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USE OF FORTIFIED SKIMMED BREAST MILK TO FEED INFANTS WITH POSTOPERATIVE CHYLOTHORAX

By

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Certificate of Approval

This is to certify that the Master's Thesis of

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List of Abbreviations

ANOVA- Analysis of Variance

ARA- Arachidonic Acid

ASD- Atrial Septal Defect

CDC- Centers for Disease Control and Prevention

CHD- Congenital Heart Defect

DHA- Docosahexaenoic Acid

DOL- Day of Life

DORV- Double Outlet Right Ventricle

ELBW- Extremely Low Birth-Weight Infants

FSBM- Fortified Skimmed Breast Milk

HLHS- Hypoplastic Left Heart Syndrome

IRB- Institutional Review Board

LCT- Long-Chain Triglycerides

MCT- Medium-Chain Triglycerides

MCTF- MCT Formula

OHSU- Oregon Health & Science University

PDA- Patent Ductus Arteriosus

PICU- Pediatric Intensive Care Unit

POD- Postoperative Day

TPN- Total Parenteral Nutrition

VSD- Ventricular Septal Defect

WHO- World Health Organization

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Abstract

Use of fortified skimmed breast milk to feed infants with postoperative chylothorax

Background: Breast milk is the best source of nutrition for the infant but infants suffering from post-surgical chylothorax cannot consume breastmilk due to its high fat content. There is an interest among health care providers and mothers of infants with chylothorax to use skimmed, supplemented breast milk instead of specialized infant formulas.

Objective: The purpose of this study was to assess the nutritional intake, tolerance and growth of infants fed fortified skimmed breast milk compared to infants fed specialized infant formulas for the treatment of chylothorax following cardiothoracic surgery.

Study design: Expressed breast milk was skimmed by allowing it to sit undisturbed for at least 24 hours in the refrigerator to separate the fat and non-fat fractions. Skimmed breast milk contained inadequate energy for infants after cardiothoracic surgery so the skimmed breast milk was fortified with MCT ProCal™ (Vitaflo USA, Alexandria, VA) or Monogen™ (Nutricia North America, Gaithersburg, MD), medium-chain triglyceride containing supplements, to reach ~22 kcal/oz before feeding to the infant. Infant intake of total energy and protein, incidence of emesis and diarrhea and daily weights were recorded during the inpatient stay. Weight was recorded at follow up outpatient visits when infants were also assessed for reoccurrence of chylothorax.

Results: Eight infants with chylothorax were fed fortified skimmed breast milk and 9 infants were fed specialized infant formula following surgery. There was no difference in energy and protein intake per kg of body weight, no difference in incidence of emesis or diarrhea and no difference in weight gain between treatment groups.

Conclusion: Fortified skimmed breast milk offers potential benefits to mothers who wish to resume breast feeding after resolution of chylothorax and possibly for the infant in the form of the other benefits of breast milk over formula feeding. The refrigeration and syringe method to skim breast milk was an effective method to skim the breast milk. The use of fortified skimmed breast milk was therapeutically equivalent to specialized infant formulas in our study and may be an additional therapeutic option to successfully treat infants with chylothorax.

Chapter 1- INTRODUCTION AND SPECIFIC AIMS

Introduction

Congenital heart defects (CHD) are the most common birth defect affecting approximately 40,000 newborns every year in the United States (1). Many infants suffering from CHD require surgical repair or catheter intervention in the first year of life. One post-surgery complication is the development of chylous effusion or chylothorax in the pleural space (2). Chylothorax in infants is caused by the disruption or obstruction of the thoracic duct that results in the leakage of chyle or lymphatic fluid from intestinal origin into the pleural space (3). Nutritional management of chylothorax consists of a diet low in long-chain triglycerides (LCT) and enriched with medium-chain triglycerides (MCT). This therapy circumvents the lymphatic system since LCT are absorbed via the lymphatic system while MCT are absorbed via the portal vein. This nutritional intervention is typically achieved by implementing enteral feeding with a specialized formula low in LCT and high in MCT (4, 5).

Breast milk is recognized as the optimal source of nutrition for almost all infants including those who are born prematurely or those who are critically ill. For infants suffering from chylothorax, providing breast milk as a nutrition source has not been feasible because of its high LCT content. Some research suggests that breast milk skimmed of almost all natural fat and fortified with MCT could be beneficial to infants suffering from postoperative chylothorax (6).

Previous studies have used fortified skimmed breast milk as part of the nutritional management of chylothorax with positive outcomes (6-9). However, more studies with a control group need to be conducted to determine if infants who consume fortified skimmed breast milk have the same outcomes as infants who consume specialized formula.

The goal of this project was to determine if infants with postoperative chylothorax who consume fortified skimmed breast milk have similar nutrient intakes and similar or better growth outcomes as infants who consume a specialized formula low in LCT and high in MCT.

Specific aims

Aim 1: To compare nutrient intake and feeding tolerance among infants with chylothorax who consume fortified skimmed breast milk versus specialized formula.

Hypothesis 1*:* We hypothesized that infants with chylothorax fed fortified skimmed breast milk would have similar nutrient intakes compared to recommendations and fewer intolerance symptoms compared to infants receiving specialized formula.

Aim 2**:** To compare weight gain and linear growth among infants with chylothorax who receive fortified skimmed breast milk versus specialized formula.

Hypothesis 2: We hypothesized that infants with chylothorax who consume fortified skimmed breast milk would have comparable or better weight gain and linear growth for sex and age as infants receiving specialized formula.

Chapter 2- BACKGROUND

Chylothorax

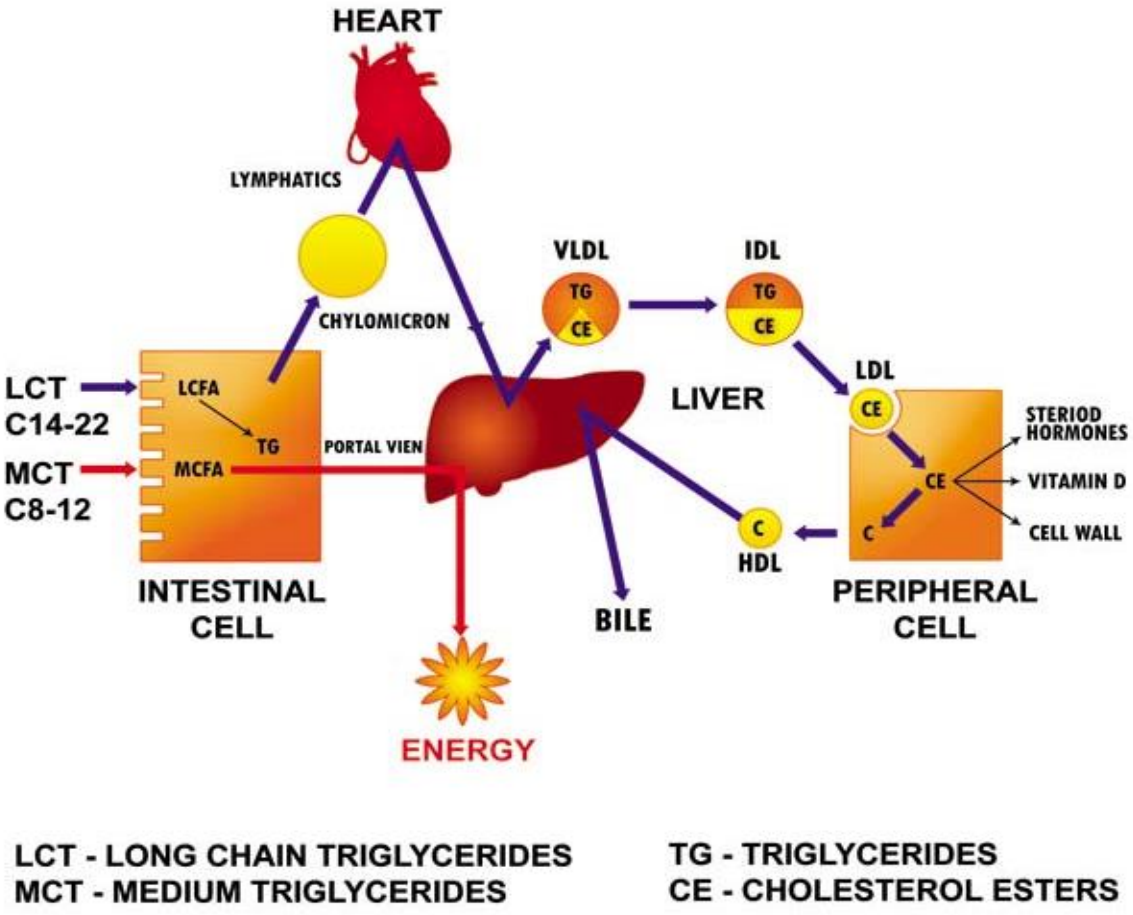
Development of chylothorax

According to the Centers for Disease Control and Prevention, 25% of infants born with CHD require surgical intervention in the first year of life (10). In children with CHD, chylothorax after surgery occurs in 2.3-6.6% of reported cases (2, 11, 12). Chylothorax is caused by damage to the thoracic duct during surgery, increased venous pressure, malignancies, or in some cases, congenital abnormalities (2, 13, 14). Chylothorax is characterized by the accumulation of chyle in the pleural space (3). Chyle refers to the milky white appearance of fluid which consists of a mixture of lymphatic fluid and chylomicrons of intestinal origin.

Lymphatic fluid (lymph) from the lower limbs, abdomen, intestinal chyle, left side of the thorax, head, neck and upper limb drain into the thoracic duct. The lymph drains from the thoracic duct into the left subclavian vein and into the systemic circulation (3). Intestinal chyle makes up most of the lymphatic fluid and its main components are chylomicrons derived from exogenous fat absorbed and packaged within the intestinal cells (3, 15). Schlierf et al. reported the composition of human chyle following single fat feedings in a male patient. The analysis of the chyle indicated that the composition of the chylomicrons was highly influenced by the type of fat fed. They also found that fatty acids with a chain length of more than 18 carbons were present in significant proportions in the chyle (15). Tamir et al. studied the chyle composition before and after MCT

feedings in a child with chylothorax and found that after MCT feedings the chylous effusion decreased and only 1-3% of the total MCT intake was found in the chyle (16). As shown in Figure 1, MCTs are loosely bound to albumin and are directly transported to the liver through the hepatic portal circulation, bypassing the lymphatic system. In contrast, LCTs are packaged into chylomicrons within intestinal enterocytes after absorption and are transported through the lymphatic system into systemic circulation (17).

