How We Approach: Pediatric Congenital Chylous Effusions and Ascites

Taizo Nakano[1], Yoav Dori[2], Lindsey Gumer[1], Deborah Liptzin[1], Lauren Hill[1], and Ann Kulungowski[1]

[1]Children's Hospital Colorado
[2]Children's Hospital of Philadelphia

April 26, 2021

Abstract

Congenital lymphatic leak may develop in patients with maldeveloped lymphatics and result in life-threatening fluid and electrolyte imbalance, protein deficiency and immunodeficiency. Rapid diagnosis and therapy are necessary to prevent these complications; however, the field lacks clinical trials to support standardized diagnostic treatment guidelines. We present our current multidisciplinary approach to the diagnosis and management of congenital lymphatic leak including chylous pleural effusion and ascites. Depending on the rate of lymphatic leak, therapy can range from observation with nutritional modifications to surgical and interventional procedures aimed to reduce lymphatic drainage. Modalities to image central and peripheral lymphatics have advanced considerably. Genetic variants and subsequent targets that drive lymphatic maldevelopment have expanded the repertoire of possible pharmacotherapeutic options.

INTRODUCTION

The development of a lymphatic leak in the pleural space (chylous effusion or chylothorax) or in the abdominal cavity (chylous ascites) is a rare and life-threatening presentation. Although chylous effusions and ascites can occur secondary to surgical or traumatic processes, this discussion focuses on non-traumatic, congenital disorders of pulmonary or intestinal lymphatic flow that result in symptomatic lymphatic leak. Early detection of a primary lymphatic disorder improves outcome and reduces complications. Without prospective trials to guide care, we present our multidisciplinary approach to the diagnosis and treatment of congenital chylous effusions and ascites.

The Lymphatic System:

The lymphatic circulatory system is a complex network of thin-walled vessels responsible for transporting lymphatic fluid collected from the interstitial tissues of the body back to the heart **(Figure 1a)** . Lymphatic fluid is propelled by both the intrinsic contraction and relaxation of lymphatic vessels and by external compressive forces of skeletal muscles.[1] Lymphatic fluid is composed of protein, fat, immune cells (primarily lymphocytes) and excess fluid collected from the soft tissues. Chyle is the fat and protein rich lymphatic fluid produced in the small intestines and makes up about 50% of the lymphatic fluid. Chyle contains high concentrations of long-chain triglycerides, lymphocytes, electrolytes, immunoglobulins, albumin, fibrinogen, glucose and fat-soluble vitamins.[2] Intestinal lymph drains to regional nodes and joins hepatic lymph through the cisterna chyli to feed into the thoracic duct. The thoracic duct is the end of the central lymphatic highway that transports lymphatic fluid to the left subclavian vein and back the blood circulatory system. The thoracic duct originates from the cisterna chyli around the level of the first and second lumbar vertebrae, lateral to the aorta **(Figure 1a)** . Lymph nodes function to regulate the content of lymph and can activate an immune response when triggered by a pathogen.

Congenital Malformations of Pulmonary and Intestinal Lymphatic Flow

Complications of congenital malformations of lymphatic flow include chylous effusions (thoracic cavity), chylous ascites (peritoneal cavity) and, even more rarely, chylopericardium (pericardial cavity). These complications are often seen in children with complex vascular anomalies including generalized lymphatic anomalies (GLA), central conducting lymphatic anomalies (CCLA), Gorham Stout disease (GS), and Kaposiform lymphangiomatosis (KLA, a proliferative disorder) **(Table 1)** or in children with known congenital syndromes associated with malformed lymphatics including Down, Turner and Noonan syndromes. These complications of lymphatic flow can result in systemic fluid and electrolyte imbalance, nutritional deficiencies, hypovolemia, and hypoalbuminemia. Progressive loss of essential proteins results in an increased risk of hemorrhagic coagulopathy from lack of prothrombin and fibrinogen.[3] Thrombophilia can occur due to loss of antithrombin. There is an additional increased risk of infection from the loss of both cellular (lymphocytopenia and low CD4+ T-cells) and humoral (hypogammaglobulinemia) immunity resulting in progressive immunosuppression.[4]

