 24-48 hours of admission.[7] Adding to the high nutritional needs, it has been hypothesized that ECMO equipment itself may incite higher protein catabolism and inflammation.[26] It is clear that ECMO patients, similar to the general critically ill population, require feeding as early as possible to mitigate the hypermetabolic state of critical illness.

Nutrition Support in the Critically Ill

Patients receiving life support are dependent on nutrition support, as they are often intubated and sedated, and in some cases, may not be able to use their GI tract.[7] Critical illness requiring ventilation or ECMO, is an indication for EN, as these patients are unable to eat by mouth.[7] It is favorable to feed the GI tract with EN over parenteral nutrition (PN) to preserve function of the GI tissue, maintain the gallbladder and pancreatic function, and allow for first-pass metabolism, which promotes better nutrient absorption and utilization.[7] EN is contraindicated for cases where the GI tract is non-functional, such as severe short bowel syndrome, ileus, mechanical obstruction, or for times of feeding intolerance and/or lack of GI access.[7] EN is always preferred over PN.[7] EN recommendations for a patient who is critically ill are individualized. The most common route of nutrition support in the ECMO patient population is EN, and there is no standard enteral formula for the ECMO population.[22]

Enteral nutrition provision requires a functional and accessible GI tract to stimulate the GALT and the MALT, to maintain cellular tight junctions and stimulate splanchnic blood flow.[7] However, patients who are undergoing ECMO therapy, or other forms of life support, cannot eat orally, putting them at risk for further nutritional deterioration and for GI mucosal atrophy.[7] Enteral nutrition support helps maintain proper gut function, enhances immunity, ameliorates disease severity, and provides nutrients to meet needs and prevent wasting.[1,7] Due to the severe consequences of starvation and its detrimental effects for the critical ill patient, it is important to initiate enteral nutrition feeding as early as possible.

Initiation of EN can be complicated and contraindicated by hemodynamic instability, but is safe to initiate when pressor doses are declining or are stabilizing.[7] In a study of 86 ECMO patients, it was safe to feed patients within an average time of 13 hours from admission.[27] Further, in a study of patients with severe hemodynamic instability on ECMO therapy, researchers found that it was safe to feed patients enterally while receiving ECMO, and 70% of patients were tolerant of nutrition support within

two weeks.[1] Patients who are critically ill and receive appropriate nutrition have had better outcomes.[19] A study conducted on 102 patients undergoing ECMO therapy revealed that patients who had >80% of estimated energy needs provided within the first 7 days fared better than those who were not provided with adequate energy (less than 80% of their needs) within the first 7 days.[19] Patients who survived treatment had received an average of 96.9% of their nutrient needs.[19] Initiating the provision of nutrition as soon as possible is now the standard of care, it is also necessary to acknowledge the potential risks to feeding a patient prematurely.[5,7]

Feeding intolerance is a significant barrier to reaching nutritional goals and can cause a myriad of GI complications, including bowel ischemia, diarrhea, constipation, ileus, and others. A study of energy deficits within an intensive care unit (ICU) setting showed that the most common reason for energy deficits were: time of initiation of feeding, day of feeding initiation, and incidence of sedation.[28] Another study found that interruptions in feedings were most commonly caused by surgical feeding holds and high gastric residuals.[29] In contrast, a separate study found that 42% of 241 ECMO patients had tube feeds held for GI complications.[30] Enteral nutrition support is often blamed for GI complications, although there are many reasons for such complications such as medications (antibiotics, opioids, paralytics, sedatives, etc.) infections, and clinical status.[31] Feeding adequacy is important for improved outcomes and it becomes even more crucial to better control GI complications in patients who are critically ill relying on EN support.

Gastrointestinal (GI) Complications

In critical illness, hypoperfusion of the GI system increases risk of adverse events when attempting to initiate EN support. GI complications include diarrhea, constipation, abdominal distention, hypo- or hyperactive bowel sounds, aspiration, paralytic ileus, mechanical bowel obstruction, and high gastric residuals.[7] Signs of intolerance to EN include abdominal discomfort, abdominal distention, and vomiting.[7] Other influencers of GI complications are medications, namely antibiotics, sedatives,

paralytics, opioids, etc.[7] These drugs are prevalently administered among patients who are critically ill and in patients receiving ECMO therapy. Therefore, provision of EN, medication management, and clinical status can all affect bowel movements, and as a standard of care, bowel movements are followed and managed throughout the clinical course.

Diarrhea

There are several methods of classifying diarrhea, such as descriptive words, like 'loose', 'watery', 'unformed' stools, use of the Bristol Stool type chart,[32] Hart and Dobb scale,[11] or by milliliters (ml) of output. It is important to classify stool and treat based on stool type. If diarrhea is persistent, ASPEN guidelines recommend using soluble fiber to help bulk stool and slow GI transit time.[7] Rectal tubes, a form of fecal management system, are used to prevent other complications, and are frequently placed if a patient has persistent diarrhea.[9] While rectal tubes are aimed at management of diarrhea, they often cause skin irritation, anal sphincter injury, and can lead to perianal infections.[9] If possible to control, clinicians may prophylactically manage diarrhea to prevent complications, such as dehydration, electrolyte imbalances, malabsorption, and skin breakdown, all of which can negatively impact clinical course.[7] Additional treatment methods are changing the type of EN formula, medication management, fluid management, and provision of a probiotic.

A prospective randomized trial investigated the use of probiotics in patients with critical illness in hopes to observe a positive effect of probiotics on diarrhea incidence.[33] The definition of diarrhea include three or more loose/unformed stools in 24-hours or liquid stool with a volume greater than 200 milliliters.[33] Patients in the intervention were given a probiotic (280 grams of inulin and 10^{10} colony forming units of *Lactobacillus rhamnosus GG* (*LGG*)) for a 7-day period and patients in the control were given a placebo for a 7-day period.[33] Ultimately, researchers found that this study did not support the provision of *LGG* for treatment of diarrhea in patients with critical illness.[33]

In a trial investigating EN in patients on ECMO support, 38% of patients (33 patients) had severe intolerance to EN within the first 5 days of initiation, and in 20 of these 33 patients with intolerance, the use of prokinetic medication ameliorated the intolerance.[27] In addition to intolerance, 40% of patients in the study required a bowel protocol, which included use of rectal tubes, to manage diarrhea.[27] Further, a retrospective study following a flexible fecal management system, rather than a traditional rectal tube, found that the fecal management system was more effective and safer to use than a traditional rectal tube.[9] While the first study highlights the prevalence of rectal tube use in this patient population, the comparison of other waste management solutions underlines issues with safety and efficacy of rectal tubes. Indeed, in a prospective study by Wilson et al, the use of rectal tubes in patients with critical illness resulted in longer LOS and higher mortality.[8] It is clear that there needs to be more investigation of solutions for diarrhea in order to prevent rectal tube placement. Diarrhea can cause complications that negatively impact patients; on the other end of the spectrum, constipation can exacerbate conditions and lead to poor outcomes.

Constipation

Constipation is a common GI complication that can negatively impact clinical status. Constipation is broadly defined as the absence of a bowel movement, yet there is not a clear definition with regard to duration of time before a bowel evacuation.[6,34] Without intervention, severe GI dysmotility can lead to bowel obstruction and bowel perforation.[7] There are copious reasons for constipation to occur in patients who are critically ill, such as the use of opioids, vasopressors, sedatives, sepsis, EN formulations, lack of physical movement, etc.[34,6] Without treatment, constipation can lead to unfavorable outcomes, such as increased mortality, longer LOS, and enteral nutrition intolerance.[34] For this reason, there are prophylactic protocols in place to promote bowel motility.

Researchers found that patients most likely be affected with constipation were those who were mechanically ventilated and receiving EN, underscoring the significance of a bowel regimen in patients

who are critically ill.[6] When defining constipation as no bowel evacuation for three days, as opposed to six days, researchers found early initiation of a bowel motility protocol using laxatives had higher efficacy.[6] Bowel motility regimens initiated before hospital day five were considered prophylactic. Further elucidated in this study, one group with constipation defined at three days and the other group with constipation defined at six days, showed the 6-day group had poorer outcomes related to duration spent on mechanical ventilation and ICU LOS.[6]

These findings emphasize the importance of a prophylactic bowel protocol for patients who are critically ill and receiving life support and/or ECMO and EN.

Gut Dysmotility and Ischemia

Ileus is a temporary loss of intestinal motility and is common barrier to the provision of EN.[7,35] Severe ileus often requires bowel rest and use ofPN.[5] With this, it is important to beware of the presence of fiber in the enteral formula and to be wary of potential for exacerbation in patients with prolonged dysmotility.[5] However, it has been shown that early feeding, within 48 hours of admission, may decrease risk of ileus.[5] In a small study conducted (in where), only 40% of the 50 patients with hypomotility received bowel medication and only 4% of patients with impaired gastric emptying (IGT) had radiologic confirmation of an ileus.[36] With scarce and conflicting evidence, it is necessary to conduct more research into the efficacy of mixed fiber sources in EN formulas and the incidence of ileus and/or bowel obstructions.

Bowel ischemia, or bowel necrosis, is a life-threatening complication that has a mortality rate ranging from 46-100%.[37] Risk factors include hemodynamic instability, and high or rising vasopressor use, at the time of initiation of EN. Provision of EN too early may cause bowel necrosis; however, studies have shown that early EN may be protective rather than harmful.[23] In a study of patients who were mechanically ventilated in the ICU, early provision of EN was not superior to PN in terms of risk for GI complications.[23] In contrast, results of this study supported early trophic feeding in the acute phase of

critical illness.[23] With these risks in mind, it is useful to mention that formula type was not a variable considered in this trial.[23] Therefore, the risk of GI complications related to formula type should be assessed. At this time, the highest risk for induction of bowel ischemia would be premature feeding in a hemodynamically instable critically ill patient.[7]

Bowel Medications

Bowel medications are included in a bowel regimen, a standard of care in ICUs cite. Medications that are routinely prescribed include stool softeners, bulking agents, osmotic and stimulating laxatives, and prokinetics.[38,39] The purpose of a prophylactic bowel regimen is to increase motility and ease for the passing of stool, thereby alleviating constipation and increasing tolerance to nutritional intake. In ECMO support, patients are more likely to require prokinetics due to significant delay of gastric emptying and may need a complete bowel regimen to promote evacuation.[26]

Laxatives are given prophylactically to ameliorate constipation.[38] In a study observing gastric hypomotility in patients who are critically ill, the most common treatment given was lactulose, an osmotic laxative, followed by sodium phosphate enemas and bisacodyl suppositories.[36] In a separate study, the most commonly used bowel medication was magnesium hydroxide.[39] Other osmotic laxatives include polyethylene glycol. Osmotic laxatives draw water into the intestine and act as a bulking agent, due to the synthetic fiber additives.[38] Stool softeners include docusate and docusate calcium, which function similarly to osmotic laxatives.[38] Stimulant laxatives include anthraquinone derivatives, (i.e. Senna, and diphenylmethane derivatives, bisacodyl), and they stimulate the nerve plexus of intestinal smooth muscle.[38] It is important to appreciate these various laxatives as standards of care and to acknowledge their differences in mechanism of action.

Pharmacological management of constipation usually includes a stool softener and a laxative.[24] If the regimen fails to elicit a bowel evacuation, enemas may be used. A randomized cross-over trial examining prophylactic bowel regimens assessed three separate protocols.[40] All regimens used a coloxyl

with senna (a combination of a stool softener and a stimulant laxative) and lactulose (an osmotic laxative).[40] The combinations varied and were initiated in concert with the initiation of enteral nutrition.[40] Researchers found that there were no significant difference in outcomes between the three regimens, and there were no major differences based on timing of laxative provision.[40] However, in this study, 10% of the 570 patients required rectal tubes, underscoring the need for further trials to pinpoint an effective regimen for management of diarrhea if laxatives contribute to overly loose stools.[40] Comparatively, timing of laxative treatment requires more research, as these studies show conflicting results.[40] In contrast, a study examining a pragmatic approach to IGT in the ICU found that daily opioid use and preventative constipation medications were actually associated with greater risk of developing IGT.[36] Further, the primary consequence of IGT was inadequate nutrition, leading to a longer LOS.[36]

Due to the difficulty of feeding tolerance in ECMO patients and their predisposition to GI complications, such as diarrhea and constipation, there is a need to investigate the effects of feeding with a bowel regimen in place. The preliminary trial of BTF formula showed that patients on laxatives had more formed stools when compared to patients on laxatives receiving non-BTF formula. Formula selection may significantly impact the need for laxatives and prokinetic therapies in patients who are critically ill.