Figure 1. Fatty Acid Circulation from the Intestinal Lumen. (38)



If white fluid effusion in the pleural space is noted, analysis of the fluid is used to confirm the diagnosis of chylothorax. The fluid is analyzed for the presence of chylomicrons, triglyceride concentration, total white cell count and percentage of lymphocytes (2, 11-13). Depending on the amount of chyle accumulation in the pleural space, dyspnea and coughing can occur, and in severe cases, significant respiratory distress and hemodynamic complications can develop (3). The fluid losses related to chylothorax lead to high morbidity and

mortality because of the large amount of lymphocyte, protein, and immunoglobulin losses from the lymphatic circulation (2). The large fluid losses can result in malnutrition, weight loss, hypoproteinemia, and hyponatremia (13, 18).

Current management practices

Therapeutic approaches for the management of chylothorax are either conservative with an elemental diet and medication, or surgical with ligation of the thoracic duct and/or placement of pleuroperitoneal shunts (2, 13). Most postoperative chylothorax cases can be treated with conservative therapy, with a 66%-85% rate of resolution (2, 11, 12, 14). The therapeutic diet consists of feeding the infant a specialized enteral formula that is low in LCT and high in MCT, or if there is no tolerance or resolution, total parenteral nutrition (TPN) is initiated. Since most of the lymphatic fluid is composed of intestinal chyle, substituting MCT for LCT results in reduced chylous effusion (19).

Medications such as somatostatin or a somatostatin analogue (octreotide) are used in conjunction with a low fat diet supplemented with MCT to effectively reduce chyle effusions. Somatostatin in patients with chylothorax has is indicated when chylous effusion doesn't decrease (7, 11-14). However, as a systemic side effect, somatostatin can inhibit gastric acid and peptide secretion and slow gastrointestinal transit time (20). In cases where conservative therapy is not effective, a surgical procedure is completed to stop chylous effusion into the pleural space. Ligation of the thoracic duct, placement of a pleuroperitoneal shunt, or pleurodesis are a last resort for the resolution of chylothorax (2).

Commercial infant formulas used for the management of chylothorax

Monogen™ (Nutricia North America, Gaithersburg, MD) is a specialized formula used to manage chylothorax. Monogen™ is a low-fat, milk protein-based, powdered formula that is low in LCT and high in MCT. It provides 24% of energy from fat, of which 80% is supplied by MCT, sufficient essential fatty acids, and a complete profile of vitamins and minerals. Monogen™ is used to treat children with long-chain fatty acid oxidation disorders, chylothorax, and other LCT absorption disorders (21). A few studies have specified the use of Monogen™ for the management of chylothorax. Cormack et al. conducted a retrospective, single institution, 2-year study examining the outcome and response to Monogen™ in the management of chylothorax in children younger than 10 years old. Monogen™ was given to 18 patients and 14 of them responded positively to the treatment by the third day. Body weight was maintained and a normal diet was resumed 4 ± 1 weeks after removal of drains without recurrence of chylothorax (22). This study demonstrated that Monogen™ can be used successfully in the treatment of chylothorax in the pediatric population unless enteral feeding is not possible. Contraindications to the use of Monogen™ include milk-protein allergy and/or poor enteral access or functionality.

Monogen™ has also been used to treat hyperchylomicronemia. Stefanutti et al. presented a case report of a 3 month old infant with severe hyperchylomicronemia and the use of Monogen™ (23). After the introduction of Monogen™, the high serum triglyceride concentration decreased since MCT are

not packaged into chylomicrons. Even though the use of Monogen™ is not recommended for children under 1 year of age because of its nutrient composition, this case study shows that Monogen™ can be used to feed infants requiring a diet low in LCT and high in MCT.

Portagen® (MeadJohnson Nutrition™, Evansville, IN) is a milk protein-based powder high in MCT used to treat children and adults. It is not recommended for use as an infant formula because it is not nutritionally complete. The fat content in Portagen® provides 40% of the total energy base, of which 87% is MCT, and corn oil provides some essential fatty acids (linoleic acid) (24). Portagen® has been used in the management of chylothorax and to treat children with long-chain fatty acid oxidation disorders. Hamdan and Gaeta fed Portagen® to an infant with chylothorax, however, the formula was not tolerated by the infant and was discontinued (7).

Enfaport™ (MeadJohnson Nutrition™, Evansville, IN) is a ready to use liquid formula developed specifically for the management of chylothorax and fatty acid oxidation disorders. It is high in protein, contains essential amino acids, and unlike Monogen™ and Portagen®, Enfaport™ contains a blend of docosahexaenoic acid (DHA) and arachidonic (ARA), and 84% MCT from total fat (25). No studies have been completed to analyze the effectiveness of Enfaport™ in the management of chylothorax.

Fortified skimmed breast milk for the management of chylothorax

Fortified skimmed breast milk can also be used successfully in the conservative management and resolution of chylothorax (7-9, 26). Lessen (2009) reported a case study of a full-term infant who was exclusively breastfed and discharged home on day of life (DOL) 2. On DOL 10 the infant underwent surgical repair of coarctation of the aorta. After surgery, the infant was readmitted to the hospital and diagnosed with chylothorax on DOL 36. The infant was fed skimmed breast milk fortified with Monogen™ powder at the time of chylothorax diagnosis. To skim the breast milk, it was refrigerated for 8 to 12 hours and the fat-free portion was extracted with a syringe from underneath the fat layer, leaving the fat in the container. The chest tube was removed on DOL 41 and the infant was discharged home eight days after admission on DOL 44 with proper weight gain (39 g/day) and no chylous drainage (9).

Chan and Lechtenberg (2007) fed skimmed breast milk that was fortified with Portagen® and Pregestimil® (MeadJohnson Nutrition™, Evansville, IN) to seven infants diagnosed with chylothorax. The use of fortified skimmed breast milk caused no re-accumulation of chylous fluid in any infant (8).

Hamdan and Gaeta (2004) presented a case study of a three month old infant who underwent bilateral cavopulmonary connection surgery and who was diagnosed with chylothorax on postoperative day (POD) 6. Draining chest tubes were placed and TPN was started to allow for enteric rest. On POD 8, the infant underwent surgical ligation of his shunt but continued to have chylous effusion resulting in weight loss, hyponatremia, hypoproteinemia and infections. On POD

28 he was started on octreotide (Sandostatin®, Novartis Pharmaceuticals, East Hanover, NJ), a somatostatin synthetic analogue, resulting in a reduction of chylous effusion. Since the infant did not tolerate Portagen® formula, skimmed breast milk was started on POD 33. Draining tubes were removed and octreotide was stopped at POD 49. The infant was discharged home on POD 67 and resumed regular breast milk feedings after two weeks with no reoccurrence of chylothorax (7).

Lastly, Kocel et al. (2015) compared chylous effusion volume, growth, and intake in eight infants with postoperative chylothorax versus eight infants fed an MCT-containing formula. They used the centrifugation method to separate the breast milk into fat and skimmed portions. Fortification of the skimmed breast milk was achieved by adding Similac® Human Milk Fortifier (Abbott Laboratories, Abbott Park, IL), MCT oil or Portagen®, and soybean oil. Infants in the formula group received Portagen®. They found that there were no significant differences in chylous effusion volume and duration between the two groups. In addition, energy and protein intake, and tolerance was comparable between both groups. However, they found that infants in the skimmed breast milk group had a statistically significant decline in mean weight-for-age and mean length-for-age z-scores from the beginning of treatment to its conclusion (26). To our knowledge this is the first study to demonstrate inadequate growth in infants receiving fortified skimmed breast milk compared with those receiving the MCT-containing formula.

Although there is still much to learn from these studies and case reports, they demonstrate that fortified skimmed breast milk can be used as an alternative to enteral specialized formulas low in LCT and high in MCT in the conservative management of chylothorax.

Breastfeeding

Benefits of breastfeeding

Breast milk provides the necessary amount of energy and nutrients to support appropriate infant growth and development. It is recommended by all national and international professional medical organizations and is the preferred source of nutrition for most infants (27). The benefits of breast milk have been demonstrated in numerous studies. These benefits include improved cognitive development, lower hospitalization rates, and decreased rates of infections compared to formula fed infants (28-30).

Vohr et al. (2006) collected nutrition data from 1035 breast fed and formula fed extremely low birth-weight infants (ELBW) at 18 months of age and assessed morbidities, neurodevelopment, and growth outcomes among the groups. The results showed a higher mental and psychomotor developmental score on the Bayley Scales of Infant and Toddler Development® among breast fed ELBW infants compared to ELBW formula fed infants. They did not find any differences in body weight, length, or head circumference, as well as morbidity and length of hospitalization among the two groups (31). These results show that breast milk can be provided to infants with higher energy needs and with medical

problems and can yield the same or improved outcomes compared to their formula fed counterparts.

Breast milk composition

Several studies have analyzed breast milk to assess its nutrient composition. It has been noted that the composition of breast milk changes throughout each breastfeeding session, with duration of breastfeeding, and age of the infant to support appropriate growth.

Boersma et al. (1991) conducted a longitudinal study comparing the lipid composition in colostrum (0-4 days), transitional milk (5-9 days), and mature milk (10-30 days) in St. Lucia, an island country in the Caribbean. Analysis of lipid composition showed greater MCT concentration in mature milk compared to colostrum and transitional milk, and LCT comprised the largest lipid component in all types of breast milk (32).

Gibson and Kneebone (1981) analyzed the fatty acid composition of breast milk collected during early postpartum (3-5 days) and later postpartum (6 weeks) stages of breastfeeding using argentation thin-layer chromatography and gas chromatography procedures to separate and analyze the polyunsaturated fatty acids. Colostrum had a lower percentage of MCT, a higher percentage of monounsaturated fatty acids, a lower percentage of polyunsaturated fatty acids, and a higher ratio of LCT to MCT compared to mature milk (33).

Bitman et al. (1983) compared the fat content of colostrum and mature breast milk from mothers of very premature (26-30 weeks gestational age), premature (31-36 weeks), and term (>37 weeks) infants at 1, 3, 6 and 12 weeks

postpartum. They found that the total fat content of breast milk increased during lactation (2.89±0.31 gm/dL at 1 week to 4.87±0.62 gm/dL at 12 weeks), while phospholipids and cholesterol concentrations declined. Concentration of MCT increased as lactation progressed and was highest in preterm milk, while concentrations of LCT decreased as lactation progressed. It was also noted that LCT concentration was higher in breast milk produced by mothers of very premature and premature infants compared to breast milk produced by mothers of term infants. The authors concluded that elevated MCT concentrations in preterm milk, which doubled as lactation progressed, and elevated LCT may be of special benefit for premature infants (34).

Little is known about the nutrient composition of skimmed breast milk.