Congenital lymphatic leak can occur in utero due to obstructions and leaks of the lymphatic system. The accumulation of large fluid volumes in the thorax or abdomen can lead to cardiac failure and obstruction of venous return leading to non-immune hydrops fetalis, polyhydramnios, and fetal demise. Historically, mortality for congenital chylothorax has been reported to be high around 10-20%.[5, 6] New imaging, surgical and interventional techniques have reduced mortality significantly in certain populations.[7]

Chylous effusions

Chylous effusions or chylothorax occurs when there is lymphatic chyle in the chest cavity and/or pleural space as a result of intrinsic abnormalities of the lymphatic system or secondary to thoracic duct injury (trauma, surgery, malignancy, cardiovascular disease). Primary disorders of pulmonary and pleural lymphatic flow predispose to impaired lymphatic drainage, increased trans-pleural filtration pressure (lymphatic hypertension), retrograde lymphatic flow and increased permeability that results in chylous effusion or chylothorax**(Figure 1b)** . These disorders are sometimes referred to as pulmonary Lymphatic Perfusion Syndromes (PLPS). Chylous effusions typically present with respiratory symptoms such as dyspnea, chest pain, cough, and fatigue.

Abnormal development of the native lymphatic system presents as lymphangiomatosis or lymphangiectasia. Lymphangiomatosis is a generalized term for the over-proliferation of malformed and poorly functional lymphatics in the lungs **(Figure 1b)** . Abnormal lymphatics can infiltrate a single organ or present as multifocal disease with infiltrations into bone and surrounding tissue. Pulmonary lymphangiomatosis can present with non-specific respiratory symptoms of progressive cough, wheezing, or dyspnea. Congenital pulmonary lymphangiectasia is characterized by dilated lymphatics in the subpleural and interlobular lymphatic vessels that fail to drain appropriately. Primary pulmonary lymphangiectasia is hypothesized as a failure of the normal large lymphatic channels to regress mid-lung development (at ˜20 weeks). Lymphangiectasia commonly presents with non-specific respiratory distress.

Chyle aspirated via thoracentesis is milky in appearance with lymphocyte predominance and biochemical analysis often with a triglyceride concentration >110 mg/dL. In the unfed state, chylous fluid can be clear yellow in the absence of chylomicrons.

Chylous ascites

Primary maldevelopment of the intra-abdominal lymphatic vessels predisposes to disruption of lymphatic flow resulting in non-traumatic leakage of chyle through intestinal villi into the abdominal cavity resulting in chylous ascites. Chylous ascites typically presents with abdominal distention and discomfort, clinical dehydration, malnutrition, electrolyte imbalance, peripheral edema and immunosuppression. Hypoproteinemia, specifically hypoalbuminemia, can cause decreased vascular oncotic pressure and cause “third-spacing” soft tissue edema.

Congenital causes like intestinal lymphangiectasia or lymphatic malformations demonstrate disrupted or

dilated lymphatic vessels that are prone to exudative leakage of lymphatic fluid through a fistula into the peritoneum **(Figure 1b)** .[1] Steinmann et al reviewed 190 patients with chylous ascites noting 32% were caused by lymphatic anomalies. Furthermore, 84% of these predominantly pediatric vascular anomalies were classified as lymphangiectasia or Waldmann's disease (dilated lymphatic vessels that lack valves in the submucosa of the small bowel).[8]

Paracentesis plays both a diagnostic and therapeutic role in the management of chylous ascites. In the feeding child, chyle aspirated via abdominal paracentesis appears milky white in appearance and biochemical analysis demonstrates elevated triglyceride concentration >110 mg/dl (similar to chylous effusions mentioned above).