Enteral Formula

There are several types of enteral formulas, formulated for specific purposes. A clinician will choose a formula based on the needs and diagnosis of the patient.[7] An example of a formula with a purpose are immune modulating formulas, as well as formulas for specific disease states, such as renal, diabetic, etc. Formulas differ in composition, specifically in macronutrients, osmolality, electrolytes, and vitamins and minerals.[7] Specifically for patients receiving critical care, there are immune-enhancing formulas, which include omega-3 fatty acids. However, to illustrate the nuances of formula selection,

omega-3 fatty acids are appropriate for patients who have had trauma but not for patients with sepsis.[7] Currently, there is no formulation unique to ECMO patients.[22]

Formulas may be disease-specific due to their nutritional composition and ingredient list. Recently, there has been increased demand for a whole food formula. These formulas are known as BTFs and are made from blenderized whole fruits and vegetables. Comparatively, non-blenderized formula ingredients are derived from highly processed sources, such as whey protein isolate, and manufacturers can condense formulas in their liquid forms.

Compleat© Organic Plant Based EN formula is a commercially prepared BTF made entirely of real food. In each 300 mL packet of BTF, there are 380 calories, 19 grams protein, 15 grams fat, 41 grams carbohydrate, and 6 grams of fiber. In one liter of BTF, there are the equivalent of 3 cups of fruits and vegetables. This BTF is an entirely vegan formula, free of soy, corn, and dairy. To compare, carbohydrates in non-BTF formulas are typically maltodextrin or corn syrup solids, while BTF's sources of carbohydrates are from fruits, vegetables, and brown rice syrup.[7] The BTF's fiber sources include fruits, vegetables, inulin, and fructo-oligosaccharides, and the BTF's protein content comes from hydrolyzed pea protein, whereas protein in non-BTFs commonly contains hydrolyzed whey protein or whey hydrolysate.[7] Due to the preservation of the food matrix, this commercially prepared BTF contains both soluble and insoluble fiber.

Enteral formulation is a contributing factor to diarrhea in critically ill patients due to alterations in gut physiology, reduction of transit time, and elimination of both pathogens and normal flora due to frequent need for antibiotics.[6,11] Without the normal flora, the production of short chain fatty acids diminishes.[11] The inclusion of fiber allows for recolonization of the gut and provides both immune benefits and GI benefits.[7,39] Additionally, the inclusion of fiber both bulks stool and prolongs transit time, allowing for improved nutrient absorption. In the general public, fiber can help bulk stool and normalize frequency of bowel movements. The inclusion of fiber in EN feeds may improve diarrhea for several

reasons, such as the binding of bile salts, the elongation in intestinal transit time, and production of short chain fatty acids.[14]

There are two types of fiber: soluble and insoluble.[7] The mechanism by which fiber affects stooling depends on the type of fiber.[7] Soluble fiber can be partially digested and contributes to formed stools, while insoluble fiber is resistant to digestion and bulks stool, increasing frequency of stooling as a result of added stool weight.[7] Typically, insoluble fiber is excluded from enteral feeds due to concerns for safety, so it is much more common for formula to include soluble fiber.[7] Soluble fiber is recommended as an adjunctive therapy for a patient with critical illness who is suffering from persistent diarrhea while receiving a standard formula (without fiber added).[5,7]

For nutritional management of diarrhea, Chittawatnarat et al compared a mixed fiber and a non-fiber diet for septic patients in the surgical ICU.[41] Of note, exclusion criteria barred mixed fiber provision in patients with obstruction or ileus.[41] The mixed fiber group had significantly less diarrhea– even while receiving antibiotics and there were no reported adverse events during the study duration.[41] Spapen et al investigated the efficacy of soluble fiber in feeds for septic patients, excluding patients with severe ileus or obstruction.[14] Patients in the fiber group (n=13) were given a solution containing 22 grams of soluble fiber per liter, while the control group (n=12) received an isocaloric feed without added fiber.[14] Results showed that there was a significant reduction in diarrhea in the fiber group, but there were no significant differences in outcomes between either group.[14] These studies highlight the efficacy of providing fiber for diarrhea; moreover, the addition of fiber in feeding can also improve GI motility and bowel movement consistency related to constipation.

In a study completed in ICUs in Spain, the patients with the highest incidence of constipation were on a fiber-free formula, whereas the least constipated patients were receiving a diet containing fiber.[39] The lowest incidence of constipation were in the patients receiving soluble fiber.[39] The lowest incidence of constipation were in the patients receiving soluble fiber.[39] Another study by Schultz et. al

explored a combination of fiber-free formula with pectin, a fiber-free formula with placebo, a fiber formula with pectin, and a fiber formula with placebo in a group of 44 patients who were critically ill.[11] The groups with the lowest amount of subjects with diarrhea were the fiber formula with pectin group and, interestingly, the fiber-free formula with placebo.[11] Finally, in a study evaluating fiber supplementation in both healthy and critically ill, there was a marked increase in production of short chain fatty acids and partial restoration of the microbiota in response to fiber supplementation.[42] These studies showcase the versatile benefits of fiber in management of GI complications seen in critical illness.

While these studies have illustrated the role fiber can play in management of GI complications, there is still debate on whether fiber is safe for patients who are critically ill.[7] Case reports from the 1990s, although of small sample size, reported incidence of small bowel obstructions which occurred in patients receiving formulas containing insoluble fiber.[43,44] Fiber may exacerbate constipation, leading to an obstruction or ileus.[7] The ASPEN guidelines recommend to avoid using soluble and insoluble fiber in patients at risk of severe dysmotility or bowel ischemia.[7] ASPEN recommends use of commercial mixed-fiber formula or supplemental fiber in patients with persistent diarrhea.[5] Further, for patients on a fiber-free formula suffering from persistent diarrhea, ASPEN recommends using a soluble fiber supplement/additive if the patient is hemodynamically stable.[5] Therefore, fiber can be administered safely in stabilized critically ill patients to ameliorate GI issues, as diarrhea and constipation may also lead to negative outcomes.

It is known that ECMO patients do have higher incidence of hypomotility and often require more prokinetic medication.[45] With the right combination of EN formula and bowel medication, it is possible to optimize frequency and stool type in this patient population. Recently, BTFs have become more available to clinicians, but there is little research on BTF formula use in the critically ill and how this formula may affect GI complications. A German study compared a commercially prepared BTF formula

to a non-BTF formula in patients who were critically ill with neurological injuries.[10] Researchers found that food-based formula was successful at reducing number of days of diarrhea and total number of watery stool evacuations.[10] There were no adverse events seen in this critically ill population.[10] It is clear that more research is necessary to determine how BTF and the fiber in them affects the critically ill.

Recovery

Nutrition influences feeding adequacy and GI complications, both of which can affect LOS, cost, and mortality. Provision of adequate nutrition throughout the clinical course of a patient who is critically ill is important. Patients who are critically ill rarely meet their nutritional needs for several reasons, likely due to their hypermetabolism, their frequent interruptions in feeding, their high doses of vasopressor medications, and more.[7,28] These factors can lead to a cumulative energy deficit at the end of the clinical course, leading to longer [7]LOS in the ICU, longer length of total hospital stay, and higher incidences of mortality.[,46] Additionally, ECMO patients receive even less nutrition when compared to the a mechanically ventilated patient, meaning that patients on ECMO therapy are at higher nutritional risk.[47]

GI complications are often nosocomial and can drastically complicate a patient's clinical course. With the use of laxatives, patients oscillate between severe constipation and severe diarrhea. Patients receiving ECMO therapy have higher incidence of GI complications, require constant bowel medication, and frequently require rectal tubes. Additionally, these patients are at higher risk for complications, costs, and mortality during their admission.

There is a clear gap in research focusing on ECMO patients and nutritional needs. To best understand how we can mitigate these risks and complications related to the provision of nutrition, we need to appreciate how fiber-containing formula may decrease incidence of diarrhea and thus, rectal tube use. By resolving these GI complications with feeding, we may improve the clinical picture, reduce wounds and infections, reduce cost, and reduce nursing workload. For these benefits, BTF may offer a new direction for enteral formulation specific to the critically ill undergoing ECMO therapy.

The aim of this study is to investigate the safety and efficacy of using BTF for improvement of GI complications in patients undergoing ECMO support. We hope to understand how BTF formula can improve GI complications in patients with high needs undergoing ECMO therapy and receiving standard bowel regimens.

.

Methods

Study Design

This study was a retrospective chart review of critically ill patients on ECMO and EN support in the neurotrauma intensive care unit (NTICU) at Legacy Emanuel Medical Center (LEMC) between January 2018 and September 2020. The purpose of this chart review was to determine if commercially available BTF improved diarrhea, decreased use of rectal tubes, contributed to formed bowel movements with laxative use, and adequately nourished patients. The electronic medical chart was used to determine patients eligible for study inclusion and subsequent analysis for study aims. Inclusion and exclusion criteria are listed in Table 1. Inclusion criteria were: 1) patient must have underwent ECMO support for a period greater than 4 days, and 2) received EN at their respective goal rate. If the patient met these two inclusion variables, the exclusion criteria was applied. Exclusion criteria aimed to eliminate any confounding bowel diseases or conditions that were identified at baseline. If a patient had a history of irritable bowel syndrome, irritable bowel disease, ileus, short bowel syndrome, ischemic bowel, bowel obstruction, enteric fistula, or gut-malabsorptive disorder, that patient was excluded. Additionally, patients could not have been on parenteral nutrition, nor were patients included if they had been treated for COVID-19. If a patient had met any of the exclusion criteria, the patient was excluded from the review. Approval was obtained for this research from the Legacy Research Institute and a waiver of oversight was granted from the OHSU Institutional Review Board (IRB #22341).

Table 1: Inclusion and Exclusion Criteria for Study Participants	
Inclusion Criteria	Exclusion Criteria
1. Critically ill with an illness or injury requiring VV ECMO therapy in NTICU at LEMC 2. Received non-blenderized and/or blenderized enteral formula as primary tube feeding formula	1. Contraindications to enteral feeding and/or confounding diseases affecting bowel function noted at beginning of hospital stay: ileus, small bowel obstruction, short bowel syndrome, ischemic bowel, IBD, IBS, enteric fistula, gut malabsorptive syndrome. 2. Patients who received ECMO for COVID-19. 3. Patients receiving TPN.

Data Collection Methods

Chart review

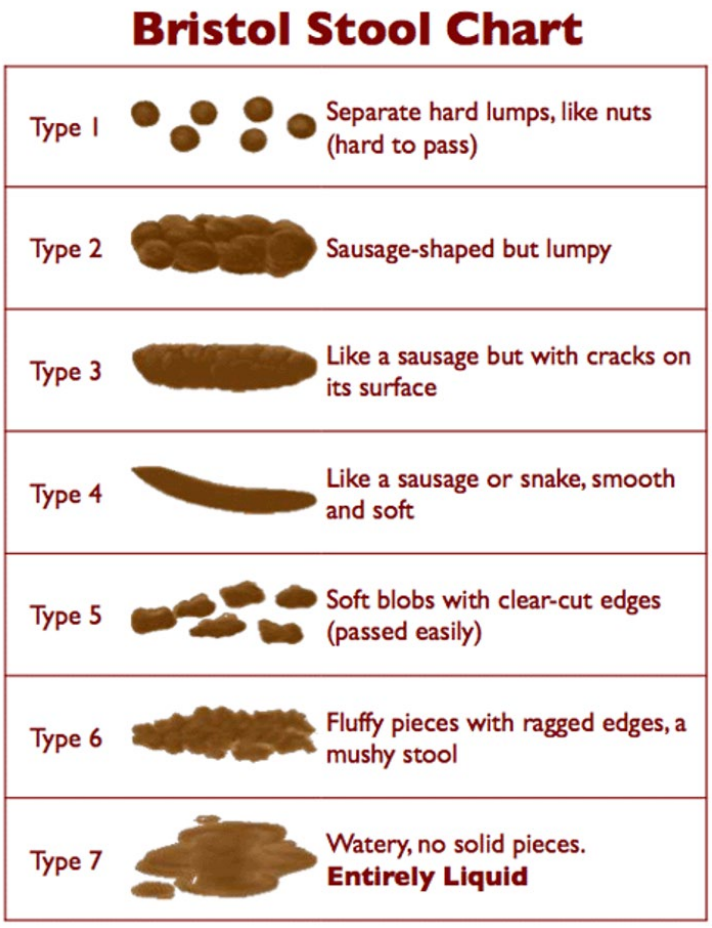
This retrospective chart review used the Epic© software system (Epic, Verona, Wisconsin) employed at LEMC. If a patient met inclusion criteria and was selected for chart review and data analysis, the patient was given a participant ID number to provide anonymity. All patients included were separated into two groups for analysis and compared to determine the relationship between BTF and non-BTF formulas on incidence of diarrhea and rectal tube use, bowel medication regimens, and adverse effects related to fiber. Data was obtained from the medical record using data collection sheets (Appendix A). Data obtained included, and not limited to, was: gender, race, admit weight (kilograms), age (years), sex, medication provision, nutrition prescriptions, nutrition provision (kilocalories per day and kilocalories per kilogram), formula type, total formula in milliliters, bowel movement data (Bristol type stool chart, BM/day, total BMs), rectal tube use, if appropriate, days on rectal tube, rectal tube output, and rectal tube-related skin injury, reported adverse events, total hospital LOS, outcomes (mortality). Standardized definitions and the Bristol Stool Chart classification system guided the chart review and analysis. The time frame for assessment of nutrition provision, GI complications (diarrhea,

constipation, adverse events), and bowel medication use was between the days the patient was receiving ECMO therapy while also receiving EN. Study endpoints included patient expiration, change of formula from BTF to non-BTF (or vice-versa), initiation of TPN, and/or decannulation from ECMO.