Evaluation of the fat separation and removal process in breast milk

Centrifugation

Chan and Lechtenberg (2007) used centrifugation (3000 r.p.m. and 2˚C for 15 minutes) to separate the fat from the nonfat portion of breast milk. The fat content of the skimmed breast milk was analyzed by the creamatocrit method (8). The creamatocrit method is a simple and fast technique used to estimate the lipid concentration and energy density of breast milk samples. After the sample is centrifuged, fat and skim fractions of breast milk are measured and an estimated percent and grams of fat in the sample is calculated by the machine. After centrifugation and fat removal, the skimmed portion contained 0±1% fat of total

volume compared to 5±1% fat of total volume before centrifugation (8). The method for physical removal of the fat layer was not described.

Hamdan and Gaeta (2004) also used centrifugation to separate the fat from the nonfat portion of breast milk and noted it contained compared the total fat concentration before and after centrifugation to the fat content in Portagen® formula. The fat content of centrifuged skimmed breast milk was 0.02% fat of total volume, regular breast milk was 3.5% fat of total volume, and Portagen® was 3.1% fat of total volume (85% of the fat coming from MCT) (7). The method used for fat analysis or removal was not described.

Separation by centrifuge or refrigeration/ spoon and syringe removal method

Drewniak et al. (2013) evaluated fat separation and removal methods. The samples were centrifuged or refrigerated to separate the fat and the syringe and spoon methods of fat removal were compared. The syringe method resulted in 34% less residual fat (1.2 gm/dL, 95% confidence interval [CI], 1.1-1.4) than the spoon method (1.9 gm/dL, 95% CI, 1.5-2.3). For the fat separation assessment, a syringe was used to remove the skimmed breast milk. Refrigerated centrifuged, non-refrigerated centrifuged, and refrigeration methods to separate fat from non-fat components of breast milk were compared. Centrifuged methods (1.0 gm/dL, 95% CI, 0.8-1.1) proved to be more effective at fat separation than the refrigerated method (3.4 gm/dL, 95% CI, 3.0-3.7; $P<0.0001$). Triglyceride content

of the skimmed fraction was measured using an enzymatic colorimetric test with a Roche Modular analyzer (35).

Separation by refrigeration and syringe removal method

Lessen (2009) used the refrigeration and syringe method to skim breast milk. The breast milk was refrigerated and left undisturbed until a layer of fat rose to the top; a syringe and a nasogastric tube were used to empty the skimmed breast milk from the bottle, leaving the fat in the container (9). However, no analysis was performed to measure the fat content in the skimmed milk.

Significance

During the first year of life, infants grow at a fast rate and need adequate nutrition to grow and develop appropriately. There is a growing interest among mothers to provide breast milk to their infants, especially if they are hospitalized for a condition such as chylothorax. With current management practices of chylothorax, mothers who want to continue to breastfeed their infant are not able to do so. The published studies to date demonstrate that infants with chylothorax can be successfully treated with fortified skimmed breast milk. However, studies have not compared outcomes between infants fed the standard specialized formula versus those fed fortified skimmed breast milk.

The goal of this project was to compare effectiveness of fortified skimmed breast milk versus specialized MCT-containing formula in the management of chylothorax following cardiothoracic surgery in infants.

Chapter 3- METHODS

Study design

This was a prospective clinical trial that compared the effectiveness of fortified skimmed breast milk versus specialized MCT-containing formula (Enfaport™ or Monogen™) in the management of chylothorax in infants following cardiothoracic surgery. We compared growth, nutritional intake, and feeding tolerance, as well as the effectiveness of the skimming technique between two groups of infants:

1. Infants of mothers with breast milk who were willing to perform the breast milk skimming technique.
2. Infants of mothers without a breast milk supply who were fed the specialized formula.

Infants of mothers in the fortified skimmed breast milk group whose breast milk supply diminished or stopped and who subsequently required specialized formula were analyzed separately from those infants in the fortified skimmed breast milk group. All infants participating in the study were followed for 4 months after chylothorax diagnosis to assess growth and reoccurrence.

Study population

Infants, ages birth to 12 months, who underwent cardiothoracic surgery and who developed postoperative chylothorax at Doernbecher Children's Hospital, Portland, Oregon were eligible to participate. Seventeen infants, nine in the specialized formula group and eight in the fortified skimmed breast milk group

were recruited to participate in this study. Participants were eligible for enrollment regardless of ethnicity, race, or gender. The study was approved by the Oregon Health & Science University (OHSU) Institutional Review Board (IRB, eIRB #7747). Informed consent was obtained from a parent at the time of chylothorax diagnosis.

Clinicians and nurses who monitor infants postoperatively in the pediatric intensive care unit (PICU) for evidence of white or cloudy chest tube drainage informed Cindi L. Farnstrom, MN, CPNP (or her designee) when it occurred. Infants and their mothers were screened to determine if they met the following inclusion criteria.

Table 1. Inclusion/Exclusion Criteria

Inclusion	Exclusion
• Infants from birth to 12 months of age • Infants who underwent cardiothoracic surgery and developed postoperative chylothorax • Infants of mothers who had breast milk production and wanted to use the breast milk skimming technique	• Infants in state custody (foster care) • Infants with milk protein allergy • Infants born with congenital chylothorax • Infants who developed chylothorax from other surgeries (non-cardiac)

• Infants of mothers who didn't have breast milk production and wanted to participate in the study	

Study protocol

Chest tube fluid analysis

If the clinical and nursing staff noticed white or cloudy chest tube drainage, a sample was sent to the OHSU laboratory per standard of care protocols. The composition of chyle determined the appropriate management of the chylous effusion.

The fluid was analyzed for the presence of chylomicrons, cell count with differential, and triglycerides. Our criteria for diagnosis of chylothorax was based on standard values of: cell count greater than 1000 cells/L, 90% lymphocytes, triglyceride concentration above 1.1 mmol/L, and the presence of chylomicrons.

Skimming technique

Mothers who consented to the skimmed breast milk technique were taught how to prepare and skim the breast milk by the study investigators. Each mother was provided with written instructions to skim the breast milk which were available in English and Spanish. Each mother practiced skimming the breast milk and demonstrated the appropriate technique to remove all of the fluid skimmed portion. Nursing staff caring for these infants were also taught the technique by the investigators. The technique is as follows:

1. Expressed breast milk was separated into skim and fat fractions after the milk remained undisturbed in the refrigerator for at least 24 hours and the fat portion rose to the top. If there was not distinct separation, the expressed breast milk sample remained undisturbed and refrigerated for up to 48 hours.
2. A 6-inch long sampling straw attached to a 30-60 ml syringe was carefully placed into the bottom of the expressed breast milk container. The skimmed portion found below the layer of fat was carefully removed with suction, leaving the fatty portion in the container.
3. If any fat was seen on the tip of the sampling straw, it was wiped off or removed by pushing some of the milk through the tip into the fat collection container.
4. The skimmed breast milk was transferred from the syringe into a labeled clean empty container, placed back in the refrigerator and allowed to sit undisturbed for another 24-48 hours.
5. Steps 2-4 were repeated to ensure the milk was adequately skimmed before feeding to the infant.
6. The fatty portion was labeled, frozen, and saved to be fed to the infant after full feedings were resumed.

Skimmed milk fat content

Two 1 mL samples of skimmed breast milk were collected and analyzed during the hospitalization for fat and energy content with the Medela® Creamatocrit Plus™ (McHenry, IL) centrifuge. A small portion of the skimmed

breast milk sample was transferred to a capillary tube and spun in the centrifuge for 3 minutes. The centrifuge contains a built-in tray reader that allows the investigator to manually determine the energy content in kcal/oz and kcal/L, and the fat content in g/L by following the instructions on the machine after the sample has been centrifuged. We expected the skimmed breast milk sample to contain <0.9 gm of fat per 100 kcal, or to be ~8% fat from total calories. For example, in a sample with energy content of 1200 kcal/L we would expect about 10.8 g/L or less of fat content in the sample. This is calculated by multiplying the total energy content per liter by 0.9 gm and then dividing it by 100. Based on the fat content of the skimmed breast milk, the appropriate amount of fortification with MCT ProCal™ (Vitaflo USA, Alexandria, VA) or Monogen™ (Nutricia North America, Gaithersburg, MD) powder was determined by the dietitian.

Fortification

Fortification of the skimmed breast milk with MCT ProCal™ or Monogen™ powder was needed to achieve an adequate energy intake since the removed fat is estimated to provide 50% of the total energy of breast milk. Mothers were given instructions and a recipe for mixing the skimmed breast milk with the study supplied fortifier (MCT ProCal™, Monogen™, or Enfaport™). The recipe was provided to the mother and nursing staff by Alisa Tortorich, RD. After the mother was taught the skimming technique in the hospital she was able to help skim the breast milk in the hospital and then fully do it after discharge. The goal was to increase the energy content of skimmed breast milk to 20-30 kcal/oz. For instance, if the skimmed breast milk contained 12 kcal/oz, and MCT Procal

contains 6.5 kcal/g, the mother would be instructed to add 12 gm of MCT Procal to 6 oz of skimmed breast milk to increase the energy density to 25 kcal/oz. In addition, infants in this group received a multivitamin since the main fortifier in the study, MCT Procal, doesn't contain some vitamin and minerals and some of micronutrients may have been lost during the skimming process.

Specialized formula

Specialized formula (Enfaport™ or Monogen™) was fed to the formula group per standard of care procedures. Table 2 details the nutrient composition of the formulas and fortifiers that were used in the study.

Table 2. Nutrient Composition of Formulas Used in this Study

Per 100 kcal	Enfaport™	Monogen™	MCT ProCal™
Protein, g	3.5	2.9	1.9
Total Fat, g	5.4	2.6	9.6
MCT, %	84	80	98
Carbohydrate, g	10.2	16.1	3.1
Vitamin A, IU	350	257	
Vitamin D, IU	50	62	
Vitamin E, IU	4	0.9	
Vitamin K, mcg	12	5	
Thiamin, mcg	80	83	
Riboflavin, mcg	90	123	
Vitamin B6, mcg	68	95	
Vitamin B12, mcg	0.3	0.2	
Niacin, mcg	1000	928	
Folic acid, mcg	16	11	
Pantothenic acid, mcg	500	347	
Biotin, mcg	3	5	
Vitamin C, mg	12	8	
Choline, mg	24	13	
Inositol, mg	17	20	
Calcium, mg	94	61	68
Phosphorus, mg	52	47	66
Magnesium, mg	11	8	<1.5
Iron, mg	1.8	1	
Zinc, mg	1	0.7	
Manganese, mcg	25	78	
Copper, mcg	75	80	
Iodine, mcg	15	9.6	
Selenium, mcg	2.8	2.5	
Sodium, mg	30	47	37
Potassium, mg	115	85	95
Chloride, mg	87	50	<9.1
Chromium, mcg		2.3	

Data collection

Mothers in both groups were asked to complete a daily feeding log while the infant was in the hospital. This feeding log included times and amounts of formula or fortified skimmed breast milk consumed by the infant, stool consistency, vomiting episodes, and tolerance rating. However, only one of the mothers returned this feeding log. Therefore, inpatient maternal feeding log data was not included in the analysis. Fortified skimmed breastmilk or formula intake, stools, and vomiting were also recorded daily in the medical record following the standard of care procedures by nursing staff while the infants were hospitalized. Once discharged, mothers were asked to continue to complete the daily feeding log for 4 to 6 weeks (until the infant was transitioned to regular breast milk or regular formula) and to bring the record to follow-up visits with the infant's cardiologist. The feeding logs were to be collected by the investigators at these visits, however, only one mother returned the logs. Therefore, outpatient maternal feeding log data was not included in the analysis. The first clinic visit usually occurred 2 weeks after discharge. The next visit was usually 1 month later (e.g. 6 weeks after discharge) and a subsequent visit occurred 2 or 3 months later based on the infant's health status. Upon completion of the transition to regular breast milk or regular formula (transition took approximately 1-2 weeks), mothers were asked to complete a questionnaire to understand how stressful the feeding method was for them.