DIAGNOSIS OF A LYMPHATIC LEAK

Clinical history, physical examination, laboratory evaluation including fluid analysis and imaging are necessary to diagnose a lymphatic leak.

Imaging Techniques

Plain film X-ray: Plain film radiography is often used as first-line imaging to demonstrate a lymphatic leak. Chest x-ray often demonstrates a pleural effusion and abdominal x-ray may suggest the presence of peritoneal fluid.

Ultrasound: Ultrasonography is particularly sensitive for detecting the presence and quantity of fluid. Ultrasonography can demonstrate dilation of intestinal loops, diffuse thickening of walls and mesenteric edema. Sonographic evaluations are limited in the setting of obesity or complex multiloculated ascites.

Computed Tomography (CT): CT can identify focal lymphatic malformations, thoracic lymphangiectasia or lymphangiomatosis, but distinguishing lymphatic fluid from non-lymphatic effusions is difficult. Abdominal and pelvic CT scans obtained with oral and intravenous contrast enhancement may demonstrate diffuse, nodular, small bowel wall-thickening and edema.[4] Chylous ascites may demonstrate a unique biphasic fat-fluid level when the patient to positioned lying flat.[9]

Conventional Intranodal Lymphangiography: Percutaneous canulation of groin lymph nodes followed by injection of an oil-based iodinated contrast agent allows for imaging of the central conducting lymphatic vessels with adequate characterization of patterns of lymphatic flow.[10] Compared to historic use of pedal lymphangiography, direct contrast injection into lymph nodes of the groin has a higher success rate to produce informative diagnostic imaging of abdominal and thoracic lymphatics. Although modern interventional practices have shortened procedure time and decreased cumulative fluoroscopy exposure, anesthesia is required for pediatric patients and should be discussed when reviewing the risks and benefits of pursuing lymphangiography. Conventional intranodal lymphangiography is contraindicated in patients with a known right to left cardiac shunt given the potential stroke risk.

Non-contrast Magnetic Resonance Lymphangiography: Static T2 weighted non-contrast MR lymphangiography has a high sensitivity and specificity to demonstrate abnormal lymph vessels and abnormal draining patterns in the peripheral lymphatic system.[11] Non-contrast MR lymphangiography can image both central and peripheral lymphatic systems but is a static image with no data to characterize lymphatic flow. Magnetic resonance imaging (MRI) reduces ionizing radiation exposure but may require sedation for prolonged studies.

Dynamic Contrast-Enhanced MR Lymphangiography (DCMRL): DCMRL is the current imaging modality of choice to image the central lymphatic system, identify lymphatic leaks and plan interventional or surgical procedures.[10] However, the availability of DCMRL can vary nationally and success of imaging can be operator dependent. The technique has several advantages over conventional fluoroscopic lymphangiography including that it is 3D, has good distal distribution of contrast, and has good tissue contrast. Intranodal DCMRL (IN-DCMRL) involves ultrasound guided groin lymph node access followed by injection of a gadolinium contrast agent into the lymph node and then dynamic and static contrast enhanced MRI imaging of the abdomen and thorax.[12, 13] This technique is good for imaging the central lymphatic system including the

cysterna chyli and thoracic duct (TD) and is the default imaging modality for pulmonary lymphatic disorders that are often supplied by fluid that originates from the TD **(Figure 2a)** . IN-DCMRL allows for evaluation of the central lymphatic system prior to interventions or surgery; however, the two main contributors to central lymphatic flow, the liver and the mesentery, which play a key role in several disease processes such as protein losing enteropathy (PLE) and ascites, are not often imaged with IN-DCMRL. Recently, intrahepatic (IH) and intramesenteric (IM) DCMRL allow imaging of these two important lymphatic streams.[14, 15] Intrahepatic and intramesenteric DCMRLs are the imaging modalities of choice for imaging abdominal lymphatic abnormalities such as PLE and ascites and should be used in conjunction with IN-DCMRL in cases with multicompartment lymphatic disorders to better characterize the extent of the lymphatic abnormality and to plan treatments **(Figure 2b, 2c).**