Bristol Stool Chart Classification System

The Bristol Stool Chart was employed for assessment of stooling consistency. Stools that resembled any category on the chart were noted as so. The NTICU used this stool typing methodology before this review, so it was used to define patient stool types. Constipation is Bristol type 1-2, while diarrhea is Bristol type 6-7, as seen in Figure 1.[38]

Figure 1: Stool Classification Chart[32]



Definitions of GI Complications

a) Constipation

For this study constipation was defined as three days without a bowel movement.[7,32] Instance of constipation was noted after three days without a charted bowel movement in the patient medical record on the intake/output flowsheet.

b) Diarrhea

There is no universally accepted definition of diarrhea. For this study diarrhea is defined as abnormal volume or consistency of stool.[7] Abnormal volume of diarrhea was output greater than 500 mL every 24 hours, or ≥3 stools per day for at least two consecutive days. On the Bristol Stool Chart, diarrhea is Type 6-7 stools.[32] For ease, stooling will be considered as diarrhea if it falls under Bristol type 6-7 stools, volume >500mL/24 hours, and/or ≥3 stools/day for two consecutive days.[32] For diarrhea incidence, average BST over course was used due to irregular charting practices.

c) Ileus

Ileus is a functional obstruction of the intestines, in which motility is inhibited, and was considered an adverse outcome.[7] Provider notes were reviewed to determine if ileus occurred.

d) Bowel Obstruction

A small bowel obstruction (SBO) may be caused by a mechanical obstruction or postoperative ileus.[7,39] SBOs are detected via exploratory laparotomy or radiography/computed topography.[39] It is considered a perforation if there is vascular compromise or frank perforation.[7,39] Providers' diagnosis of an SBO was identified by patient chart review.

e) Ischemic Bowel (Intestinal Ischemia)

Ischemic bowel results from reduced blood flow to the GI tract.[7,40] Diagnosis includes lab tests, like complete blood count (CBC), chemistry, coagulation panel, and arterial blood/gas lactate.[40]

Other investigations are mesenteric angiography, mesenteric duplex ultrasound, and magnetic resonance angiography.[40] Providers' diagnosis of ischemic bowel was identified by patient chart review.

f) Emesis

Events of emesis were recorded under provider notes and could be found using the intake/output flowsheet.

g) Rectal tube associated skin injury

Indications of rectal skin injury was identified in wound ostomy staff notes, as well as provider chart notes.

Bowel Medications

First-line treatments for constipation are usually hydrophilic colloids (psyllium, bran methylcellulose, and polycarbophil), stool softeners, and osmotic laxatives (lactulose, polyethylene glycol, sorbitol, magnesium salts).[1] Second-line treatments for constipation is more intensive, requiring the use of stimulants (senna/docusate, bisacodyl/docusate, or casanthranol/docusate) and lubricants (mineral oil).[1] In cases where these second line therapies do not work, combination therapy of osmotic laxatives combined with suppositories or enemas may be used.[1]

The NTICU often used what may be considered as second-line treatment for constipation prophylaxis, and most of the medications were "as needed" or "PRN" medications, wherein the provider decided if the medication was necessary the day of use. The NTICU's first line bowel regimen consists of sennosides (stimulant laxative) and docusate sodium (stool softener), adding polyethylene glycol (osmotic laxative) and bisacodyl (stimulant laxative) with provider discretion. These four medications were considered as the first line of defense for this chart review.

If stooling was still not achieved, the NTICU added less commonly used medications, such as magnesium citrate, lactulose, milk of magnesia, mineral oil enemas, docusate enemas, and

methylnaltrexone. These medications were considered the second line of treatment for the purpose of this chart review.

The three most common bowel regimens were grouped together as there was seldom use of second line medication but common use of first line medication. The first group was a combination of a stool softener (docusate sodium) and stimulant laxative (sennosides), the second bowel regimen included these two medications and an osmotic laxative (polyethylene glycol). The third bowel regimen included these three with bisacodyl.

Calculations

Dosing of Medication

Medication doses varied as many bowel medications were given "as needed". When medication prescription was a dose multiple times a day, the dose was simply added and made a daily sum. If different days had different doses, a grand average was taken of all different doses multiplied by respective dosing days then divided by total days on the drug.

Assessing Fiber Intake

Amount of fiber included in enteral formulas was recorded in order to compare fiber provision. The amount of fiber was calculated by multiplying the grams of fiber provided per milliliter of formula by the total formula provided in milliliters. This value denotes total grams of fiber provided by feeding within a 24-hour period.

Assessing Energy and Protein Provided by Formula

Energy provided by milliliter of formula were multiplied by average total milliliters of formula provided. Protein was calculated using this method but with protein in grams per one milliliter of formula multiplied by average total daily provision. For BTF formula, the average percent of the goal total formula was used to determine protein and calorie provision. This calculation ensured that energy and protein provision was not overestimated, as BTF requires additional water to be added prior to

provision. The percent of the total 24-hour milliliter goal was then multiplied by the prescription's calories and protein.

Measuring Feeding Adequacy

Nutritional adequacy was measured by taking the daily energy provision compared (calculated by total rate in milliliters multiplied by calories/mL provided by formula) to the nutrition prescription. Nutritional adequacy was represented as a percentage (actual energy provided divided by estimated energy requirement). Overall average of nutritional adequacy was used to find mean energy provided compared to our estimated energy goal. Percent of needs met for calories and protein was used to assess adequacy. For feeding to be considered adequate, it must meet at least 80% or greater of the patients' energy and protein needs.[5]

For the BTF group, there was a different calculation required to measure nutritional adequacy, as Compleat© Organic Plant Based formula requires an additional 100 milliliters of water per packet, thus inflating total volume and making calories or protein per milliliter inaccurate. Therefore, the hourly goal rate (which includes water added) was multiplied by 24-hours to find the total milliliters of formula expected for one day. The total milliliters provided for that day were then compared to the goal milliliters. The proportion of milliliters provided to goal milliliters was given as a percent, and the percent was used to find the calories and protein received by multiplying the goal nutrition prescription by the percent of milliliters the subject received. This percent was then averaged over the total time the subject was on study.

Statistical Analysis

Statistical analysis was performed using Stata/IC 16.1 (College Station, Texas). Non-parametric statistical tests were performed throughout the dataset to determine significance.

Odds ratio with a 95% confidence interval was used to assess formula and its effect on incidence of diarrhea. A Wilcoxon rank sum test determined if there is a relationship between BTF formula and

non-BTF formula to days of diarrhea. A Pearson's Chi Square analysis was used to determine if there was a relationship between incidence of diarrhea, defined by average BST ≥6.0. The *p*-value must be <0.05 to be considered statistically significant, and a very significant finding considered if $p<0.005$. Odds ratio with a 95% confidence interval was used to assess the treatment (blenderized formula) and its influence on rectal tube use. A Pearson's Chi Square analysis tested for the strength of the relationship between rectal tube use and formula type. Time on a rectal tube, measured in days, and rectal tube output were compared using a Wilcoxon rank sum analysis.

A Pearson's Chi Square analyzed for significant differences in first line bowel medication and second line bowel medication provision between groups. A p-value<0.05 was considered significant and a very significant finding considered if $p<0.005$. A Wilcoxon rank sum tested for differences in days of medication provision and dosing of medication. A multinomial regression assessed the outcome of diarrhea incidence, defined by an average Bristol type 6-7 stools, with use of specific first line bowel medications and formula type.

Bowel medication regimens were separated and used for comparison between subjects on both formula groups. Grouped bowel regimens were formed and analyzed by Pearson's Chi Square test. A Wilcoxon rank sum test was employed to find the significance of proportion of diarrhea following medication provision, days of diarrhea following medication provision, and average BST. The aim determined how combinations of common bowel medications influenced stool type and incidence of diarrhea.

Odds ratio was used, followed by the use of fisher's exact test to examine formula administration on risk of bowel obstruction or ischemia as there were less than five observations in two of the quadrants. Other signs of feeding intolerance were tested using Pearson's Chi Square.

Energy needs were calculated using the Mifflin St. Jeor equation, as well as calories per kilogram (kcals/kg) of admit body weight (BW) or ideal body weight (IBW) and protein in grams per kilogram of

admit BW or IBW. Nutritional adequacy (calories and protein provided by enteral formula divided by estimated needs) in both formula groups and compared using a Wilcoxon rank sum analysis. A p-value<0.05 was considered significant and a very significant finding considered if $p<0.005$.

An odds ratio with 95% confidence interval examined odds of skin injury with the treatment (rectal tube use). A Chi Square analysis determined significance of relationship with $p<0.05$ and a very significant finding considered if $p<0.005$. Days on a rectal tube were tested using a Wilcoxon rank sum test, and a multinomial regression gauged the outcome of rectal tube-related skin injury with formula type and days spent with a rectal tube placed.

Table 2: Statistical Plan

Specific Aims & Exploratory Aims	Hypotheses	Statistical Tests
Specific Aim 1: To determine the relationship between blenderized formula and the incidence of diarrhea and rectal tube use in patients on ECMO therapy.	**Hypothesis**: We hypothesize that the odds of diarrhea and rectal tube use will be lower in patients on blenderized formula when compared to patients on non-blenderized formula.	**Statistical Test:** A Wilcoxon rank sum (p<0.05) was used to assess continuous or interval data between formula groups (bowel movement frequency, total bowel movements over course, average BST). Odds ratio and 95% confidence interval for odds of diarrhea by formula type. Chi Square analysis used to determine significance for formula groups and diarrhea. Odds ratio and 95% confidence interval for rectal tube use and formula type. Chi square analysis for rectal tube use and formula type. Days on rectal tube and rectal tube output were analyzed via Wilcoxon rank sum test. Simple logistic regression and 2x2 Epi table between rectal tube use by formula. Simple logistic regression and 2x2 Epi table for diarrhea incidence and formula type.
Specific Aim 2: To understand how formula influences bowel medication use in ECMO patients.	**Hypothesis 1**: We hypothesize that patients on blenderized formula will require more laxatives compared to patients on non-blenderized formula; however, compared to patients on a non-	**Statistical Test:** Wilcoxon rank sum test was used to determine if there is a significant difference (p<0.05) in medication dosing and days on medications between formula groups. Chi square analysis for laxative use and blenderized formula. Multinomial regression analysis between diarrhea

	blenderized formula using laxatives, patients on blenderized formula will have more formed stools and less diarrhea.	incidence (outcome) with formula type and first line bowel medications.
	Hypothesis 2: We hypothesize in patients receiving bowel medications to promote bowel movements, those on blenderized formula will have less incidence of diarrhea than compared to patients on non-blenderized formula.	**Statistical Test:** Wilcoxon rank sum observed for differences in days of diarrhea 24-72 hours following medication provision respective to formula type and bowel regimen. Wilcoxon rank sum observed for differences in days of diarrhea following medication provision by total diarrhea, represented as a percent, by formula group respective to each bowel medication regimen. Wilcoxon rank sum determined significant relationship for average BST by formula type on respective bowel medication regimen.
Specific Aim 3: To assess if fiber in enteral formula increases odds of adverse GI events, such as bowel ischemia or bowel obstruction, in critically ill patients.	**Hypothesis**: We hypothesize that formulas with intact fiber will improve diarrhea without inducing bowel ischemia or causing bowel obstructions in the critically ill.	**Statistical Test:** Wilcoxon rank sum evaluated if there is a significant difference ($p<0.05$) in grams of fiber by formula group. Fisher's Exact test was employed to test for significance in bowel ischemia or bowel perforation and formula type. Chi square analysis tested for significance of relationship between formula and adverse events (emesis, ileus, obstipation, and GI bleeding).
Exploratory Aim 1: To gauge how blenderized formula influences feeding adequacy in patients receiving ECMO therapy.		**Statistical Test:** Wilcoxon rank sum assessed for differences in predicted needs between formula groups. Wilcoxon rank sum used to determine if there was a significant difference ($p<0.05$) in feeding adequacy (calories and protein provided by feed represented as a percent of needs).
Exploratory Aim 2: To explore how rectal tubes influence skin integrity.		**Statistical Test:** Odd's ratio and 95% confidence interval for skin injury with rectal tube use. Chi square analysis evaluated the significance of the relationship. Multinomial logistic regression observing for outcome of rectal tube-related skin injury with days on a rectal tube and formula type.