Additional data recorded in the patient's record (EPIC) included the date of any recurrence including the date of any treatments such as replacement of a

chest tube, re-initiation of skimmed breast milk or specialized formula, TPN, or surgical intervention (ligation of the thoracic duct).

Outcome measures

A. Nutrition

Source of nutrition was documented in the medical record by type (TPN, fortified skimmed breast milk, or specialized formula) and route (oral, nasogastric, gastrostomy tube, or a combination). Using information from the electronic medical record (cc/d, type of feedings, energy concentration in kcal/oz, and fortification used), the actual energy intake (kcal/kg/d) and protein intake (g/kg/d) of the inpatient low-fat treatment were calculated. The estimated total energy need was also recorded in the electronic medical record. The goal for energy intake was ~120 kcal/kg/d, and the goal for weight gain was at least 10-15 grams per day. To achieve these goals, the skimmed breast milk was fortified to a concentration of 20 to 30 kilocalories per ounce depending on the infant's individual energy needs to promote growth. This is a well-established guideline to achieve adequate growth in this population of infants who often need extra calories during their recovery phase due to an increased catabolic demand.

B. Growth/anthropometric measurements

Growth was monitored per standard of care procedures with anthropometric measures. During the inpatient diet treatment, infants were weighed daily with a calibrated scale with a degree of precision of 0.01 gm. Length was measured weekly by laying the infant flat on the scale.

The measurement was obtained from the crown of the head to the bottom of the feet by aligning the trunk and feet and extending the legs until they were flat with the feet positioned vertically against the foot board.

The growth measurements of each participant were plotted on a sex-specific World Health Organization (WHO) chart as recommended by the Center for Disease Control and Prevention (CDC) (36). Through the electronic medical chart, the percentile and/or the z-score of each growth parameter was calculated to allow comparison of infants of either sex and of a broad age range (birth to 12 months) among the two groups. A z-score is an individual data point that is calculated as the difference between the patient's weight or length and the reference population mean which is then divided by the standard deviation for the reference population. A z-score between 1 and -1 is considered to be normal; a score below -2 is considered to be low; a score above 2 is considered to be high for either weight or length for age.

C. Feeding tolerance

Feeding tolerance was evaluated based on clinician and parental report of gastrointestinal symptoms (frequency of emesis and presence of diarrhea). During the hospitalization, symptoms were recorded in the electronic medical record by the nursing staff. Using a validated symptoms questionnaire, parents reported if the infant experienced emesis, fussiness, allergic reaction, hunger, constipation, diarrhea, gas, and/or spitting up prior to the initiation of skimmed breast milk or specialized

formula. They continued to monitor and report symptoms weekly thereafter until the infant transitioned back to full breast milk or standard formula. However, only one parent returned the home logs; therefore, the data for home tolerance of feeds was not used. The number of days of feeding intolerance during the inpatient diet treatment was divided by the total number of days of inpatient diet treatment to determine the percent of days with feeding intolerance. Difference in percent of days with feeding intolerance was compared between groups. In addition, feeding tolerance between the groups was compared by adding the number of emesis episodes during the inpatient diet treatment for each infant. The mean episodes in each group were averaged and used for statistical analysis.

D. Resuming full fat feedings

To monitor the resolution of the chylous effusion, chest x-rays were obtained per standard of care in both groups ~4 weeks after the start of treatment. Infants transitioned back to regular breast milk or milk-based standard infant formula of choice beginning 4- 6 weeks after the date of chest tube removal. Table 3 describes a detailed timeline of the study protocol.

Table 3. Protocol Timeline

Activity in weeks*	1	2	3	4	5	6	7	8	9	10
Cardiac Surgery										
Chylothorax Diagnosis										
Enrollment in study										
Treatment with FSBM[1] or MCTF[2]										
Chest tube removal (discharge varies)										
Follow-up visits in clinic										
Transition to full fat feeds										
Resolution of chylothorax (x-rays)										
Monitoring										

*It is expected that infants will follow a similar pattern but may take longer to transition to the next step.
[1]FSBM (Fortified Skimmed Breast Milk)
[2]MCTF (Medium-Chain Triglyceride Formula)

Statistical analysis

The primary outcomes of this study were energy and protein intake, weight gain, linear growth, and feeding intolerance. We used descriptive statistics [e.g. frequencies, mean, and standard deviation (SD)] to summarize all primary outcome variables. T-tests were used to determine significance of differences in the primary outcome variables between the two groups. To assess the differences in emesis episodes we used a Mann Whitney test. A Fisher's exact test was used to test the differences in diarrhea activity between the two groups. We used repeated measures analysis of variance (ANOVA) to assess mean weight gain at different points in time as well as mean weight z-scores at different points in time to determine if the groups differed over time. A p-value of <0.05 for each of the primary outcome variables was used to establish significance. GraphPad Prism statistical and graphing software was used to analyze the data.

Chapter 4- RESULTS

Characteristics of the study participants are described in Tables 4 and 5. Cardiac diagnosis among the formula fed infants included hypoplastic left heart syndrome (HLHS) (n=2), transposition of the great arteries (n=3), patent ductus arteriosus (PDA) (n=1), ventricular septal defect (VSD) (n=5), coarctation of the aorta (n=1), tetralogy of fallot (n=2), and atrial septal defect (ASD) (n=1); 4 of the 9 infants had more than one congenital heart defect. In the skimmed breast milk group, cardiac diagnosis included HLHS (n=1), transposition of the great arteries (n=4), VSD (n=2), coarctation of the aorta (n=3), ASD (n=3), double outlet right ventricle (DORV) (n=1), aortic stenosis (n=1), and atrioventricular canal (n=1); 5 of the 8 infants had more than one congenital heart defect.

Participants in the formula group were significantly older (17.4 ± 15.4 wks. vs. 4.7 ± 6.9 wks.; p=0.048) than participants in the skimmed breast milk group at the time of chylothorax diagnosis and start of low-fat diet treatment. This difference in age could be due to the health status at the time of the infant's birth and decision to wait for surgical repair of the congenital heart defect until the infant was older. Duration of the inpatient low-fat diet treatment was variable within each group but was not significantly different between the groups (9.0 ± 2.7 days in the formula group vs. 12.5 ± 8.2 days in the skimmed breast milk group; p= 0.49).

Table 4. Participant Demographics in Formula Group

ID	Birth Weight (kg)	Birth Length (cm)	Gender	Gestation Age (wks)	Race	Ethnicity	Cardiac Diagnosis	Major Syndromes	Age at chylothorax diagnosis (wks)	Days of inpatient low-fat treatment	Formula
1	2.64	53	Female	39 6/7	White	Non-Hispanic/Non-Latino	HLHS, Transposition of the Great Arteries	Other chromosomal anomaly	8.7	29	Monogen
2	3.28	50.5	Female	38 2/7	White	Non-Hispanic/Non-Latino	PDA, VSD, Transposition of the Great Arteries	None	2.2	13	Enfaport
3	3.34	53.3	Male	39	American Indian or Alaska Native	Non-Hispanic/Non-Latino	VSD, Coarctation of the Aorta	None	4	4	Enfaport
4	3.99	51.5	Male	39	White	Non-Hispanic/Non-Latino	VSD	None	18	6	Enfaport
5	3.4	52	Male	39 6/7	Other	Hispanic/Latino	Tetralogy of Fallot	None	34.5	6	Enfaport
6	1.91	43	Male	35	White	Non-Hispanic/Non-Latino	VSD	None	24	3	Enfaport
7	3.78	51	Female	39 1/7	Other	Hispanic/Latino	HLHS	None	3	11	Enfaport/Monogen
8	3.28	51	Male	39	White	Non-Hispanic/Non-Latino	ASD, VSD, Transposition of the Great Arteries	None	46.7	5	Enfaport
9	3.02	51	Male	39 3/7	White	Non-Hispanic/Non-Latino	Tetralogy of Fallot	None	15.7	4	Monogen
Mean	3.18	50.70							17.42	9	
SD	0.62	3.04							15.38	8.22	

Table 5. Participant Demographics in Skimmed Breast Milk Group

ID	Birth Weight (kg)	Birth Length (cm)	Gestation Age (wks)	Gender	Race	Ethnicity	Cardiac Diagnosis	Major Syndromes	Age at chylothorax diagnosis (wks.)	Days of inpatient low-fat treatment	Fortifier
1	2.84	47.5	39 1/7	Female	White	Non-Hispanic/Non-Latino	Transposition of the Great Arteries, DORV	None	4.4	13	MCT Procal
2	2.6	47	39	Female	White	Non-Hispanic/Non-Latino	ASD, Coarctation of the Aorta, Aortic Stenosis	None	2	42	Monogen
3	2.48	46	37 6/7	Female	White	Non-Hispanic/Non-Latino	Coarctation of the Aorta	Turner Syndrome	1.5	7	MCT Procal
4	-	-	38	Male	White	Non-Hispanic/Non-Latino	ASD, AV Canal	Down Syndrome	21.5	6	MCT Procal
5	3.22	49.5	39 2/7	Female	White	Non-Hispanic/Non-Latino	VSD, Coarctation of the Aorta, Transposition of the Great Arteries	None	3.2	4	MCT Procal
6	3.12	48.3	39	Female	White	Non-Hispanic/Non-Latino	Transposition of the Great Arteries	None	1.8	8	MCT Procal
7	3.26	50	39 1/7	Female	White	Non-Hispanic/Non-Latino	Transposition of the Great Arteries	None	1.8	12	Monogen
8	3.54	52	38 4/7	Male	White	Non-Hispanic/Non-Latino	ASD, VSD, HLHS	None	1.4	8	MCT Procal
Mean	3.01	42.54							4.70	12.50	
SD	0.38	17.29							6.86	12.28	

Nutrition

During the inpatient low-fat treatment, ~62% of the infants in the skimmed breast milk group were treated with the low-fat diet treatment for <10 days. In comparison, 67% of infants in the formula fed group were treated with a low-fat diet for <10 days. The minimum-maximum days of inpatient low-fat treatment for the formula fed group and the skimmed breast milk group were 3-29 days and 4-42 days, respectively.