Laboratory Analysis

First-line peripheral blood laboratory evaluation should include complete blood count with differential, complete metabolic panel including total protein, albumin, and liver functions, lactate dehydrogenase (LDH), lipid panel, and, in the case of chylous ascites, lipase. Depending on the severity of lymphatic leak, secondary laboratory evaluations may include PT/ aPTT/ INR and fibrinogen to monitor for the ongoing development of coagulopathy and an immunoglobulin panel (IgA, IgG, IgM) to monitor for the ongoing development of hypogammaglobulinemia.

Aspiration of fluid via thoracentesis or paracentesis is critical to establish a diagnosis of lymphatic leak. Simple observation of the aspirated fluid can start to differentiate the fluid as exudative (e.g. lymphatic) versus transudative (from heart failure, hepatic cirrhosis, nephrotic syndrome) in origin.[16] If the child has been enterally fed, chyle will appear cloudy, milky white although it can also appear serous, sanguineous or bloody. Evaluation of the pleural or peritoneal fluid that supports lymphatic origin include elevated concentration of protein, LDH, triglyceride, increased presence of lymphocytes, and the presence of chylomicrons **(Table 2)** . If three is concern for PLE, stool can be evaluated for alpha-1-antitrypson.

Biopsies of abnormal lymphatic tissue may help with histologic diagnosis of disease, but caution should be taken in the setting of lymphatic leak not to risk exacerbating the condition. Biopsy of involved rib bones can be particularly dangerous as this may exacerbate lymphatic leak. In conjunction with clinical history, physical examination, imaging and fluid analysis, if biopsy is felt to be helpful, biopsy of affected tissue remote from an active leak is recommended.

FIRST-LINE MANAGEMENT OF A SYMPTOMATIC LYMPHATIC LEAK

CASE 1: A newborn female with Noonan syndrome is admitted to the neonatal ICU for persistent abdominal ascites. Exam demonstrates diffuse soft tissue edema, a moderately distended abdomen, and stable vitals. Diagnostic paracentesis confirms the fluid is chylous and peripheral laboratory evaluation is notable for hypoalbuminemia, hypogammaglobulinemia and lymphocytopenia. MR lymphangiography identifies areas of likely congenital intestinal lymphangiectasia. Treatment recommendations include immediate transition to a medium-chain triglyceride diet, IV albumin repletion, and serial abdominal ultrasound surveillance to monitor rate of ascites reaccumulation. In the following 4 weeks, only one additional therapeutic paracentesis is required indicating a “low-flow” rate lymphatic leak, and the frequency of albumin replacement greatly decreases as peripheral edema resolves. After 8 weeks on a medium-chain triglyceride formula (Portagen), the fat and caloric content of her diet is slowly liberalized without further evidence of ascites or edema.

Multidisciplinary management of a symptomatic lymphatic leak centers around respiratory support, volume repletion, diet augmentation and minimally invasive attempts to treat the source of a lymphatic leak. The goal of first-line management is to encourage spontaneous and timely closure of leaking lymphatic vessels.

If the clinical scenario allows, a period of observation and medical support is indicated for both premature and term infants presenting with chylous leaks. In some instances, chylous leaks are temporary. Postnatally, lymphovenous communications can be established through collateral channels or lymph nodes (mediastinal, lumbar, renal, or hepatic) allowing chyle to regain access to the general circulation. Development of alter-

native lymphatic flow can take weeks to months. Patience must be incorporated into the care of congenital chylothorax and chylous ascites. Limiting frequent adjustments to treatment regimen is helpful so as to not confound the ability to interpret response to interventions.