Results

Demographics

One-hundred thirty-three (133) participants were identified for screening. Subjects were identified if they were receiving ECMO therapy between January of 2018 to March of 2020 (Figure 2). Based on exclusion criteria, 74 subjects were removed from the study. The 59 remaining subjects were then separated into two groups based on their enteral formula type. There were 33 subjects in the BTF formula group and 26 subjects in the non-BTF formula or control group.

Figure 2: Study Selection Process

Participant demographics were determined to be non-normally distributed using a Shapiro Wilke's test. There were no significant differences between subjects in regard to age, race, gender, admit weight (Table 3). All subjects were diagnosed with either acute respiratory failure and/or acute respiratory distress syndrome, with the etiology being infection for a majority of the subjects (n = 43 (72.9%)). There was a significant difference in diagnosis (p=0.022). All subjects were intubated, sedated, and receiving VV-ECMO support for the duration of study inclusion. There was a significant difference in

the total hospital LOS between the BTF group and the control (34.9±18.8 vs. 43.9±22.8; p=0.0406); although, there was not a significant difference in days receiving ECMO support.

Table 3: Participant Characteristics

Characteristic	Non-BTF, n = 26		BTF, n = 33	*p*
		mean±SD		
Age (years)	46.9±13.0		44.9±13.4	0.6469
Bodyweight (kg)	104.1±34.7		91.7±28.4	0.1469
Days on ECMO (d)	16.9±10.6		17.2±11.0	0.9391
LOS (d) [a, b]	43.9±22.8		34.9±18.8.	0.0406*
		n(%)		
Sex				0.315
Male	19 (73.1%)		20 (60.6%)	
Female	7 (26.9%)		12 (36.4%)	
Race				0.615
Caucasian	17 (65.4%)		20 (60.6%)	
Hispanic/Latino	2 (7.7%)		4 (12.1%)	
African American	3 (11.5%)		1 (3.3%)	
Alaskan Native/American Indian	1 (3.9%)		2 (6.1%)	
Native Hawaiian/Pacific Islander	1 (3.9%)		1 (3.3%)	
Unknown	2 (7.7%)		3 (9.1%)	
Medical Diagnosis [c, d]				0.022
ARDS	26 (100%)		26 (81.3%)	
ARF	0 (0%)		6 (18.8%)	
Etiology of Respiratory Distress				0.636
Infection	17 (65.4%)		26 (78.8%)	
Trauma	5 (19.2%)		4 (12.1%)	
Inhalation Injury	2 (7.7%)		1 (3.3%)	
Unknown	2 (7.7%)		1 (3.3%)	
Mortality	3 (11.5%)		9 (27.3%)	0.136

* indicate significant differences defined at p<0.05

[a] Shapiro Wilke's test used to determine distribution of data; [b] Wilcoxon rank sum test; [c] Pearson's Chi square analysis; [d] Fisher's exact

Abbreviations: BTF = blenderized tube feeding, ARDS = acute respiratory distress syndrome, ARF = acute respiratory failure, ECMO = extracorporeal membrane oxygenation, LOS = length of stay, n = number of subjects, (%) = percentage of subjects

Energy and Protein Requirements

All subjects received enteral nutrition support throughout their duration on ECMO. There were no significant differences in prescribed energy (kcal/day) between the BTF group and the control group (1691.6±319.8 vs. 1829.7±320.7; *p*=0.1601) (Table 4). There were no significant differences in days fed and the number of days where feeds were interrupted. Overall, predicted needs and time receiving enteral nutrition were similar between groups. There were significant differences in protein provided by formula alone, yet a significant difference remained after including protein provided by formula and supplement. The BTF group received less protein from formula and less protein overall even with the protein supplement included.

Table 4 – Predicted and Prescribed Nutritional Needs

	Non-BTF, n = 26	BTF, n = 33	*p*
	mean±SD		
Energy Prescription (kcals/kg)	30.2±17.9	29.9±16.9	0.9635
Protein Prescription (gm/kg)	2.0±0.32	1.9±0.23	0.0976
Energy Provided by Formula (kcals/d)	1829.7±320.7	1691.6±319.8	0.3689
Protein Provided by Formula (gm/d) [a]	117.0±32.9	88.4±14.4	<0.01*
Energy Provided by Formula & Supplement (kcals/d)	1997.6±410.4	1940.8±286.4	0.6300
Protein Provided by Formula & Supplement (gm/d) [a]	140.7±27.9	126.2±21.0	0.0345*
Percent Goal Received	90.3%±7.3%	88.4%±12.6%	0.7027
Days Fed (d)	13.5±10.4	13.6±10.8	0.9390
Feed Interruptions (d)	2.6±2.9	2.6±2.7	0.7846

* Indicate statistically significant measured at the *p*=0.05 level
[a] Wilcoxon rank sum analysis
Abbreviations: BTF = blenderized tube feeding, n = number of subjects, gm = grams, kcals = kilocalorie, kg = kilogram, d = day

Bowel Patterns

Total stools over subjects' time receiving ECMO therapy and EN course were recorded, as well as bowel movements per day (Table 5). There was a very significant difference in total bowel movements over the ECMO course. The BTF group had significantly more stools than the non-BTF group (38.2±31.3 days vs. 23.5±21.3 days; $p<0.001$), and there was a very significant difference in average bowel frequency, measured as bowel movements per day with the BTF group having more frequent stools as compared to non-BTF group (2.9±1.4 vs. 1.5±0.6; $p<0.001$). There were non-significant differences in days of diarrhea between BTF and non-BTF groups (4.5±3.4 days vs. 5.9±6.5 days; $p=0.975$). There was a significant difference in average Bristol Stool Type (BST) between the BTF and non-BTF groups (5.4±0.9 vs. 6.6±0.3; $p<0.001$), with the BTF group having more formed, soft stools and the non-BTF having mostly mushy and/or loose stools.

Table 5 – Bowel Patterns

	Non-BTF, n = 26	BTF, n = 33	*p*
	mean±SD		
Total BMs [a]	23.5±21.3	38.2±31.3	<0.001*
Frequency (BMs/d) [a]	1.5±0.6	2.9±1.4	<0.001*
BST [a]	6.6±0.3	5.4±0.9	<0.001*
Days with Diarrhea (d)	5.9±6.5	4.5±3.38	0.975

* indicates statistical significance measured at the p=0.05 level;
[a] Wilcoxon rank sum test
Abbreviations: BTF = blenderized tube feeding, BST = Bristol Stool Type, n = number, (%) = percentage, d = days, BM = bowel movement

A simple logistic regression showed a very significant difference in risk of developing diarrhea between groups ($p<0.001$). The odds ratio for developing diarrhea was 0.017 for subjects receiving BTF compared to those on non-BTF formula. The relative risk of developing diarrhea in the BTF group was

31.5% of that in patients who received non-BTF formula, and the risk of developing diarrhea in the non-BTF group was 3.17 times higher than the BTF group (Table 6).

Table 6 - Epi 2-By-2 Table Analysis for Risk of Diarrhea

	Diarrhea	No Diarrhea	Total	Increased Risk*	Odds
BTF	10	23	33	30.3	0.435
Non-BTF	25	1	26	96.2	25.000
Total	35	24	59	96.2	1.458

Point Estimates & 95% CIs:	
Increased Risk Ratio	0.32 (0.19, 0.53)
Odds ratio	0.02 (0.00, 0.15)
Attributed risk *	-65.85 (-83.19, -48.52)
Attributed risk in population *	-36.83 (-51.38, -22.28)
Attributed fraction in exposed (%)	-217.31 (-435.38, -88.06)
Attributed fraction in population (%)	-62.09 (-99.01, -32.02)
Chi 2 = 26.133; p = <0.001	

* indicates statistical significance measured at the p=0.05 level
Abbreviations: BTF = blenderized tube feeding, CI = confidence interval

Rectal Tube Use

There was significant inverse relationship with rectal tube use and the use of BTF. With 16 subjects having a rectal tube in the non-BTF group and only 8 having a rectal tube in the BTF group, there was significantly higher use of rectal tubes in the non-BTF group than the BTF group (61.5% vs. 24.2%; p=0.0139) (Table 7). Further, the average length of time spent with a rectal tube was significantly higher in the non-BTF group compared to the BTF group (6.6±8.4 days vs. 0.9±2.0 days; p=0.0012). Average rectal tube output in the BTF group was 568.8±243.0, meanwhile the output from the non-BTF group was 651.0±278.5 (p=0.0062).

Table 7 - Rectal Tube Usage				
Rectal Tube Data	Non-BTF, n = 26		BTF, n = 33	*p*
		n(%)		
Subjects with RT [b, c, d]	16 (61.5%)		8 (24.2%)	0.003*
		mean±SD		
Time with RT (d)[a]	6.6±8.4		0.9±2.03	0.0012*
RT Output (mL)[a]	651.0±278.5		568.8±243.0	0.0062*

* indicates statistical significance measured at the p=0.05 level

[a] Wilcoxon rank sum test; [b] Pearson's Chi square analysis; [c] Fisher's Exact test; [d] Odd's ratio and 95% CI.

Abbreviations: BTF = blenderized tube feeding, RT = rectal tube, n = number, (%) = percentage, d = days, mL = milliliters

A simple logistic regression suggests that incidence of rectal tube placement was significantly lower in subjects who received BTF formula compared to those who did not (*p*=0.003). A two-by-two Epi table also indicated that BTF subjects had fewer rectal tube placement than those on non-BTF formula (*p*=0.004). The risk for rectal tube placement in the BTF group was 39.9% of the risk for rectal tube placement for those on non-BTF formula. The odds ratio for rectal tube placement was 0.200 (95% CI = 0.065, 0.614) for patients on BTF compared to non-BTF (Table 8).

Table 8 - Epi 2-By-2 Table Analysis for Rectal Tube Placement					
	RT	No RT	Total	Increased Risk*	Odds
BTF	8	25	33	24.2	0.320
Non-BTF	16	10	26	61.5	1.60
Total	24	35	59	40.7	0.686
Point Estimates & 95% CIs:					
Increased Risk Ratio				0.39 (0.20, 0.77)	
Odds ratio				0.20 (0.00, 0.61)	
Attributed risk *				-37.30 (-61.03, -13.56)	
Attributed risk in population *				-20.86 (-43.37, 1.65)	
Attributed fraction in exposed (%)				-153.85 (-398.74, -29.20)	
Attributed fraction in population (%)				-51.28 (-94.90, -17.43)	
$Chi^2 = 8.383$; $p = 0.004$					

Abbreviations: BTF = blenderized tube feeding, RT = rectal tube, CI = confidence interval

Use of Bowel Medications

The most common bowel medication administered was a stimulant laxative (sennosides), followed by an osmotic laxative (polyethylene glycol) (Table 9). There were no significant differences between formula groups with any of the singular medications for first-line medications. There were no significant differences in dosing or time on any of the first-line bowel medications (Table 10). Due to the small number of participants receiving second line bowel medications, tests for significance were not conducted (Table 11, Table 12).