Unpaired t-tests were used to determine the differences in mean energy intake per kilogram of body weight, and mean protein intake per kilogram of body weight between the groups. Mean energy intake between the two groups was not statistically different (Formula: 73.62 ± 21.85 kcal/kg/day vs. Skimmed Breast Milk: 84.11 ± 14.12 kcal/kg/day; p= 0.29) (Figure 2). The recommended energy intake for each infant was compared to their actual mean energy intake per kilogram over the inpatient period. None of the infants in either group met their estimated energy requirements. In the formula group infants met between 50-89% of their energy needs while infants in the skimmed breast milk group met between 63-97% of their energy needs, the differences were not statistically significant (formula: 65 ± 15% vs skimmed breast milk: 76 ± 11%; p=0.11). Mean protein intake between the two groups was also not statistically different (2.42 ± 0.72 g/kg/day vs. 2.56 ± 0.55 g/kg/day; p=0.77) (Figure 3). The recommended amount of protein for neonates (< 4 weeks old) is 2.5-3.0 gm/kg/d, and for infants (>4 weeks old) is 2.0-2.5 gm/kg/d. Of the formula fed infants, ~66% (n=6) met 100% of the protein requirement for their age while ~77% (n=7) of them met at

least 90% of the protein requirement for their age. In the skimmed breast milk group, ~62% (n=5) of the infants met 100% of the protein requirement for their age while 100% (n=8) met at least 90% of the protein requirement for their age.

Mean volume of enteral feedings consumed in milliliters per day between the groups was statistically different with the formula group having a greater intake than the skimmed breast milk group (414.5 ± 77.87 ml/d vs. 324.7 ± 89.79 ml/d; p= 0.0431). However, volume of enteral feeding intake among the groups was similar when adjusted for body weight (formula: 87.87 ± 18.79 ml/kg/d vs. skimmed breast milk: 94.98 ± 22.59 ml/kg/d; p= 0.489). The differences in volume of intake per day is therefore most likely related to differences in age at chylothorax diagnosis. The number of days of TPN and/or lipid infusion during low-fat diet treatment was not significantly different between groups (formula group: 1.22 ± 1.99 days vs. skimmed breast milk group: 5.88 ± 10.12 days; p= 0.195). In the formula group, 3 of the infants received TPN and/or lipids during low-fat treatment while 5 infants in the skimmed breast milk group received TPN and/or lipids during low-fat treatment. The infants who were on TPN and/or lipids for longer than 10 days were more likely to have difficulty with feeds and consuming an adequate volume. Emesis occurred at an average of 39% of the inpatient diet treatment days in the formula group and an average of 37% of the inpatient diet treatment days in the skimmed breast milk group. There were no statistically significant differences in feeding intolerance during the inpatient diet treatment as measured by number of vomiting episodes (p=0.795) and presence of diarrhea (p=0.334).

Figure 2. Mean Inpatient Energy Intake

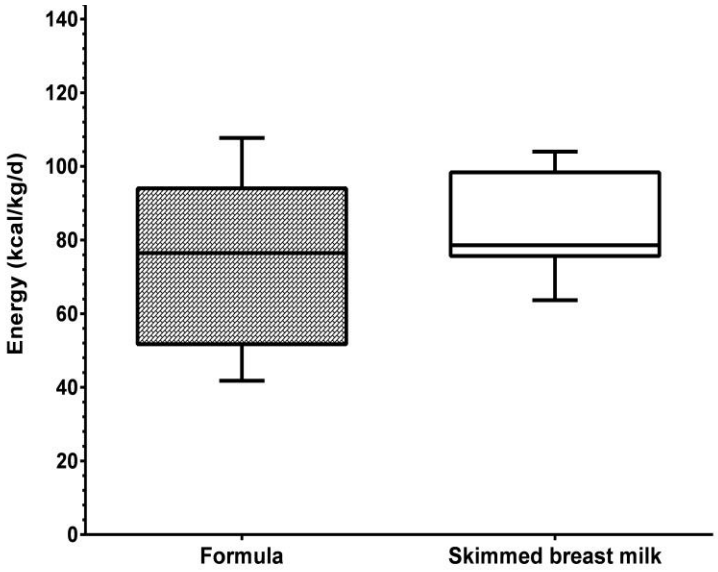


Figure 3. Mean Inpatient Protein Intake

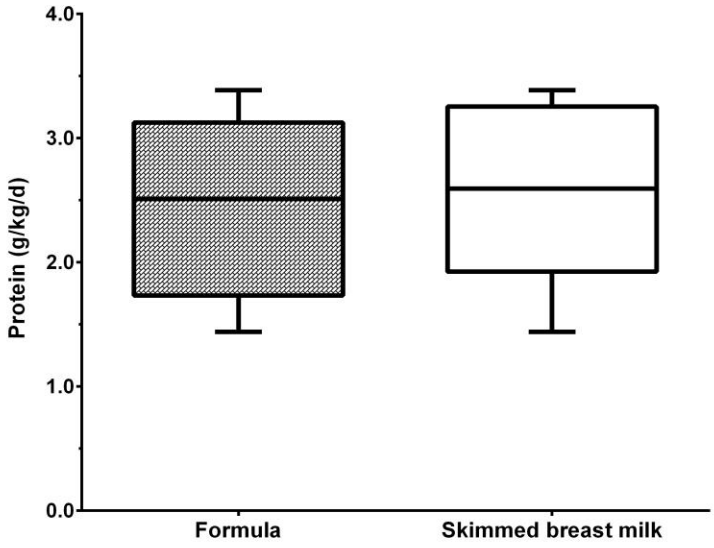


Figure 2 represents the mean energy intake in kcal/kg/d during the inpatient diet treatment. Figure 3 represents the mean energy intake in gm/kg/d during the inpatient diet treatment. The line in between the boxes represents the median while the box itself represents the interquartile range. The whiskers on the top and the bottom of the boxes represent the highest to the lowest values in the data set.

Table 6. Mean Inpatient Energy and Protein Intake, Volume of Enteral Feedings and Days on TPN During Inpatient Diet Treatment for Chylothorax

ID	Inpatient energy intake (kcal/kg/d)	Estimated energy needs (kcal/kg/d)	Inpatient protein intake (g/kg/d)	Protein Needs (gm/kg/d)	Inpatient enteral volume (ml/d)	Days on TPN/Lipids after chylothorax diagnosis
Formula Group						
1	108	120-125	3.38	2	341	4
2	105	120-130	3.38	2.5	383	5
3	83	130-135	2.68	2	364	0
4	78	135-145	2.87	2	534	0
5	67	90-100	2.10	2	468	0
6	54	100-110	1.87	2	352	0
7	76	125-130	2.51	2.5	338	2
8	42	80-90	1.44	2	527	0
9	50	100-110	1.60	2	424	0
Mean	74		2.42		415	1.22
SD	22		0.72		78	1.99
Skimmed Breast Milk Group						
1	77	100-110	2.02	2	209	7
2	97	100-120	2.78	2.5	241	30
3	77	110-120	2.37	2.5	276	0
4	64	90-100	1.80	2	475	0
5	80	120-125	2.95	2.5	378	0
6	99	120-125	2.60	2.5	269	6
7	104	125-135	3.56	2.5	383	2
8	75	120-125	2.39	2.5	367	2
Mean	84		2.56		325	5.88
SD	14		0.55		90	10.12

Growth

Change in body weight after surgery, diagnosis of chylothorax and initiation of treatment is the primary measure to determine if the infant is receiving adequate nutrient intake. Individual weight throughout the inpatient low-fat treatment is displayed in Figure 4. Mean weight percentile at discharge between the formula group and the skimmed breast milk group was not statistically different (11.37 ± 3.73 %ile vs. 13.97 ± 3.54 %ile; p= 0.623). Mean length percentile at discharge between the two groups was not statistically significant (38.25 ± 9.28 %ile vs. 33.08 ± 12.00 %ile; p= 0.733). To determine if the two groups differed in change in weight and weight-for-age z-scores over time, a repeated measures analysis of variance was completed. Mean change in weight was measured in grams per day between time of surgery and chylothorax diagnosis, chylothorax diagnosis and discharge, discharge and first clinic visit, and in between clinic visits. Change in weight over time was statistically significant within each group (All time points: p= 0.0037). However, there were no differences between the formula group and the skimmed breast milk group (All time points: p= 0.216). Both groups followed the same linear trajectory over time (interaction; p= 0.729) (Figure 5). However, infants in both groups did not gain the expected amount of weight (10-15 g/d). Table 7 shows a detailed average change in weight during the aforementioned points in time. Mean weight-for-age z-scores at the time of surgery, chylothorax diagnosis, and discharge were not significantly different over time (p= 0.623) (Table 8). Mean weight-for-age z-scores were also not significantly different between the groups over time (p=

0.538). Table 9 shows the mean, standard deviation and level of significance for all the tested outcome variables.