Antenatal interventions for congenital chylous collections include serial ultrasounds, intrauterine interventions such as thoracoamniotic shunt, and rarely, intrauterine chemical pleurodesis[17]. Thoracoamniotic shunting for congenital chylothorax and reversal of hydrops significantly improves survival; prematurity portends a worse prognosis and increased mortality.[17] The longer the interval between thoracomaniotic shunting for congenital chylothorax and delivery, the more likely the reversal of hydrops and neonatal survival.[17]

Low-flow lymphatic leaks ($<$ 500 ml/day in adults, or roughly $<$ 20 ml/kg/day in children) may close spontaneously and/or respond to supportive care medical management. High flow lymphatic leaks ($>$ 1 L/day in adults, or roughly $>$ 20 ml/kg/day in children) tend to require more aggressive therapy including surgical or interventional procedures to reduce morbidity and mortality.[18] **(Figure 3).** Maintaining a drain until the patient is tolerating a full diet allows for monitoring of continued leak. Alternatively, serial abdominal or chest ultrasonography are utilized when necessary to monitor reaccumulation.

Drainage: In symptomatic chylous effusion, intermittent aspiration of fluid and/or placement of thoracostomy tube for continuous drainage can be necessary to improve symptoms, allow for better lung expansion, and decrease the size of potential pleural space to help seal the lymphatic leak. Despite drainage, some lymphatic leaks persist, leading to the need for chronic drainage. Mechanical ventilation is sometimes necessary. Similarly, in symptomatic chylous ascites, intermittent aspiration of fluid and/or placement of a peritoneal drain for continuous drainage may be indicated to decrease abdominal distention and improve lung expansion. Thoracentesis or peritoneal fluid aspiration allows for fluid analysis to confirm the fluid is lymphatic in origin **(Table 2)** .

Nutritional Management: Goals of nutritional supportive care include decrease chylous production and accumulation of effusion or ascites, maintenance of adequate nutrition and electrolytes, and protein repletion. A symptomatic chylous effusion or ascites should be monitored for twenty-four hours to establish a baseline rate of lymphatic leak. Daily weights should be documented to monitor for shifts in fluid balance.

Patients who demonstrate a "low-flow" rate ($<$ 20 ml/kg/day) of lymphatic leak may benefit from a trial off long-chain-fats (LCF) to a medium-chain-triglyceride (MCT) based formula. Long chain fats (LCF) make up most of our dietary fat. Their digestion is complex and involves both the gastrointestinal and lymphatic systems. Chyle from intestines is a protein rich fluid - returning between one-fourth to one-half of plasma protein in circulation to the body. LCFs are ingested and released as micelles with fat in the small bowel. Here, the micelles interact with pancreatic lipase, breaking down the LCF. Micelles transport fatty acids to intestinal villi where they are absorbed. Medium chain triglycerides (MCT), however, are easily absorbed across the small intestine into the portal system without requiring transport into the lymphatic system. Because of this, a diet including MCT products should not increase the production of lymphatic fluid. Slowly, over the course of weeks, a low-fat diet associated with MCT may resolve clinical and biochemical complications. If drain output does not decrease after 1-2 weeks on MCT diet, transitioning to complete gut rest with total parenteral nutrition with or without octreotide as an adjunct should be considered.

Formulas that contain high levels of MCT include Portagen, Progestimil, and Enfaport **(Table 3)** . Newborns whose enteral intake consists exclusively of MCT containing formulas are at risk for developing essential fatty acid (EFA) deficiency. A fatty acid profile and fat-soluble vitamins (Vitamin A, D, E, K) should be monitored in these patients after 1-2 weeks of initiating an MCT based formula and consider adding an EFA supplement to the diet. EFA deficiency can develop within the first few weeks of a lymphatic leak and presents with skin rashes, impaired wound healing, thrombocytopenia and growth delays. Lipids are an essential part of development of the nervous system; the developmental impact limiting lipid intake may impact early brain growth. As a lymphatic leak improves, fatty acid profile should be monitored every 3 months until normalized and then every 6 months after.