Table 9 – First Line Medications

	Non-BTF, n = 26	BTF, n = 33	*p*
	n (%)		
Sennosides	16 (61.5%)	24 (72.7%)	0.361
Docusate Sodium	17 (65.4%)	19 (57.6%)	0.202
Pericolace	10 (38.5%)	11 (33.3%)	0.683
Polyethylene Glycol	21 (80.8%)	26 (78.79%)	0.851
Bisacodyl	12 (46.2%)	19 (57.6%)	0.383

* indicates statistical significance measured at the p=0.05 level
Abbreviations: BTF = blenderized tube feeding, n = number, (%) = percentage of group

Table 10 – Dosing and Time on First Line Medication			
	Non-BTF, n = 26	BTF, n = 33	*p*
	mean±SD		
Sennosides			
Days of mg (d)	8.4±9.2	6.5±4.7	0.4445
Dose (mg)	18.0±9.4	17.64±7.5	0.4268
Days of mL (d)	9.3±9.6	8.4±7.7	0.4422
Dose (mL)	14.6±12.1	13.9±5.1	0.6619
Docusate Sodium			
Days (d)	10.9±10.2	6.3±5.0	0.2374
Dose (mg)	137.1±74.9	150.7±50.9	0.9686
Pericolace			
Days (d)	6.1±4.3	7.6±4.8	0.8514
Dose (tabs)	1.7±0.5	1.9±1.1	0.6945
Polyethylene Glycol			
Days (d)	8.2±8.9	5.2±3.9	0.4194
Dose (gm)	19.9±5.0	23.2±7.7	0.3220
Bisacodyl			
Days (d)	2.5±1.4	1.9±0.9	0.7571
Dose (mg)	10±0	10.3±1.2	0.3360

* indicates statistical significance measured at the p=0.05 level
Abbreviations: BTF = blenderized tube feeding, n = number, (%) = percentage of group, tabs = tablets, mg = milligram, mL = milliliter, gm = grams, d = days

Table 11 – Second Line Bowel Medications

Medication	Non-BTF, n = 26	BTF, n = 33	*p*
	n (%)		
Milk of Magnesia	4(15.4%)	2(6.06%)	0.239
Lactulose	1 (3.9%)	5 (15.2%)	0.154
Magnesium Citrate	2(7.69%)	6(18.18%)	0.243
Methylnaltrexone	3(11.5%)	5(15.2%)	0.687
Docusate Enema	0(0%)	2(6.1%)	0.202
Mineral Oil Enema	1(3.9%)	3(9.1%)	0.426

Abbreviations: BTF = blenderized tube feeding, n = number, (%) = percentage of group

Table 12 – Second Line Bowel Medications			
Medication	Non-BTF, n = 26	BTF, n = 33	*p*
	mean±SD		
Milk of Magnesia			
Days (d)	1.3±0.5	1±0	0.2322
Dose (mL)	45±17.3	45±21.2	0.2441
Lactulose			
Days (d)	1±0	3.2±3.9	0.1494
Dose (mg)	200±0	53.7±22.7	0.1806
Magnesium Citrate			
Days (d)	1.5±0.7	1.2±0.4	0.2693
Dose (mg)	296±0	296±0	0.2467
Methylnaltrexone			
Days (d)	1±0	1.2±0.4	0.6620
Dose (mg)	12±0	11.6±0.9	0.7189
Docusate Enema			
Days (d)	0±0	1±0	0.2054
Dose (1 enema)	0±0	1±0	0.2054
Mineral Oil Enema			
Days (d)	1±0	1±0	0.4302
Dose (1 enema)	1±0	1±0	0.4302

Abbreviations: BTF = blenderized tube feeding, n = number, (%) = percentage of group, tabs = tablets, mg = milligram, mL = milliliter, gm = grams, d = days

The most commonly grouped medications were combined into three regimens (Table 13, Figure 3). Bowel Regimen 1 included a combination of sennosides, a stimulant laxative, and docusate sodium, a stool softener. The second regimen (Bowel Regimen 2) included sennosides, docusate sodium, and polyethylene glycol, an osmotic laxative. Finally, Bowel Regimen 3 included sennosides, docusate sodium, polyethylene glycol, and bisacodyl, a stimulant laxative. The first bowel medication combination

was the most common with 25 subjects on BTF and 23 subjects on non-BTF (p=0.214). The second bowel regimen was seen in 22 subjects in the BTF group and 20 subjects in the non-BTF group, and there was not a significant difference between proportion of subjects receiving this regimen between groups (p=0.388). The third bowel regimen was used in 14 subjects on BTF and 10 on non-BTF formula, and there was not a significant difference in proportion of subjects on this regimen (p=0.684).

Table 13 – Grouped Bowel Regimens

Bowel Regimen	Non-BTF, n = 26	BTF, n = 33	*p*
	n(%)		
Bowel Regimen 1	23 (88.5%)	25 (75.8%)	0.214
Bowel Regimen 2	20 (76.9%)	22 (66.7%)	0.388
Bowel Regimen 3	10 (38.5%)	14 (42.4%)	0.684

* Indicates statistical significance measured at the p=0.05 level
Abbreviations: BTF = blenderized tube feed, BST = Bristol Stool Type, n = number, (%) = percentage, d = days

Figure 3: Subjects Per Bowel Regimen by Formula Type

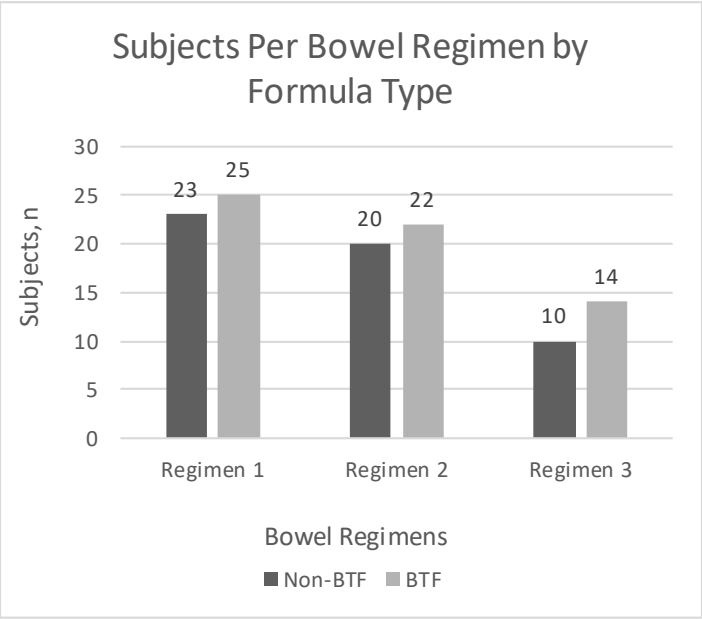


Figure 3. Subjects separated by bowel medication regimen and respective formula group. Subjects represented by (n) denoted above each bar.

Abbreviations: BTF = blenderized tube feeding, non-BTF = non-blenderized tube feeding

To assess the relationship between medication and diarrhea incidence, days between medication provision and diarrhea were recorded and proportion of diarrhea following medication was calculated. The number of days between medication dosing and diarrhea was not significant for any patient receiving any type of bowel regimen. There was also no significant difference in the proportion of patients experiencing diarrhea after receiving medication in any of the groups.

A significant difference in BST was seen between the BTF groups and the non-BTF groups for all bowel regimens (Table 14). For those receiving the first bowel regimen average BST in the BTF group was 5.0±0.8 while the average BST in the non-BTF group was 6.0±0.4 (p<0.001). For those receiving the second bowel regimen, average BST in the BTF group was 4.92±0.73 while the average BST in the non-BTF group was 5.9±0.3 (p=0.0010). For those receiving the third bowel regimen, the average BST in the BTF group was 4.9±0.7 while the average BST in the non-BTF group was 5.9±0.3 (p=0.0014). Overall, there was a lower BST in the BTF group, indicating that even with medication provision, there was a lower incidence of loose stools in the BTF group even when compared to the non-BTF group (Figure 4).

Table 14 – Bowel Pattern by Regimen

Bowel Regimens	Non-BTF, n = 26	BTF, n = 33	*p*
	mean±SD		
Bowel Regimen 1			
Days Diarrhea Following Med (d)	4.2±4.9	3.3±2.8	1.0
Percent Diarrhea Following Med (%)	74.48%±0.35%	73.3%±0.4%	0.7910
BST [a]	6.0±0.4	5.0±0.8	<0.001*
Bowel Regimen 2			
Days Diarrhea Following Med (d)	3.0±0.3	3.6±0.4	0.8026
Percent Diarrhea Following Med (%)	72.9%±0.4%	55.7%±0.4%	0.3018
BST [a]	6.2±0.4	4.6±1.3	0.0010*
Bowel Regimen 3			
Days Diarrhea Following Med (d)	2.3±0.2	2.7±0.2	0.6129
Percent Diarrhea Following Med (%)	50.3%±0.4%	78.9%±0.4%	0.0954
BST [a]	5.9±0.3	4.9±0.7	0.0014*

* indicates statistical significance measured at the p=0.05 level

[a] Wilcoxon rank sum test

Abbreviations: BTF = blenderized tube feed, BST = Bristol Stool Type, n = number, (%) = percentage, d = days

Figure 4: Bristol Stool Type by Formula Versus Bowel Medication

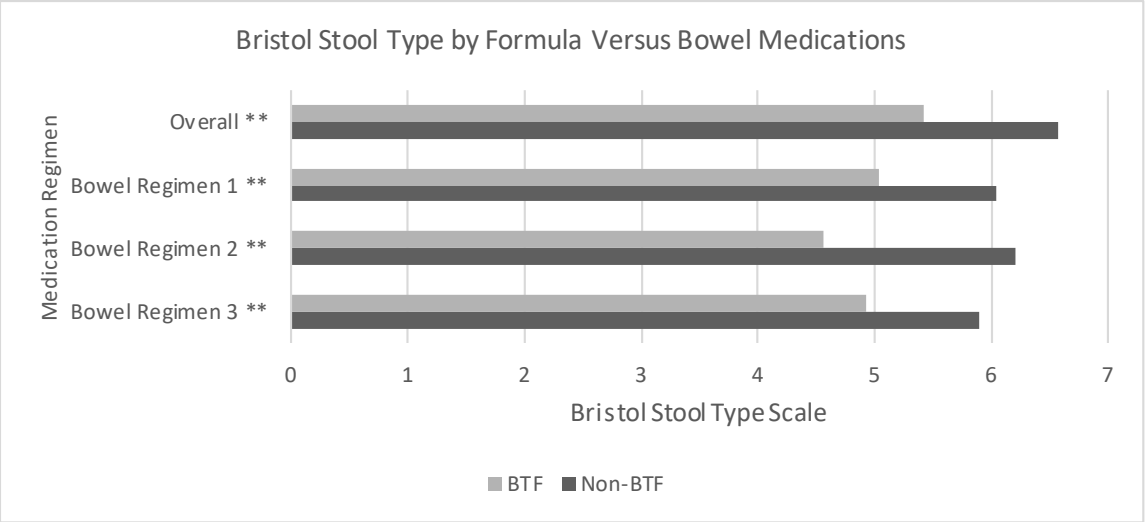


Figure 4. Average Bristol Stool Type respective to each bowel regimen. * Indicates statistical significance at $p<0.05$ level. Abbreviations: BTF = blenderized tube feeding, non-BTF = non-blenderized tube feeding

GI Complications, Adverse Events and Constipation

Enteral feeding tolerance was similar between the groups indicated by the lack of significant differences in the incidence of ileus, obstipation, emesis or bloody stools between the BTF and non-BTF groups. Adverse events observed in this study were ischemic bowel and bowel obstruction (Table 15). There were two instances of bowel obstruction in the BTF group, but these were not significant due to small case number.

Table 15 - GI complications and adverse events			
GI Complications	Non-BTF, n = 26	BTF, n = 33	*p*
	n (%)		
Ileus	4 (15.4%)	8 (24.2%)	0.401
Obstipation	1 (3.9%)	1 (3.0%)	0.863
Emesis	6 (23.1%)	8 (24.2%)	0.917
Bloody Stools	7 (26.9%)	7 (21.2%)	0.609
Adverse Events			
	n (%)		
Ischemic Bowel	0 (0%)	1 (3.0%)	0.371
Bowel Obstruction	0 (0%)	2 (6.1%)	0.202

* Indicates statistical significance measured at the p=0.05 level
Abbreviations: n = number; (%) = percentage of group, BTF = blenderized tube feeding, GI = gastrointestinal

The average amount of days without a bowel movement were 2.1±2.0 days in the BTF group and 2.6±2.4 days in the non-BTF group (Table 16). There was no significant difference in days without a bowel movement between groups. There was also no significant difference in instances between the two groups with only five instances of constipation in the BTF group and three instances of constipation in the non-BTF group. Overall, the data suggests that formula type did not significantly impact rate of constipation and days without a bowel movement.