Figure 2. Weight Trajectory During Inpatient Diet Treatment for Chylothorax

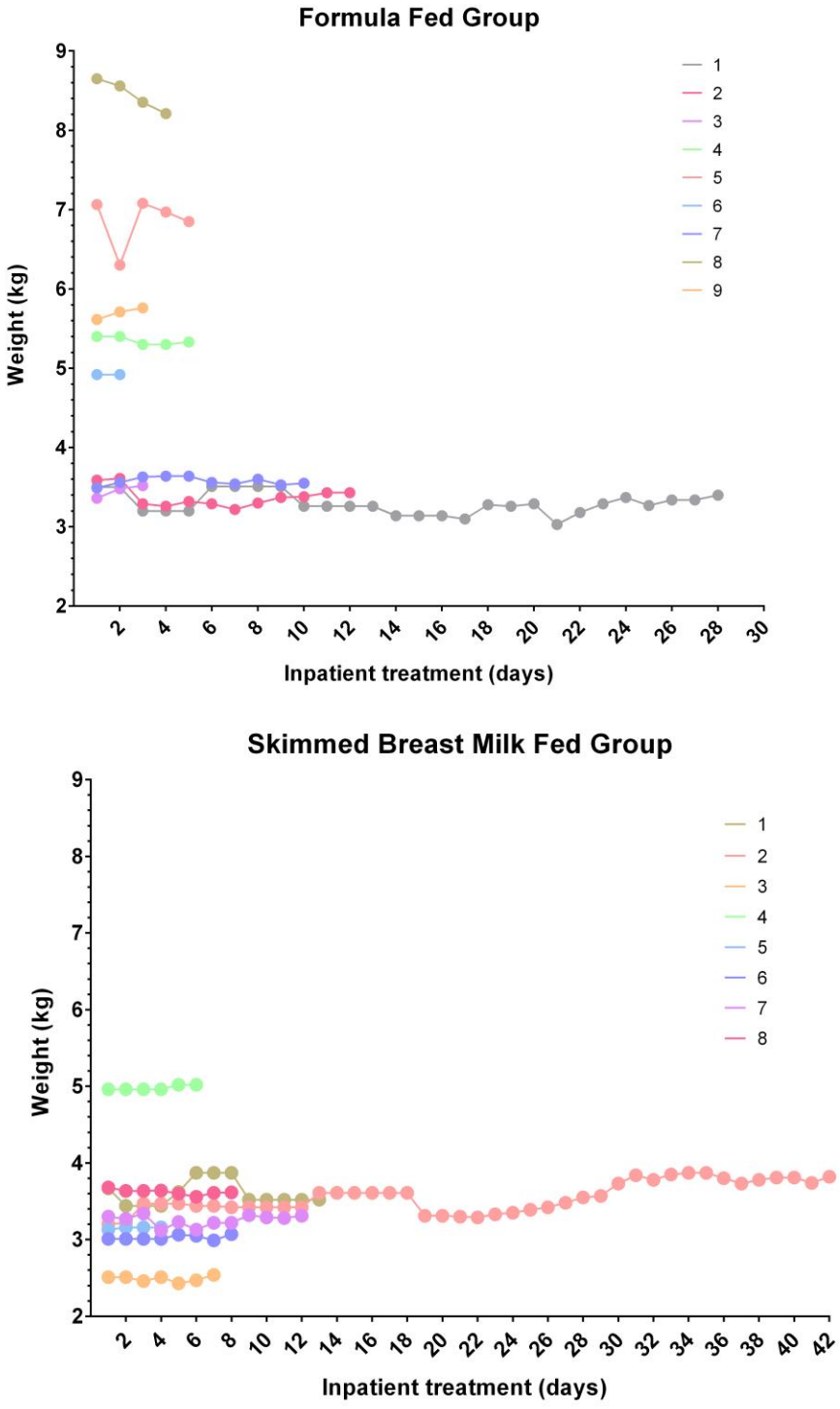


Figure 4 represents the weight trajectory of each infant during the inpatient diet treatment. Each point represents a daily weight in kg and each line represents an infant.

Figure 3. Mean Rate of Weight Change at Different Points during the Low-fat Diet treatment

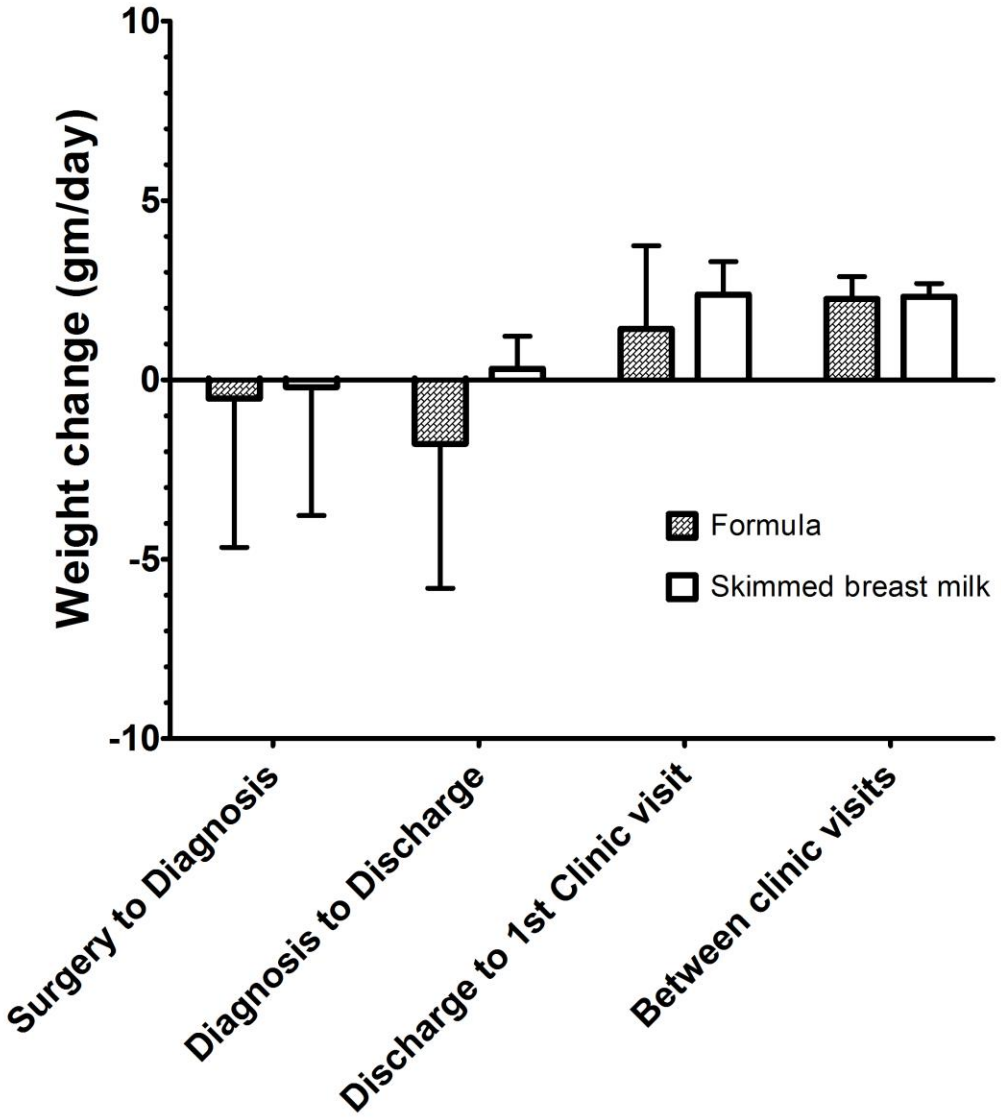


Figure 5 represents the weight change between surgery and chylothorax diagnosis, chylothorax diagnosis and discharge, discharge and the first clinic visit, and between clinic visits. The boxes represent the mean weight change for each group and the whiskers represent the standard deviation.

Table 7. Mean Rate of Weight Change from Cardiothoracic Surgery to Outpatient Cardiology Clinic Visits

ID	Between surgery and diagnosis (g/d)	Between diagnosis and discharge (g/d)	Between discharge and first clinic visit (g/d)	Between clinic visits (g/d)
Formula Group				
1	1.67	-0.34	3.64	1.45
2	0.00	-1.08	1.69	1.79
3	-9.33	-3.00	-3.50	2.98
4	4.38	-1.17	3.05	2.97
5	2.38	-7.17	0.16	1.58
6	-5.00	2.00	2.78	2.36
7	0.25	-0.18	3.75	2.84
8	0.83	-8.80	-0.08	2.14
9	0.11	3.75	1.30	-
Mean	-0.52	-1.78	1.42	2.264
SD	4.15	4.03	2.32	0.622
Skimmed Breast Milk Group				
1	3.46	-1.15	-	-
2	6.33	1.48	1.13	2.041
3	-5.00	0.43	3.80	-
4	0.00	1.00	2.64	2.204
5	-2.50	0.75	1.44	2.336
6	-2.38	0.75	2.24	2.673
7	-0.71	0.08	2.29	2.893
8	-0.83	-0.88	3.10	1.802
Mean	-0.20	0.31	2.38	2.325
SD	3.58	0.91	0.92	0.368

Table 8. Mean Weight-for-Age Z-scores Between Surgery and the Low-fat Treatment Period

Formula Group			
ID	Weight z-score at surgery (kg)	Weight z-score at diagnosis	Weight z-score at discharge
1	-1.75	-0.71	-2.27
2	0.18	0.18	-0.81
3	-1.20	-0.95	-1.30
4	-2.64	-1.73	-2.08
5	-8.22	-1.31	-1.96
6	-	-8.22	-8.22
7	0.30	0.08	-0.51
8	-0.67	-1.09	-1.15
9	-0.76	-0.87	-0.74
Mean	-1.845	-1.624	-2.116
SD	2.751	2.548	2.374
Skimmed Breast Milk Group			
1	-1.34	-0.74	-1.31
2	-1.4	-0.97	-1.41
3	-1.43	-2.32	-8.22
4	-1.04	-8.22	-1.06
5	0.16	-0.78	-0.83
6	-0.25	-1.01	-1.24
7	-0.01	-0.34	-1.04
8	0.43	0.09	-0.41
Mean	-0.610	-1.786	-1.940
SD	0.773	2.690	2.557

Table 9. Summary of Descriptive Statistics for Outcome Variables

	Formula (n=9)	Skimmed Breast Milk (n=8)		
		Mean ± SD	95% CI	P-value
Age at chylothorax diagnosis (wks.)	17.42 ± 15.376	4.70 ± 6.864	-25.33 to -0.12	**0.0481***
Inpatient energy intake (kcal/kg/day)	73.62 ± 21.849	84.11 ± 14.122	-30.66 to 9.68	0.2854
Inpatient protein intake (g/kg/day)	2.42 ± 0.722	2.56 ± 0.552	-0.84 to 0.63	0.7693
Feeding volume (ml/day)	414.5 ± 77.869	324.7 ± 89.794	3.20 to 176.40	**0.0431***
Feeding volume (ml/kg/day)	87.87 ± 18.787	94.98 ± 22.593	-28.50 to 14.27	0.4891
TPN/Lipids (# of days)	1.22 ± 1.986	5.88 ± 10.120	-2.66 to 11.97	0.1953
Length at discharge (%ile)	38.25 ± 27.851	33.08 ± 31.762	-26.81 to 37.16	0.7338
Weight at discharge (%ile)	11.37 ± 11.194	13.97 ± 10.032	-13.65 to 8.45	0.6232
Duration of inpatient low-fat diet treatment (# of days)	9.00 ± 8.216	12.50 ± 12.282	-7.183 to 14.18	0.4957

Chapter 5- DISCUSSION

This study aimed to compare the growth and nutritional intake of infants with postoperative chylothorax fed fortified skimmed breast milk or standard MCT-containing formula. There was no chylothorax reoccurrence in participants of either diet group suggesting that both diet interventions can be effective in the therapeutic management of postoperative chylothorax. Although growth was not ideal in either group, there were no significant differences between groups when comparing weight-for-age z-scores (Table 8) and change in weight over time (Table 7). Both groups had a slow weight gain velocity and declined in their weight-for-age z-scores from the time of surgery to the time of discharge. However, both groups grew along in a similar linear growth trajectory. Protein and energy intake was similar in both groups when compared to the recommended intake for age and weight. While not statistically different, the fortified skimmed breast milk group had higher protein and energy intake per kilogram of body weight and met a higher percentage of their protein and energy needs for their age.