In patients with a "high-flow" rate (> 20ml/kg/day) of lymphatic leak and those who are refractory to MCT formula, more aggressive nutritional restriction is indicated. Cessation of all enteral nutrition to reduce the production of chyle driven by dietary fat intake may be indicated. Total parenteral nutrition (TPN) with intravenous lipids is initiated to replete caloric and electrolyte deficiencies and improve fluid balance. Intravenous lipids are delivered directly into the blood stream, do not travel through the lymphatic system and are not contraindicated in the treatment of high-flow lymphatic leak.

Laboratory monitoring: With a symptomatic lymphatic leak, electrolyte and organ function should be evaluated with a complete metabolic panel. Protein loss can be estimated by serum albumin and IgG level. A complete blood count helps monitor progressive lymphopenia. The frequency of laboratory monitoring is relative to the rate of lymphatic loss. Whereas high-flow lymphatic loss may require metabolic panel monitoring multiple times daily, low-flow lymphatic loss often only requires once daily monitoring and frequency can be liberalized as symptoms resolve to spare cumulative blood loss.

Albumin repletion: The efficacy of albumin replacement, in general, has been controversial in critical care medicine. Although not a direct therapy for lymphatic leak, repletion of albumin is often performed when disease is complicated by serous effusions or symptomatic limb edema (third spacing). Albumin provides an increase in intravascular oncotic pressure and causes mobilization of fluids from interstitial into intravascular space. For effusions or ascites with hypoalbuminemia, 25% albumin (250 mg/ml) can be given at 1g/kg/dose infused over 2 to 3 hours. The dose can be repeated up to three times per day until the serum albumin is > 2.5 g/dL; maximum dose of 25 g/dose.[19] Side effects of an albumin infusion may include hypertension, tachycardia, fever, chills, rash, nausea and vomiting. Serial albumin infusions intravenously may reduce edema, but the impact is often transient.

Octreotide: Octreotide is a synthetic somatostatin analogue commonly used to treat secretory diarrhea, esophageal varices, and post-gastrectomy dumping syndrome. The mechanism of action of octreotide involves reduced splanchnic blood flow, portal pressure, and intestinal absorption of fats. Additionally, octreotide decreases gut motility and splanchnic lymphatic production. In the setting of high-flow or refractory lymphatic leak evidence supports the use of octreotide to reduce the rate of lymphatic leak in both congenital and acquired chylous effusion and ascites. An initial dose is commonly 1-2 mcg/kg/hour as a continuous intravenous infusion, titrating up to a clinical response with a median maximum dose of 10 mcg/kg/hour. Although octreotide can be delivered subcutaneously, there is greater evidence of efficacy in children and neonates when given intravenously. Duration of therapy commonly ranges from 7 to 14 days.[20] Congenital lymphatic leak tends to require higher doses and a longer duration of therapy compared to acquired lymphatic leak. Side effects include bradycardia, hypertension, worsening of underlying pulmonary hypertension, hyperglycemia, and headache. Octreotide may be considered immediately in patients with high-flow output with symptomatic electrolyte and protein losses, or in patients who have failed an NPO trial of 1-2 weeks.

IgG repletion: Although not a direct therapy for lymphatic leak, adjuvant IgG repletion may be necessary. IgG repletion via intravenous immunoglobulin (IVIG) should be reserved for patients actively fighting infectious complications. In this case, low dose infusions of ˜400mg/kg can be given to maintain a minimal physiologic IgG. Transfused immunoglobulins are quickly depleted by continuous lymphatic leak making it difficult to maintain higher serum concentrations. In the patient without active infections, serial IVIG infusions given to improve the serum IgG value risk the introduction of a considerable fluid burden that may cause more harm to fluid balance than active benefit.