Table 16 – Constipation			
	Non-BTF, n = 26	BTF, n = 33	*p*
	mean±SD		
Days of No BM (d)	2.6±2.4	2.12±2.0	0.3976
	n (%)		
Incidence of Constipation	3 (11.5%)	5 (15.2%)	0.687

* Indicates statistical significance measured at the p=0.05 level
Abbreviations: BTF = blenderized tube feeding, BST = Bristol Stool Type, n = number, (%) = percentage, d = days, BM = bowel movement

Enteral Feedings

There was not a significant difference in energy provision (measured in kcals) between the BTF group and the non-BTF group (1787.0±490.6 vs. 1683.5±329.9; *p*=0.3136), nor was there a difference in calories per kilogram received (29.9±16.9 vs. 30.2±17.9; *p*=0.8307). However, there was a significant difference in protein received between the BTF and non-BTF groups (103.2±20.4 vs. 120.7±23.4; *p*=0.0118), and there was a significant difference in grams protein per kilogram of bodyweight between the two groups with the BTF group receiving 1.8±0.3 and the non-BTF receiving 1.5±0.3 (*p*=0.0045). Nutritional adequacy is described in Table 18. Despite differences in grams of protein provided, there was no significant difference in nutritional adequacy between groups (*p*=0.3361). Figure 5 describes the differences between calories and protein by formula.

Table 17 - Enteral Provision

	Non-BTF, n = 26	BTF, n = 33	*p*
	mean±SD		
Energy Provision (Kcals)	1683.5±329.9	1787.0±490.6	0.8307
Protein Provision (gm)[a]	120.7±23.4	103.2±20.4	0.0118*
Fiber in Feeds (gm)[a]	3.4±5.3	31.3±6.3	<0.001*
Energy Provision (kcals/kg)	20.9±6.9	20.2±6.2	0.8070
Protein Provision (gm/kg) [a]	1.8±0.3	1.5±0.3	0.0045*

* Indicate statistically significant measured at the *p*=0.05 level
[a] Wilcoxon rank sum analysis
Abbreviations: BTF = blenderized tube feeding, n = number of subjects receiving enteral feeds respective of formula. of the mean. Gm = grams; kcals = kilocalorie; kg = kilogram

Table 18 – Feeding Adequacy			
	Non-BTF, n = 26	BTF, n = 33	*p*
	mean±SD		
Energy Needs Met	89.2%±12.0%	87.1%±12.5%	0.9149
Protein Needs Met	87.1%±13.4%	82.4%±13.3%	0.3361

* Indicate statistically significant measured at the *p*=0.05 level
Abbreviations: BTF = blenderized tube feeding, n = number of subjects receiving enteral feeds respective of formula

Figure 5: Calories and Protein Provided by Formula

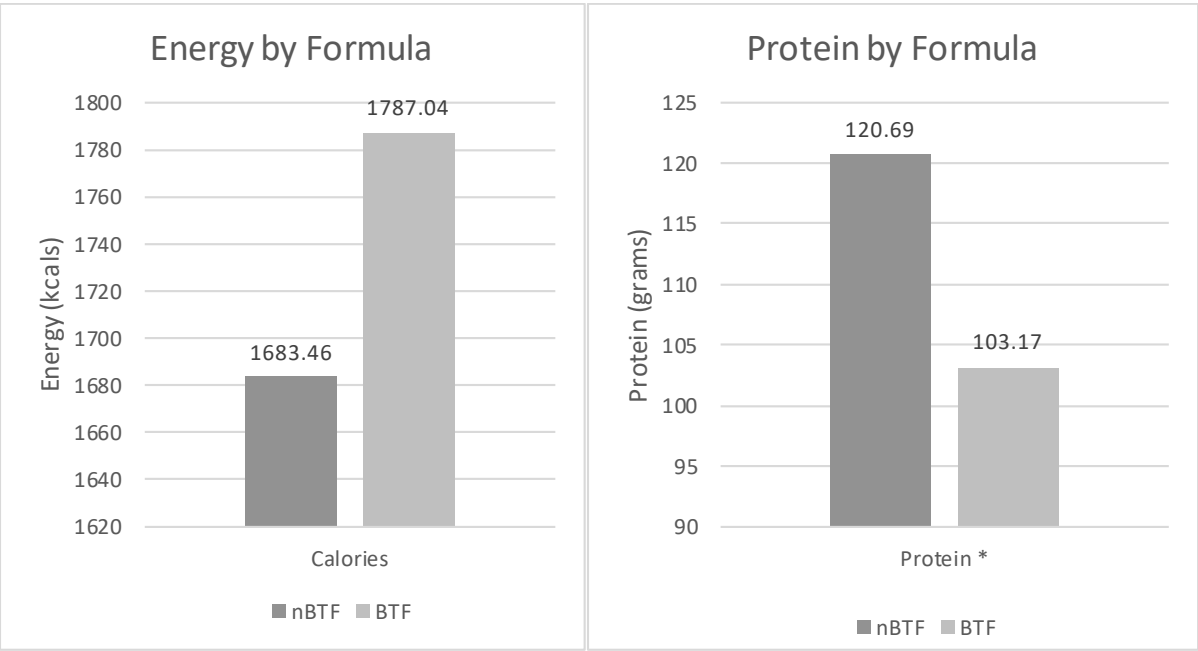


Figure 5. Calories and protein provided by each formula, represented with added supplemental protein provided. * Indicates statistical significance at p=0.05 level. Abbreviations: BTF = blenderized tube feeding, n BTF = non-blenderized tube feeding

Rectal Tube Associated Skin Injury

In the non-BTF group, 16 participants had rectal tubes placed while eight subjects in the BTF had rectal tubes placed (Table 19). The odds of a patient in the BTF group of requiring a rectal tube was 0.200 compared to the non-BTF group. Performing Fisher's exact test on rectal tube related skin injury between BTF and non-BTF formula, there was not a significant difference between groups (4 vs. 8; *p*=0.077).

A multinomial logistic regression was performed to further investigate the association between formula types, rectal tube use, and days on a rectal tube. There was a significant association between days spent with a rectal tube and rectal tube related skin injury (p=0.030).

There is a very significant relationship between number of days on rectal tube and rectal tube-related skin injury (p<0.001). Formula type was not associated with rectal tube-related skin injury. However, blenderized formula type was associated with a reduction in time spent on a rectal tube.

Table 19 – Rectal Tube-Related Skin Injury

	Non-BTF, n = 26	BTF, n = 33	*p*
	n (%)		
Subjects with RT [a, b, c]	16 (61.5%)	8 (24.2%)	0.003*
Incidence of RT-Related Skin Injury [a, b, c]	8 (30.7%)	4 (12.1%)	0.077

* Indicates statistical significance measured at the p=0.05 level
[a] Pearson's Chi square analysis; [b] Fisher's Exact test; [c] Odd's ratio and 95% CI.
Abbreviations: BTF = blenderized tube feeding, n = number, (%) = percentage, d = day

Discussion

The objective of this study was to describe the relationship between BTF formula and incidence of diarrhea and rectal tube placement, as well as to observe the safety of administering a formula high in fiber to patients who are critically ill and receiving ECMO therapy. The most significant findings of this study were the reduction in diarrhea and subsequent reduction in rectal tube placement in patients receiving BTF formula when compared to patients on a non-BTF formula.

There is strong evidence that the BTF group had more well-formed stools with a higher average BST, and less diarrhea compared to the non-BTF group. The findings are consistent with research by Schmidt et. al. who observed BTF use in the critically ill population.[10] This study included 32 patients in the intervention group and 35 patients in the control, and provided a commercially prepared BTF composed of chicken, carrot, and calabash, with an alternative for dairy intolerance provided as turkey hen with maize and carrots.[10] The researchers found that there was a higher BST score in the non-BTF group (7.0) compared to the BTF group (4.0).[10] In contrast to this review, Schmidt et al recorded the number of days with Type 7 stools and days with ≥3 type 7 stools.

The significant difference in bowel pattern found in this study may be attributed to formulation differences of the enteral formulas. The BTF group received significantly more fiber with an average of 31.3 grams of fiber per day compared to 3.4 g fiber from the non-BTF group. The non-BTF group, which received a variety of non-blenderized enteral formulas, had looser stools and/or more diarrhea. This group received an average of 3.4 grams of fiber per day. These findings are similar to the current literature.[10,14,41]

A meta-analysis performed by Kamarul Zaman et al in 2015 queried 14 studies that investigated prebiotic and fiber provision in patients receiving EN.[48] The consensus of the meta-analysis was that fiber supplementation reduced diarrhea incidence in patients on EN as a whole.[48] The dose between studies ranged from 5 grams to 39 grams per day with the most common fiber added into enteral

formula and used as a supplement as soy polysaccharide.[48] Fiber did not improve diarrhea when the reviewers examined only the critically ill population.[48] This finding opposes the finding of this study, where patients receiving 31 grams of fiber on average did have an improved stooling pattern with fewer loose stools. There were eight studies involving patients who were critically ill in the ICU, which were declared to be heterogenous.[48] The amount and type of fiber varied in each study, and the main forms of fiber given were soy polysaccharide, banana flakes, guar gum, pectin, and/or mixed fiber.[48] There were only three studies that provided comparable amounts of fiber to that of this review. Mixed fiber was provided at 15-17 grams per liter in three of the eight studies, but there were two separate additional forms added: fructo-oligosaccharides (FOS), pectin, and oligofructose/inulin.[48] Guar gum was provided at 22 grams per liter in two studies, while soy polysaccharide was given at 14.4 grams per liter in one study and 21 grams per liter in another.[48] The only study involving banana flakes included fiber at 1.5 grams per day.[48] Of these, the most comparable to the commercially produced BTF used in this review, which provides 20 grams of mixed fiber per liter, were those studies providing 15-17 grams of mixed fiber.[48]

Of the comparable studies, only two observed for events of diarrhea, and these studies had drawn different outcomes. In Chittawatnarat et al, 17 septic patients received fiber, and authors concluded that formula containing mixed fiber was safe and efficacious to use in septic patients at risk for diarrhea.[41,48] Meanwhile, Schultz et al assessed four study groups of patients who were critically ill receiving Jevity© Plus (intervention) or Osmolite©/Promote© (fiber-free, placebo group).[11] These combinations were fiber formula with pectin, fiber formula with placebo, fiber-free formula with pectin, and fiber-free formula with placebo.[11] There were no significant differences between the four groups in terms of percent of subjects with diarrhea versus percent of patients with no stool or formed stool.[11]

Clearly, it is hard to compare the results of this meta-analysis to the results of this study due to study inclusion within the meta-analysis and lack of homogeneity.[48] Authors theorized that the

antibiotics and severity of illness played a role in the severity of diarrhea and offset the effects of fiber.[48] This review was conducted in 2015, but 14 of the included studies were from the 1990s with additional studies from the early 2000s.[48] It is possible that improvements in treatments over the last thirty years may impact results. Authors concluded that a large limitation to this study was the heterogeneity of the subjects included, for there were non-critically ill patients being compared to patients with critical illness.[48]

There is concern that adding insoluble fiber or using a high fiber containing formula will cause constipation, bowel obstruction and/or bowel ischemia. However, there have been very limited studies that observe fiber provision in the critically ill due to the generally accepted ASPEN criteria that discourages fiber provision in this population, although the Quality of Evidence grade is recognized as "Low". The two case studies cited for the ASPEN consensus were conducted in 1990 and 1999. The case study published in 1999 was a retrospective audit that focused on burn trauma patients who had been treated three years earlier for acute bowel obstruction.[49] Study criteria required patients be fed enterally and had undergone surgery for bowel obstruction or bowel perforation.[49] There were four patients total who had suffered from these conditions.[49] The first patient had 92% total surface area burn, and the second had 50% total surface area burn.[49] These two patients were close in age, the first patient being 39 and the second being 44, and both patients both became hemodynamically unstable, were fed while receiving vasopressors, and experienced small bowel obstructions.[49] The third patient was a young woman experiencing toxic epidermal necrolysis syndrome, who had an epidermal loss of over 95% body surface area.[49] The patient was fed consistently and came off of vasopressor support on day 11, where she then had a bowel obstruction on day 15.[49] Surgeons found a very dilated small bowel filled with thick fecal content, and the obstruction was thought to be inspissated formula.[49] The last patient was a young man who had a total burn surface area of 6.5% with inhalation injury; again, this patient became hemodynamically unstable at day 15 and underwent surgery for his bowel obstruction.[49]

All four patients had bulk fiber supplementation, posttraumatic ileus and secondary sepsis, all of which contributed to the inspissated formula within the intestinal tract.[49] Authors appreciated two studies that found that ischemic complications were possibly related to hypotension and burn trauma but also to feeding jejunostomies.[49] Due to the severe injuries inflicted upon these subjects, this case report is not readily comparable to the patients in this study.