Prior to the start of this study there were no reports in the literature comparing the use of fortified skimmed breast milk to the standard MCT-containing formula. However, Kocel et al. (2015) recently published data using a similar study design to that reported here. In their research, they found that infants receiving fortified skimmed breast milk had a significantly lower rate of linear growth and weight gain compared to infants fed the standard MCT-containing formula. Their fortification of skimmed breast milk included a

combination of Similac® Human Milk Fortifier, MCT oil, and soybean oil to provide essential fatty acids (26). The only other report that we are aware of that addresses weight gain in infants receiving fortified skimmed breast milk is from Lessen (2009). In this case report, skimmed breast milk was fortified with Monogen™ and was fed to a 5 week old infant with postoperative chylothorax who successfully gained weight (39 g/d) while on this treatment (9). Cormack et al. (2004) reported that 82% (14 of 17) of infants with postoperative chylothorax who were fed Monogen™ maintained their weight and had a higher weight at discharge compared to their preoperative weight. The remaining 18% (3 of 17) lost less than 3% of their total body weight (22).

In our study, 33% of infants in the formula group (3 of 9) lost 2-5% of their total body weight from the time of surgery to discharge. In the fortified skimmed breast milk group, 50% of the infants (4 of 8) lost 3-8% of their total body weight by discharge. Allen et al. (1991) also reported more than 10% weight loss in 22% (14 of 18) of their subjects fed Portagen (37). In our study, infants in the fortified skimmed breast milk group lost most of their weight right after surgery (Table 7/ Figure 5). Owens and Musa (2009) also reported a case in which the infant diagnosed with postoperative chylothorax lost ~7% of total body weight between surgery and chylothorax diagnosis (5 days) (4). In our study, the weight loss in the formula fed group occurred mostly between the initiation of low-fat feedings with MCT-containing formula and discharge (Table 7/ Figure 5).

As expected, infants in the fortified skimmed breast milk group had comparable energy and protein to those infants in the MCT-containing formula

group. Kocel et al. (2015) completed a direct analysis of the skimmed breast milk samples and compared the protein, sodium, and potassium content to that of mature breast milk reported in the literature. They found that sodium and potassium were similar in concentration to the reported content in mature milk. However, they found that protein content was slightly higher at 1.4 g/ 100ml compared to the estimated 1.1 g of protein per 100 ml in the literature (26). For our study we assumed the skimmed breast milk contained 1.1 g of protein/ 100ml based on the current literature which may have been an underestimation since we did not test the skimmed breast milk samples for specific nutrient content. However, when using 1.1 g of protein/100 ml to calculate their intake, infants in the fortified skimmed breast milk group were able to meet a higher percentage of their protein needs for age than those in the formula group. It is important to mention that all infants in both groups initially received Enfaport™ per the hospital's protocol. Some infants in the formula group were transitioned to Monogen™ formula since the infants did not tolerate Enfaport™. In the skimmed breast milk group, some infants continued some formula (Enfaport™ or Monogen™) feedings due to low breast milk supply.

Although we were expecting the infants in the fortified skimmed breast milk group to have better tolerance to enteral feeding than the formula group, both groups had similar rates of emesis and diarrhea episodes during their inpatient diet treatment period. Many of the parents in the formula group reported the infants disliked the taste of the MCT-containing formula which had to be flavored with vanilla syrup for the infants to better accept the formula. Kocel et al.

(2015) also concluded there were no differences in tolerance between the two groups, however, the formula used in this study was Portagen® (26). In the case reported by Hamdan and Gaeta (2004), the infant did not tolerate Portagen® which led the team to feed him fortified skimmed breast milk along with octreotide to resolve the intolerance as well as decrease the chylous effusion (7). Our study is the first to report the use of Enfaport™ for the management of postoperative chylothorax in infants.

The significant differences in age between the groups at the time of chylothorax may be due to the range of cardiac diagnoses and the health status of the infants at the time of birth. Depending on the severity of the cardiac diagnosis, the infants were able to wait until they are well nourished and stable to undergo cardiothoracic surgery to repair their heart abnormalities. Another impact on the age range between the groups was the fact that mothers were able to choose which diet treatment their infants would follow. Most of the infants in the formula group received formula prior to chylothorax diagnosis and infants in the skimmed breast milk group were fed breast milk prior to chylothorax diagnosis. The young age of most of the infants in the skimmed breast milk group may account for some of the differences in intake (ml/day) and duration of hospital stay.

Limitations

One of the limitations in this study is the burden of the skimming technique. The process requires a lot of patience and time to accomplish as it takes about 3-5 hours of daily pumping of breast milk in addition to the 48 hours

from the time of pumping to be able to skim the breast milk, fortify it, and feed it to the infant. During our study it was also difficult to skim the breast milk in the hospital since there is no designated mixing room. In addition, some of the milk was frozen because the staff did not follow the study protocol. This delayed the initiation of the skimmed breast milk treatment and resulted in a decrease in the supply of breast milk available to skim. Other studies have used the centrifugation method to separate the breast milk into fat and skim portions. Kocel at al. (2015) used the centrifuge method. After discharge parents were given the choice to have the breast milk samples centrifuged at the hospital or the families were able to borrow a centrifuge to skim the milk at home. One of their limitations of using this method was that there may have been a loss of macro-and micronutrients since breast milk had to be transferred to 6-8 different containers between pumping, skimming, fortifying, and feeding the skimmed breast milk to the infant (26). Chan and Lechtenberg (2007), and Hamdan and Gaeta (2004) also centrifuged the breast milk to separate it into fat and skim portions, however, there was no mention of how the breast milk was skimmed after discharge (7, 8). Centrifugation has been proven as the most effective method by Drewniak et al. (2013) to separate fat and nonfat components of breast milk and to obtain a lower percentage of fat in the skimmed portion (35). However, the refrigeration and syringe method used in this study was the most feasible to use because we did not have access to a centrifuge that could be used to separate breast milk into a skimmed portion for human consumption. With the refrigeration and syringe method, mothers could also complete this

process at home without needing much equipment. Ultimately, the skimming technique whether by centrifuge or refrigeration can be challenging for families with an infant who is recovering from cardiothoracic surgery. Thus, the use of skimmed breast milk might not appeal to some families.

We also acknowledge that the fortification process used in this study was based on previous reports in the literature since we did not analyze the breast milk samples other than measuring the fat content by the creamatocrit method a few times during the treatment period. To determine fortification needs, we used an estimated energy of 12 kcal/ oz and 1.1 g protein/ 100 ml in skimmed breast milk. The skimmed breast milk was fortified to provide 20-30 kcal/oz depending on the infants energy needs and the final energy concentration was used to estimate the infant's energy intake. Future studies should analyze the breast milk samples before and after the skimming technique since there are still many unknowns about the nutrient content of breast milk after skimming. This will give the health care team a better idea as to how to fortify the skimmed breast milk to promote better growth in this very high risk, medically fragile population. A multi-centered project following the same protocol is also needed to increase the sample size and provide stronger evidence for the use of skimmed breast milk in infants with chylothorax after cardiothoracic surgery. Further study could potentially expand the use of skimmed breast milk for the treatment of chylothorax after other surgeries and conditions. Future studies should include breastfeeding support in the protocol to help mothers maintain adequate breast milk supply during the treatment period and beyond.

Conclusion

In conclusion, we were able to accept our initial hypothesis that infants with postoperative chylothorax who consumed fortified skimmed breast milk would have similar nutrient intake compared to infants receiving the specialized MCT-containing formula. Total energy and protein intake were similar between groups but neither group met their recommended intakes for energy and protein after cardiothoracic surgery and chylothorax diagnosis. We did not find any differences in tolerance symptoms. We were also able to accept our initial hypothesis that infants with postoperative chylothorax who consumed fortified skimmed breast milk would have comparable weight gain for sex and age to the infants in the specialized MCT-containing formula group. We were unable to fully assess and compare their linear growth since the data was inconsistently retrieved.

Therefore, the results of this study suggest that the use of fortified skimmed breast milk in infants with postoperative chylothorax can be an equal alternative to a MCT-containing formula for those parents who want to continue to provide breast milk to their infants. The continual supply of breast milk through the period of chylothorax treatment also allows mothers to resume breastfeeding after the treatment has ended. Thus, infants are more likely to continue to receive the beneficial qualities that only breast milk can provide. It is known that this population tends to grow at a slower rate than most infants because of their compromised health after surgery. Since growth in both groups was not optimal, future studies should focus on improving growth outcomes in this population

regardless of the type of nutrition treatment used. This could be achieved by developing protocols that provide more immediate resolution when nutrition goals and weight goals are not being met.

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Appendix A. Evidence Table

Citation	Design	Duration of low fat treatment	Participants	Intervention/ Outcomes
Hamdan MA, Gaeta ML. Octreotide and low-fat breast milk in postoperative chylothorax. Ann Thorac Surg 2004;77:2215-7.	Case report.	48 days	3 month old male, diagnosed with chylothorax on POD 6.	TPN and centrifuged low-fat breast milk were combined on postoperative day 33. Chylothorax resolved on postoperative day 49. Patient was discharged on postoperative day 67. Breast feeding resumed two weeks later, there was no chylothorax reoccurrence.
Chan GM, Lechtenberg E. The use of fat-free human milk in infants with chylous pleural effusion. J Perinatol 2007;27:434-6.	Breast milk separation into fat and skimmed portions was achieved by centrifugation at 3000 r.p.m. for 15 min at 2˚C.	7-34 days	7 infants (1-8 months old) with acquired or congenital chylothorax fed fortified skimmed breast milk.	The mean fat removed was 5±1 g/dl (mean) which was consistent with fat content prior to centrifugation. No differences in electrolyte content was noted between the full-fat and the skimmed breast milk. Skimmed breast milk was fortified with protein, Portagen or Pregestimil, and glucose polymers. Two infants also required TPN and Intralipids. No chylothorax reoccurrence was noted in any of the infants.