Fever management: Fluid within an effusion or ascites is at risk of becoming infected. Providers should have a low threshold to evaluate and treat febrile patients with a lymphatic leak. Consider oral antibiotic course for fever without a source and consider intravenous broad coverage antibiotics for fever with culture positive focal source. In the setting of chylous ascites, gram-negative coverage, such as a third-generation cephalosporin is generally recommended. Although the literature lacks recommendations for the initiation of Pneumocystis jiroveci pneumonia (PJP) prophylaxis in the setting of lymphatic leak, we have applied a general recommendation often used for patients with immunodeficiency; PJP prophylaxis is considered when

the absolute lymphocyte count is < 500 cells/μL, or, if available, when the CD4+ T cell lymphocyte count is < 200 cells/μL.

MANAGEMENT OF REFRACTORY LYMPHATIC LEAK

CASE 2: A newborn male is admitted to the neonatal ICU for respiratory distress secondary to large bilateral pulmonary effusions. The infant is intubated and multiple chest tubes are placed to maintain adequate ventilation. Aspirated fluid is milky white in color and confirmed chylous with a high triglyceride and lymphocyte content. Peripheral laboratory evaluation is notable for hypoalbuminemia, hypogammaglobulinemia and lymphocytopenia. In addition to continuous chest tube drainage, acute interventions include complete gut rest with total parenteral nutrition and intravenous lipids, IV albumin replacement, and initiation of octreotide infusion. Despite maximizing these interventions, chylous output remains > 20ml/kg/day. Intranodal Dynamic Contrast-Enhanced MR lymphangiography (IN-DCMRL) demonstrates a diffuse Central Conducting Lymphatic Anomaly (CCLA) with extensive abdominal and thoracic lymphangiomatosis. Interventional radiology acutely performs lymphatic interstitial embolization while hematology/oncology initiates oral sirolimus pharmacotherapy. After 8 weeks of sirolimus therapy, although now extubated and protein replete, the infant remains with a single chest tube in place and continues to struggle advancing beyond a medium chain triglyceride formula.

Surgical and endolymphatic strategies for treatment of congenital chylous effusions and ascites are usually employed after failure of medical therapies. The decision to perform an intervention depends on factors related to local expertise. Many times, these invasive procedures are performed in tandem or after prior procedures have failed to stop chylous leakage.

Symptoms of refractory disease include unresponsive daily loss of chyle exceeding 100 ml/day for a 5-day period, or symptomatic nutritional, protein and/or electrolyte complications. Infants should not be allowed to progress to a state of severe hepatic cholestasis without an attempt at intervention.[21] Surgical and endolymphatic interventions include drainage, shunting, pleurodesis, ligation of lymphatics, lymphovenous anastomosis, and thoracic duct embolization.[22]

(Figure 3)

Drainage. Thoracentesis or paracentesis can be performed for symptomatic patients especially when mechanical ventilation is needed. However, drainage of large volumes of chyle can lead to fluid shifts, malnutrition, and immunocompromise due to loss of lymphocytes and immunoglobulins. In dwelling catheters can be a source for infection and can lead to a persistent chylous leak.

Shunting. Peritoneovenous or pleuroperitoneal shunts to drain chylous effusion or ascites have been utilized.[23, 24] Peritoneovenous shunts drain chylous ascites from the abdomen into the superior vena cava. Technical limitations include the size of the shunt relative to size of infant. Shunts complications include shunt occlusion, thrombosis, infection, disseminated intravascular coagulopathy, and need for shunt revision.[25] Shunting rarely provides a durable solution.

Pleurodesis. Obliteration of the potential space between the parietal and visceral pleura using chemical or a combination of chemical and mechanical pleurodesis has had some success in managing chylous effusions.[26] The procedure can be performed via tube thoracostomy or a thoracoscopic approach. Talc, povidone-iodine, and doxycycline are some of the agents used for pleurodesis.[26-28]