The second case study was from 1990. This case study focused on bowel obstructions related to intestinal bezoar found in one 45-year-old male with no past medical history of intestinal dysfunction.[50] This patient had viral pneumonia requiring intubation and received enteral feeds of Jevity© with fiber.[50] This formula was infused continuously for a goal of 125 milliliters per hour. After six hospital days (unclear how many of these days included feeding), the patient started exhibiting signs of tube feed intolerance with abdominal distention and feeding was consequently stopped.[50] The patient underwent several surgeries, ending up with an ileostomy and need for PN; notably, the patient resumed enteral feeds on a non-BTF formula without issue 13 days post-operation.[50] Authors had difficulty finding contraindications for a fiber-containing enteral formula, and authors cited that risks for intestinal impaction related to fiber included quantity of fiber, previous gastric surgery, medications that interfere with bowel function, diabetic gastroparesis, and strictures.[50] The authors then revealed that this patient was contraindicated to receiving fiber due to provision of medication interfering with bowel function (diazepam, morphine, pancuronium) and experiencing sepsis, which is known to be associated with risk of ileus.[50] These contraindications have been seen in this review's patient population, who are among the most critically ill and thus, are receiving medication that may be interfering with bowel function and are likely to be septic. However, there was no difference in the events of ileus. In addition, this review did not control for previous history of bowel surgeries, and one of the patients experiencing an adverse event did have a mentioned history of sigmoid resection. As this was a case study of one patient, there were no ways to compare this patient to other critically ill patients. Clearly, there needs to be more

research into the use of formula containing fiber, as case studies and expert opinion are ranked as level V and grade "low" according to the ASPEN Guidelines.

Given this concern over BTF formula (and fiber in general) causing constipation, which has the potential to lead to bowel obstructions, perforation, and bowel ischemia in the critically ill according to the ASPEN guidelines, this study examined this question. In this review, there was no significant association between feeding intolerance(s) and BTF formula, and there was no difference in rates of constipation. Overall, true constipation, defined as at least three days without a bowel movement, was rare in this study. Furthermore, the BTF group's significantly higher frequency of stools supports the notion that constipation was not associated with BTF formula. In terms of adverse events, bowel ischemia and bowel obstruction, were also not significant. There were three total adverse events, one case of bowel ischemia and two bowel obstructions. One subject had both bowel ischemia and bowel obstruction. This subject had become increasingly hemodynamically unstable and had been transferred from a separate hospital but did not initially require pressors. A separate subject had a bowel obstruction. This subject had multiple comorbidities and may have had a history of a sigmoid resection, although it was difficult to confirm in past medical records. Due to the small sample size of adverse events, statistical analysis was not conducted between fiber and the odds of bowel ischemia or bowel perforation. A lack of adverse events due to fiber is further illustrated by work done by Fu et al. The authors reported no adverse events after fiber supplementation in 129 critically ill patients in the ICU.[51] The average fiber provision was 13.4 grams over a 72-hour period.[51] The intervention group not only had no adverse events, but had less abdominal distention.[51] According to these studies and the current data, as well as the outdated low-grade evidence of association between adverse events and fiber, it is imperative that further research is conducted to observe the true relationship and observe appropriate dosing of fiber in the critically ill. While this study had was not free of adverse events, the small case size

was not sufficient to perform statistical analyses. Thus, more research is warranted into the use of whole fiber in enteral formula.

By far, the most significant feeding intolerance observed in this study was that of diarrhea in the non-BTF group. Diarrhea can lead to the use of rectal tubes in the critically ill, and the data suggests that there was a significant difference in the need for a rectal tube between groups with rectal tube use being significantly less in the BTF group. In the BTF group, the provision of fiber allowed for lower use of rectal tubes. Because the BTF group had less use of rectal tubes and less time spent on the rectal tube, there were less cases of rectal tube-related skin injury. Furthermore, this review concludes that RT-related skin injury was significantly associated with time spent on a rectal tube, regardless of formula, but when a rectal tube was placed, there was a significant difference in time spent on the rectal tube. For example, the average time on a rectal tube in the non-BTF group was 6.6 days, while the time in the BTF group was 0.9 days. While there was a significant association between formula, days on a rectal tube, and rectal tube-related skin injury (p=0.03), when formula was removed from a multinomial logistic regression, there was a stronger association between time and rectal tube-related skin injury (p<0.001). The increase in statistical strength after adjusting the model shows us that there is a strong relationship between time on a rectal tube and rectal tube-related skin injury. This is important because the literature indicates that RT use is associated with poor outcomes. Wilson et al was the first study to observe for frequency, indication, and adverse events related to rectal tubes in 2020.[8] Researchers found that patients with rectal tube-related skin injury had higher mortalities and longer lengths of stay.[8] Strategies that lowered risk of diarrhea requiring a rectal tube was to manipulate enteral feeding or to delay bowel regimens.[8] In 2019, Hay et al compared three different laxative regimens and their effect on incidence of diarrhea and subsequent need for a rectal tube.[40] These authors concluded that it was safe to delay prophylactic laxative use until day 6 after starting tube feeds, but there was no significant difference in the rectal tube insertion rate.[40] These studies both suggested that medication

may be causing diarrhea so severe that it requires a rectal tube, but this review holds different results.[8,40]

In this study, bowel medication provision was broken down by first line medications, second line medications, and by grouped bowel regimens. Individual bowel medication provisions were not significantly related to diarrhea incidence according to BST ≥ 6.0. Unexpectedly, patients on grouped bowel regimens seemed to have more formed stools than patients without bowel medication, especially patients on BTF formula. As laxative use and regimen intensity increased, the average BST remained low or even experienced a reduction. The average stool type for patients on the highest tier bowel regimen 3 had BST 4.9 stools (smooth, sausage-like), while patients in the non-BTF had 5.9 (soft blobs, borderline-mushy stools). This seemingly answers the hypothesis that patients on BTF formula receiving bowel medications had more formed stools compared to the non-BTF group. It was surprising to see that the second line bowel medications were also of no significance purely due to the lack of meaningful observations. These medications were not widely given and could not be correlated with diarrhea. However, the hypothesis that the BTF group required more laxatives compared to the non-BTF group was proven to be false.

In a retrospective audit of 50 critically ill patients, authors found that 78% of patients reviewed developed diarrhea at one point during their 5-month review window.[52] Observing for diarrhea risk factors, GI pro-motility medications were studied for association with incidence of diarrhea.[52] All patients were on non-BTF formulas, and authors concluded that the formula was not associated with diarrhea development.[52] However, length of time on formula was associated with development of diarrhea.[52] As for medication provision, time on antibiotics increased diarrhea incidence; however, diarrhea was not associated with pro-kinetics, neuromuscular blockade medication, or aperients.[52] This result reflects the result in this chart review, where aperient-type medication was not found to be significantly associated with risk of diarrhea. These researchers also called for a definition of diarrhea

that includes frequency, consistency, duration, and weight.[52] Another likeness is the call for a more universally accepted definition of diarrhea. Because of the lack of measured output, this review was unable to use several other definitions of diarrhea that involved weights.

The decision to provide an "as needed" bowel medication was an unexpected confounder. The results indicate that patients likely had more formed stools when receiving laxatives due to the providers' discretionary decisions. A subject may have been more likely to receive an "as needed" laxative if the subject was more likely to be constipated, and on the other hand, a patient was less likely to receive an "as needed" laxative if the subject was already suffering from frequent, loose stools. Therefore, this review was not able to conclude that it was the laxatives at fault for causing diarrhea, but the review did show the ability of the BTF group to withstand the increasing use of laxatives provided in bowel regimens. Current literature suggests that there were similar observations in a study by Nguyen et al, where constipation prophylaxis reflected a higher incidence of constipation, similar to how laxatives in this review reflected more formed stools.[36] Authors concluded that the hypomotility was not drug-related but rather, the hypomotility simply reflected the high analgesic needs of that critically ill population.[36]

Nutritional adequacy was explored in this study. To compare, it was necessary to measure protein and energy needs, energy and protein provision by formula, and the adequacy of nutrition. The two groups had similar estimated needs and nutrition prescriptions. The main difference was in protein provision, although it was adequate to meet estimated needs. Both groups received more than 80% of their protein and energy needs in the course of their ECMO therapy. The differences in formula ultimately altered protein provision, since there is less protein provided by BTF formula compared to non-BTF formula. In practice, this difference requires that patients on ECMO and receiving BTF need more supplemental protein packets. There was a significant difference in this supplementation between groups, as non-BTF formula meets protein needs more readily than BTF formula can. Because of this,

there was a significant difference in total protein provided to each patient group. Charting practices may have under reported the amount of supplemental protein added daily. If clinicians are using BTF formula in a critically ill population, it will need to become standard practice to give adequate protein supplementation and to document all protein supplement provision. The only study of BTF formula in the critically ill adult population did not explore feeding adequacy but did explore nutritional status, finding that both groups had a stable BMI throughout the trial.[10]

A major strength of this study was its novelty. There is limited research exploring BTF formula with whole foods and fiber, especially for use in the critically ill population. To current knowledge, this would be the first study exploring specific formula use, especially BTF formula, in patients on ECMO support. An additional strength of this study is the exploration of the use of fiber in the critically ill. The use of fiber in this population has been long debated and scarcely researched in practice. This study was able to investigate formula type, bowel pattern, and bowel medication use in a highly vulnerable population, allowing for future research into this area.

One major limitation for this study was the definition of diarrhea. In the literature, diarrhea has several different definitions. For one, the Hart and Dobb Scale is a useful measurement tool that involves an algorithm that includes bowel movement frequency, milliliters of stool output, and consistency of stool.[41,14] Due to charting inconsistencies, it was not possible to analyze diarrhea using the Hart and Dobb Scale, as output is not routinely measured in the NTICU. Output was most likely to be measured if a rectal tube was in place. Further, consistency was measured using Bristol Stool Chart, but not all providers consistently charted each bowel movement by BST. Most were documented, but it was impossible to analyze bowel movements described as "UTA," or, "unable to assess".

Another significant limitation to this study was the charting practices prior to the review. The first example may be overall protein provision, where protein supplementation must be given by nursing staff in addition to enteral formula. This provision may not have been documented accurately, likely

underreporting the amount of protein that the BTF group was receiving. A second example of charting practices was the "UTA" or leaving a blank in the description for stool consistency. These stools could only be counted toward the total count and the frequency measurement. The final example was stool output. Output was not a reliable measurement in this chart review, as it was not measured in all subjects. This finding reflects the standardized practice to only measure output in patients with a rectal tube. Measurement of output would indeed increase nursing workload, but it would be a better approach to use the Hart and Dobb Scale to formally measure diarrhea.[14] The Hart and Dobb scale allows for international comparison, is reportedly easy to use for nursing, and includes the frequently used definition of diarrhea as ≥3 loose stools per day.[14] The Hart and Dobb scale allows for international comparison, is reportedly easy to use for nursing, and includes the frequently used definition of diarrhea as ≥3 loose stools per day.[14] The definition used in this study combined with charting inconsistency, may explain why days of diarrhea were not significantly different between groups. It was more reliable to measure average BST for diagnosis of diarrhea.

This study also had a small sample size, making some statistical analyses challenging. Due to the extremely small sample for adverse events, it was not possible or meaningful to conduct a statistical test. There were more variables than subjects in this study, which also affects the significance. However, most of the significant findings were very significant with a *p*-value under 0.001, so these would not be altered if a post-hoc adjustment was conducted. The *p*-values that were borderline, under 0.05 but not less than 0.005, are likely to become null after adjustment.

The provision of a real food, blenderized formula to critically ill subjects is a novel practice due to its inclusion of whole food and whole fiber. While the BTF group had more frequent bowel movements, the bowel movements were more formed compared to the non-BTF group. Decreased rectal tube placement in the BTF group may be attributed to the differences in stool consistency, wherein the non-BTF group had more loose, watery stools and required more rectal tubes. Overall, it is

clear that the fiber and real food in BTF formula may significantly impact diarrhea in the critically ill patient on ECMO support, reducing need for rectal tube placement, reducing nursing workload, and improving patient outcomes. More research is required to further explore real food BTF formula in the critically ill, as well as finding the proper amount of fiber to provide to patients with or at risk of severe diarrhea. Research in the critically ill ECMO population should also be further explored, as these patients are at extreme risk.