Lessen R. Use of Skim Breast Milk for an Infant With Chylothorax. ICAN: Infant, Child, & Adolescent Nutrition 2009;1:303-10.	Case report. Breast milk was prepared by leaving it undisturbed in the refrigerator for 8 to 12 hours. A syringe was used to get the fat-free portion out of the container.	Unknown	Female diagnosed with postoperative chylothorax at 36 days old.	Patient was discharged 8 days after chylothorax diagnosis and on skimmed breast milk feeds fortified with Monogen powder. Infant also received daily boluses of walnut oil. Weight gain averaged 39 gm/day during admission.
Kocel SL, Russell J, O'Connor DL. Fat-Modified Breast Milk Resolves Chylous Pleural Effusion in Infants With Postsurgical Chylothorax but Is Associated With Slow Growth. Journal of Parenteral and Enteral Nutrition 2015. In print	The skimmed breast milk group was fortified with MCT oil, Human Milk Fortifier, and Soybean oil. Breast milk was skimmed by centrifugation during the treatment period. Infants in the formula group received Portagen.	4 weeks	8 infants in formula group 8 infants in skimmed breast milk group	Infants in the skimmed breast milk group had statistically significant lower weight and length z-scores at the end of treatment. While the formula group had no statistically significant changes. They found no differences in nutrient intake and tolerance between the groups.

Appendix B. Original IRB Consent Form

Oregon Health & Science University
Consent Form

IRB#: 7747
Protocol Approval Date: 3/17/2015

OREGON HEALTH & SCIENCE UNIVERSITY
Consent Form

TITLE: A comparison of the effectiveness of fortified skimmed mother's milk versus specialized formula in the management of chylous effusion in infants following cardiothoracic surgery

PRINCIPAL INVESTIGATOR: Cindi L. Farnstrom, RN, MN, CPNP (503) 418-5750

CO-INVESTIGATORS: Alisa Tortorich RD, CSP, LD (503) 418-5257
Rich Reed, PA (503) 418-6825

SPONSOR: Gerber Foundation

PURPOSE:

You and your infant have been asked to be in this research study because your infant has developed a chylothorax after cardiothoracic surgery. A chylothorax is a collection of fluid around the lungs that can occur after cardiac surgery. The fluid contains chyle, a milky substance consisting of fat droplets. The usual way of treating a chylothorax is a low fat diet. This is usually done with a specialized low fat infant formula The use of skimmed breast milk has not been studied to determine if it is a good alternative to specialized formula in the treatment of chylothorax.

The purpose of this study is to learn if using skimmed breast milk is at least as good as specialized formula, our current standard of care, in the treatment of chylothorax. To do so, we will enroll your infant into one of two groups, a skimmed breastmilk group or a specialized formula group. We will collect information about the treatment response and outcomes for this condition to learn if the use of skimmed breast milk is a safe alternative to specialized formula. It will also help us to learn more about feeding symptoms of the two groups and the feeding method. Information collected will include nutrition, weight gain, teaching needs, surgical and discharge information. This information will be entered into a secure database and stored in a repository indefinitely for further evaluation. This information may also be used to help create best practice guidelines for feeding in postoperative chylothorax management.

PARTICIPATION:

To qualify for this study, your infant must meet the following criteria:

1. Be an infant birth to 12 months of age
2. Undergo cardiothoracic surgery
3. Develop a chylous effusion
4. Be a breastfed or formula fed infant

You and your infant will be enrolled in this study for approximately 4 months. We will see you in clinic at your regular follow-up visits. No additional visits or tests are needed specifically for this study.

About 50 subjects will be enrolled in this study at OHSU.

PROCEDURES:

You and your infant will be enrolled in one of two groups in this study.

Group 1: Infants of mothers who have breast milk and whose mothers are willing to learn the skimming technique will be invited into the skimmed mother's milk group.

Group 2: Infants of mothers who do not have breast milk or whose mothers do not want to learn the skimming technique will be invited into the specialized formula group.

If you have breastmilk and want to provide this to your infant, you will be taught the skimming technique to remove the fat from the milk. The milk will then be tested for fat content and calories at least 2 times while in the hospital. A carbohydrate fortifier will be added to increase the calories of the milk.

If you and your infant are in the skimmed mother's milk group and you stop producing milk or you do not want to continue the skimming technique, you will be reassigned to the specialized formula group for the remainder of the study. You will be asked to continue the intake log and feeding symptom questionnaire as described below.

If you do not have breastmilk or do not want to perform the skimming, your infant will receive specialized formula, our standard of care in the treatment of chylothorax.

For both the skimmed breastmilk group and the formula group, we will ask you to complete a daily feeding log and feeding symptom questionnaire that will take approximately 10 minutes each time. This will begin at the time of diagnosis and continue after discharge until your infant has transitioned to regular breastmilk or regular formula. This transition takes 4 to 6 weeks from the time of discharge from the hospital, but may take longer. Once your infant has transitioned to regular breastmilk or regular formula, you will be asked to complete a feeding method questionnaire.

For both the skimmed breastmilk group and the formula group, chest xrays will be required during the hospitalization and at follow-up visits as per our standard of care. Your infant will not require additional tests outside of our standard of care during

participation in the study.

We will collect information daily from you and the medical record while your infant is in the hospital. We will also collect information from you and the medical record after discharge at routine visits to the clinic after hospital discharge until your infant is back on regular breastmilk or formula. Information collected will include chest tube drainage, chest x-ray findings, nutrition information, growth information, and feeding symptoms.

For both study groups, you and your infant will be seen in the cardiology clinic beginning at 2 weeks after discharge from the hospital and then 1 to 3 months later depending on your infant's clinical condition and cardiologist's recommendation. These clinic visits will happen even if you withdraw from the study as this is our standard of care. During these clinic visits, we will collect information about the return of fluid around the lungs, growth and nutrition that is also part of our standard of care. As part of the study, we will also collect information from your intake log and feeding symptoms questionnaire.

For both study groups, we will collect information about whether or not the fluid returns around the lungs for up to four months after you leave the hospital. This will be done by collecting information from the medical record. You will not be asked to record any information after your infant is transitioned to regular breastmilk or regular formula (usually up to 6 weeks after hospital discharge, but it may take longer).

For the skimmed breast milk group, if the chylothorax does not resolve the infant will be changed to specialized formula or IV nutrition. If a subject chooses to withdraw from the skimmed breast milk group he/she will be moved to the specialized formula group. If not continuing in the study at all, the infant will still receive specialized formula as this is our standard of care. Data will no longer be collected.

For the specialized formula group, if the chylothorax does not resolve, the infant will be transitioned to an alternative formula or IV nutrition. Information will continue to be collected. If choosing to withdraw, the infant will still received specialized formula or IV nutrition as this is our standard of care. Data will no longer be collected.

Storage of Data for Future Research

You will be asked later in this form if you are willing to allow data to be collected during this research to be used for future research. If you agree to allow information about your infant to be stored for future use, you will be asked to place your initials in a box at the end of this consent form

If you have any questions regarding this study now or in the future, contact Cindi Farnstrom at (503-418-5750) or Alisa Tortorich at (503) 418-5257

RISKS AND DISCOMFORTS:

Skimming breast milk is an experimental procedure. There is a chance that skimmed breast milk is not as good as the specialized formula and your infant will be in the hospital for a longer period of time. There is a chance that your infant will need different therapy for the chylothorax such as intravenous nutrition. However, this is a risk for all infants with chylothorax regardless of the use of formula or skimmed

mother's milk. We do not know if the risk is higher when receiving skimmed mother's milk.

BENEFITS:

You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

ALTERNATIVES:

You may choose not to be in this study. Your infant will be treated with the specialized formula as this is our standard of care.

CONFIDENTIALITY:

We will not use your name or your identity for publication or publicity purposes. Research records may be reviewed and/or copied by the sponsor, the OHSU Institutional Review Board, the Office for Human Research Protections (OHRP), or any other applicable agency**.**

We will protect your privacy in the following ways:

1. We may collect your infant's birthdate as part of our data gathering and the dates of his/her surgical procedures, but your child's birthday, name or other protected information will not be included in the database. All data will be de-identified before being entered in the database.
2. Only the investigators or those involved in the study will have access to your information.

The specific health information we will collect from you or your infant will include weight, nutrition information, feeding information, surgery information, discharge information, and clinic visit information. The purpose of our use and disclosure of this health information are described in the Purpose section of this Consent and Authorization Form.

COSTS:

Some of the services or items in this study are part of the regular treatment for your condition. These would be performed or used even if you were not in this study. The costs for these services or items will be billed to your insurance. You will be responsible for any costs your insurance does not cover. If you have any questions about these costs, or what out-of-pocket expenses you may be responsible for, contact your insurance company. If you are uninsured, you will be responsible for these costs.

LIABILITY

If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact Cindi Farnstrom at (503) 418-5750 or Alisa Tortorich at (503) 418-5257

You have not waived your legal rights by signing this form. If you are harmed by the study procedures, you will be treated. Oregon Health & Science University does not offer to pay for the cost of the treatment. Any claim you make against Oregon Health & Science University may be limited by the Oregon Tort Claims Act (ORS 30.260 through 30.300). If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

PARTICIPATION:

If you have any questions regarding your rights as a research subject, you may contact the OHSU Research Integrity Office at (503) 494-7887.

You do not have to join this or any research study. If you do join, and later change your mind, you may quit at any time. If you refuse to join or withdraw early from the

study, there will be no penalty or loss of any benefits to which you are otherwise entitled.

If the investigators publish the results of this research, they will do so in a way that does not identify your infant.

Your infant's health care provider may be one of the investigators of this research study, and as an investigator is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way involved in this project. You do not have to be in any research study offered by your physician.

You may be removed from the study if the investigator or sponsor stops the study, your infant's disease gets worse, or if your infant fails to respond to treatment.

If you choose to withdraw from the study and are in the skimmed breast milk group, your infant will receive the specialized formula; our standard of care. Data will no longer be collected.

If you choose to withdraw from the study and are in the specialized formula group, your infant will continue to receive specialized formula as this is our standard of care. Data will no longer be collected.

If you choose to withdraw from the study, you will still be required to complete follow-up clinic visits and any necessary chest x-rays at the discretion of your provider as this is our standard of care.

Storage of Data for Future Research

The data that we will collect from you will be stored in a repository that collects and stores data for future research projects. The data will not be stored with your name or any other identifier (de-identified). Therefore, there will not be a way for us to identify and destroy your information if you decide in the future that you do not wish to participate in the research repository. The information will be de-identified before being entered into the database on a locked, password protected, computer at OHSU to protect your privacy. Please initial next to one of the statements below. If you choose to withdraw from the repository the data previously stored will be retained, however future information collected during the study will not be stored. If you choose to not have data stored in the repository, you may still participate in the study.

Choose one and initial	***Statement of Additional Use of Data***
	I agree to allow storage of my data for future research.
	I do not agree to allow storage of my data for future research.

SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study. We will give you a copy of this signed form.

OREGON HEALTH & SCIENCE UNIVERSITY
INSTITUTIONAL REVIEW BOARD
PHONE NUMBER (503) 494-7887
CONSENT/AUTHORIZATION FORM APPROVAL DATE

Mar. 17, 2015

Do not sign this form after the expiration date of: Mar. 16, 2016

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date