References

1. Makikado LDU, Lasierra JLF, Pérez-Vela JL, et al. Early enteral nutrition in adults receiving venoarterial extracorporeal membrane oxygenation: an observational case series. *JPEN J Parenter Enteral Nutr.* 2013;37(2):281-284.
2. Raymond E. Nutritional considerations in multiple organ dysfunction syndrome requiring extracorporeal therapy. *SUPPORT LINE.* 2014;36(2):21-26.
3. Bear DE, Smith E, Barrett NA. Nutrition Support in Adult Patients Receiving Extracorporeal Membrane Oxygenation. *Nutr Clin Pract.* 2018;33(6):738-746.
4. Sanchez ML. Mechanical ventilation in patients subjected to extracorporeal membrane oxygenation (ECMO). *Med Intensiva.* 2017;41(8):491-496.
5. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. *JPEN J Parenter Enteral Nutr.* 2016;40:159-211.
6. Reis AMD, Fruchtenicht AV, Loss SH, Moreira LF. Use of dietary fibers in enteral nutrition of critically ill patients: a systematic review. *Rev Bras Ter Intensiva.* 2018;30(3):358-365.
7. Mueller CM, Marian M, McClave SA, Miller SJ. *The ASPEN Nutrition Support Core Curriculum 3rd edition* 3rd ed: American Society for Parenteral and Enteral Nutrition; 2017.
8. Wilson N, Bellomo R, Hay T, et al. Faecal diversion system usage in an adult intensive care unit. *Crit Care Resusc.* 2020;22(2):152-157.
9. Goh M, Chew M-H, Au-Yong P-S, Ong C-E, Tang C-L. Nonsurgical faecal diversion in the management of severe perianal sepsis: a retrospective evaluation of the flexible faecal management system. *Singapore Med J.* 2014;55(12):635-639.
10. Schmidt SB, Kulig W, Winter R, Vasold AS, Knoll AE, Rollnik JD. The effect of a natural food based tube feeding in minimizing diarrhea in critically ill neurological patients. *Clin Nutr.* 2019;38(1):332-340.
11. Schultz AA, Ashby-Hughes B, Taylor R, Gillis DE, Wilkins M. Effects of pectin on diarrhea in critically ill tube-fed patients receiving antibiotics. *Am J Crit Care.* 2000;9(6):403-411.
12. Wanik J, Teevan C, Pepin L, et al. Implementation of a Bowel Protocol to Improve Enteral Nutrition and Reduce Clostridium difficile Testing. *Crit Care Nurse.* 2019;39(6):e10-e18.
13. Schmidt SB KW, Winter R, Vasold AS, Knoll AE, Rolinik JD. The effect of a natural food based tube feeding in minimizing diarrhea in critically ill neurological patients. *Clin Nutr.* 2019;38(1):332-340.
14. Spapen H, Diltoer M, Van Malderen C, Opdenacker G, Suys E, Huyghens L. Soluble fiber reduces the incidence of diarrhea in septic patients receiving total enteral nutrition: a prospective, double-blind, randomized, and controlled trial. *Clin Nutr.* 2001;20(4):301-305.
15. Tarleton SM, Kraft CA, DiBaise JK. Fiber-enriched enteral formulae: advantageous or adding fuel to fire? *Practical Gastoenterology.* 2013;37(12):11-22.
16. CI: Enteral nutrition and fiber 2012. Academy of Nutrition and Dietetics. Recommendations summary Web site. Published 2012. Accessed2020.

17. Bouin M, Savoye G, Maillot C, et al. How do fiber-supplemented formulas affect antroduodenal motility during enteral nutrition? A comparative study between mixed and insoluble fibers. *Am J Clin Nutr.* 2000;72(4):1040-1046.
18. Hunt MF, Suarez-Pierre A, Zhou X, et al. Nutritional support in postcardiotomy shock extracorporeal membrane oxygenation patients: A pospective, observational study. *J Surg Res.* 2019;244:257-264.
19. LU M-C, YANG M-D, LI P-C, et al. Effects of nutritional intervention on the survival of patients with cardiopulmonary failure undergoing extracorporeal membrane oxygenation therapy. *In Vivo.* 2018;32(4):829-834.
20. Lindholm JA. Cannulation for veno-venous extracorporeal membrane oxygenation. *J Thorac Dis.* 2018;10:S606-S612.
21. Seres DS, Ippolito PR. Pilot study evaluating the efficacy, tolerance and safety of a peptide-based enteral formula versus a high protein enteral formula in multiple ICU settings (medical, surgical, cardiothoracic). *Clin Nutr.* 2017;36(3):706-709.
22. Sen A, Callisen HE, Alwardt CM, et al. Adult venovenous extracorporeal membrane oxygenation for severe respiratory failure: Current status and future perspectives. *Ann Card Anaesth.* 2016;19(1):97-111.
23. Jean Reignier JB-H, Laurent Brisard, Jean-Baptiste Lascarrou, Ali Ait Hssain, Nadia Anguel, et al. . Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet.* 2018;391:133-143.
24. Heinonen T, Ferrie S, Ferguson C. Gut function in the intensive care unit - What is 'normal'? *Aust Crit Care.* 2020;33(2):151-154.
25. Nassar AP, Jr., da Silva FM, de Cleva R. Constipation in intensive care unit: incidence and risk factors. *J Crit Care.* 2009;24(4):630 e639-612.
26. Ridley EJ, Davies AR, Robins EJ, et al. Nutrition therapy in adult patients receiving extracorporeal membrane oxygenation: a prospective, multicentre, observational study. *Crit Care Resusc.* 2015;17(3):183-189.
27. Ferrie S, Herkes R, Forrest P. Nutrition support during extracorporeal membrane oxygenation (ECMO) in adults: a retrospective audit of 86 patients. *Intensive Care Med.* 2013;39(11):1989-1994.
28. Wandrag L, Gordon F, O'Flynn J, Siddiqui B, Hickson M. Identifying the factors that influence energy deficit in the adult intensive care unit: a mixed linear model analysis. *J Hum Nutr Diet.* 2011;24(3):215-222.
29. Yip KF, Rai V, Wong KK. Evaluation of delivery of enteral nutrition in mechanically ventilated Malaysian ICU patients. *BMC Anesthesiol.* 2014;14:127.
30. MacGowan L, Smith E, Elliott-Hammond C, et al. Adequacy of nutrition support during extracorporeal membrane oxygenation. *Clin Nutr.* 2019;38(1):324-331.
31. *The ASPEN Adult Nutrition Support Core Curriculum.* 3rd edition ed: American Society for Parenteral and Enteral Nutrition; 2017.
32. Bristol stool chart. Continence Foundation of Australia. Faecal Web site. Published 2021. Updated April 2021. Accessed2020.
33. Ferrie S, Daley M. Lactobacillus GG as treatment for diarrhea during enteral feeding in critical illness: randomized controlled trial. *JPEN J Parenter Enteral Nutr.* 2011;35(1):43-49.

34. Guerra TL, Mendonca SS, Marshall NG. Incidence of constipation in an intensive care unit. *Rev Bras Ter Intensiva*. 2013;25(2):87-92.
35. Sheean PM, Peterson SJ, Zhao W, Gurka DP, Braunschweig CA. Intensive medical nutrition therapy: methods to improve nutrition provision in the critical care setting. *J Acad Nutr Diet*. 2012;112(7):1073-1079.
36. Nguyen T, Frenette AJ, Johanson C, et al. Impaired gastrointestinal transit and its associated morbidity in the intensive care unit. *J Crit Care*. 2013;28(4):537 e511-537.
37. Kim Sabino JF, Scott May, Dorothy Wakefield. Safety and tolerance of enteral nutrition in the Medical and Surgical Intensive Care Unit patient receiving vasopressors. *Nutr Clin Pract*. 2019;0(0).
38. Tack J, Muller-Lissner S. Treatment of chronic constipation: current pharmacologic approaches and future directions. *Clin Gastroenterol Hepatol*. 2009;7(5):502-508; quiz 496.
39. Perez-Sanchez J, Fernandez-Boronat J, Martinez-Mendez E, et al. Evaluation and handling of constipation in critical patients. *Enferm Intensiva*. 2017;28(4):160-168.
40. Hay T DA, Rachnitzer T, Fetterplace K, Reilly R, Ankravs M, et al. The hospital-based evaluation of laxative prophylaxis in ICU (HELP-ICU): A pilot cluster-crossover randomized clinical trial. *J Crit Care*. 2019;52:86-91.
41. Chittawatanarat K, Pokawinpudisnun P, Polbhakdee Y. Mixed fibers diet in surgical ICU septic patients. *Asia Pac J Clin Nutr*. 2010;19(4):458-464.
42. O'Keefe SJD. The Need to Reassess Dietary Fiber Requirements in Healthy and Critically Ill Patients. *Gastroenterol Clin North Am*. 2018;47(1):219-229.
43. Scaife CL SJ, Morris SE Intestinal obstruction secondary to enteral feedings in burn trauma patients. *J Trauma*. 1999;47(5):859-863.
44. McIvor AC MM, Curtas S, Warren J, Kaplan DS Intestinal obstruction from cecal bezoar; a complication of fiber-containing tube feedings. *Nutrition*. 1990;6(1):115-117.
45. Scott LK, Boudreaux K, Thaljeh F, Grier LR, Conrad SA. Early enteral feedings in adults receiving venovenous extracorporeal membrane oxygenation. *JPEN J Parenter Enteral Nutr*. 2004;28(5):295-300.
46. Osooli F AS, Farsaei S, Adibi P. Identifying Critically Ill Patients at Risk of Malnutrition and Underfeeding: A Prospective Study at an Academic Hospital. *Adv Pharm Bull*. 2019;9(2):314-320.
47. Park J, Heo E, Song IA, et al. Nutritional support and clinical outcomes in critically ill patients supported with veno-arterial extracorporeal membrane oxygenation. *Clin Nutr*. 2019.
48. Kamarul Zaman M, Chin KF, Rai V, HA M. Fiber and prebiotic supplementation in enteral nutrition: A systematic review and meta-analysis. *World J Gastroenterol*. 2015;21(17): 5372-5381.
49. Scaife CL, Saffle JR, Morris SE. Intestinal obstruction secondary to enteral feedings in burn trauma patients. *J Trauma*. 1999;47(5).
50. McIvor AC, Meguid MM, Curtas S, Warren J, Kaplan DS. Intestinal obstruction from cecal bezoar; a complication of fiber-containing tube feedings. *Nutrition*. 1990;6(1):115-117.
51. Fu Y, Moscoso DI, Porter J, et al. Relationship Between Dietary Fiber Intake and Short-Chain Fatty Acid-Producing Bacteria During Critical Illness: A Prospective Cohort Study. *JPEN J Parenter Enteral Nutr*. 2020;44(3):463-471.

52. Jack L, Coyer F, Courtney M, Venkatesh B. Diarrhoea risk factors in enterally tube fed critically ill patients: A retrospective audit. *NTENS CRIT CARE NUR.* 2010;26(6):327-334.

APPENDIX A: Data Collection Sheets

Subject ID _____ Formula Group: _____ Prescribed Calories: _____ Prescribed Protein: _____ Goal Rate (mL/hr): _____
Total mL/day: _____ Estimated needs: _____

Formula changes during course? _____ If so, new goal rate (mL/hr): _____ calorie provision per mL: _____ protein provision per mL: _____

Date of Transfer/Admit at LEMC: _____ Date of ECMO: _____ Feeds at other hospital? _____ Rectal tube at time of admit? _____

Feeding: Average total mL provided: _____ Average supplement mL provided: _____ Avg percent goal received: _____

Date of Feed	Feeding Day	Formula type	Total mL	Protein Supplement	Fiber Supplement	Percent of goal nutrition provision	Interruption (if applicable):	Reason for interruption (if applicable):	Formula change?	Reason for change (if applicable):
	1									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									
	11									
	12									
	13									
	14									
	15									
	16									
	17									
	18									
	19									
	20									

Bowel Movements: Frequency over course: _____ Total Stools per period: _____ Average Stool Type Per BM: _____

Avg Output (mL): _____

Date of Feed	Feeding Day	Formula type	Bristol Stool Type	Frequency	Output (mL)	Ileus	SBO	Ischemia	Constipation	Obstipation	Bloody stool	Vomiting
	1											
	2											
	3											
	4											
	5											
	6											
	7											
	8											
	9											
	10											
	11											
	12											
	13											
	14											
	15											
	16											
	17											
	18											
	19											
	20											

Medications Avg doses:

Date	Feeding Day	Sennosides Dose	Ducosate Sodium Dose	Pericolace Dose	Polyethylene Glycol Dose	Bisacodyl Dose	Lactulose Dose	Milk of Magnesia Dose	Magnesium Citrate Dose	Methylnaltrexone Dose
	1									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									
	11									
	12									
	13									
	14									
	15									
	16									
	17									
	18									
	19									
	20									