Surgical ligation. In preparation for surgical exploration due to chylous effusion or ascites, efforts to maximize finding the leak should be considered. Cessation of medical therapies to limit chyle production prior to intervention combined with pre-operative fat loading can prove helpful. It is not uncommon for surgeons to allow a patient to not only eat but encourage ingestion of a high fat diet to better identify the location of the lymphatic leak. Techniques described include 1 g of Sudan III dye mixed in 30 ml of milk given 6 hours preoperatively.[21, 29, 30] Intranodal, intradermal, or subcutaneous injection of lipophilic dyes prior to exploration can be used to facilitate visualization.[21] Thoracoscopic and laparoscopic approaches limit pain and can improve visualization; conversion to an open exploration is not perceived as a failure and is

sometimes necessary for a thorough assessment. Suture ligation of the leaking lymphatic branch, thoracic duct, or cisterna chyli can be performed.[31] Fibrin glue and hemostatic or vicryl mesh are variably applied as reinforcement.[29] Lymphovenous anastomosis and lymphaticovenous bypass of the thoracic duct for the treatment of chylous leak in CCLA offers these patients a potential durable cure.[32, 33] Early results show that lymphaticovenous bypass does not ameliorate patients suffering with intestinal lymphangiectasia and protein losing enteropathy.[33] Drain placement at the time of surgical intervention is considered to manage any persistent lymphatic leak. The biggest risk of surgery is continued chylous leak.

Endolymphatic techniques. Thoracic duct or lymphatic channel embolization is a minimally invasive alternative to surgical ligation and can be successfully performed.[34, 35] It has several advantages over the surgical technique in being minimally invasive and image guided, but it can be challenging especially in premature infants and small children with small central ducts. Complete thoracic duct embolization usually involves placing microcoils and glue (n-butyl cyanoacrylate) into the thoracic duct. Selective embolization of the lymphatic channel can also be performed with coils and glue or glue alone. Selective embolization preserves thoracic duct flow which can be advantageous especially in patients with elevated central venous pressure. Lymphatic duct embolization has been successfully used in children with chylous effusions secondary to iatrogenic injury to the lymphatic duct.[35] Risks of lymphatic embolization include nontarget embolization to the periphery such as the lungs and stroke.[34]

In patients with neonatal chylothorax, Lipiodol®embolization and low-fat diet has recently been shown as effective treatment strategy.[7] In neonates with multicompartment disorders care should be taken not to occlude the central lymphatic ducts as this can lead to adverse outcomes. More selective and conservative management is favored in the neonatal population with diet and diuretics. Decompression strategies such as surgical lymphovenous anastomosis have been showing promise.

Nutritional management: Patients with high output lymphatic leak are at risk for severe nutritional deficiencies including vitamin D 25-hydroxy, zinc, copper and essential fatty acids.[36] While NPO, TPN with intralipids is necessary to prevent essential fatty acid deficiency.

Genetic sequencing: Many primary lymphatic malformations are due to sporadic somatic mutations in genes that regulate lymphangiogenesis. Gene variants often involve the VEGFC/VEGFR3 and PI3K/AKT/mTOR pathways. Additionally, some genetic syndromes are associated with abnormal lymphatic development including Down, Turner, Noonan and Cardiofaciocutaneous syndromes.[37] Identification of a genetic variant has implications for patient screening and management as potential therapeutic targets are discovered. With the identification of PI3K/AKT/mTOR variants within certain vascular malformations, their targeted inhibition is now the subject of several active clinical trials.[38] Sirolimus, an mTOR inhibitor further described below, has been utilized to improve function in patients with complex lymphatic anomalies. RAS/MAPK pathway variants have also been identified in complex lymphatic anomalies and represent a novel therapeutic target with MEK pathway inhibitors like trametinib.[39] Use of trametinib to treat symptomatic pediatric vascular anomalies currently is limited to the setting of a clinical trial or for compassionate use in the setting of a lesion with an identified RAS/MAPK pathway variant. Geneticists and genetic counselors are an increasingly important member of the multidisciplinary vascular anomalies team.

Sirolimus (Rapamune): mTOR inhibition has been increasingly utilized to improve function in symptomatic vascular anomalies. The mechanism of action is presumed to be the inhibition of an overactive PI3K/AKT/mTOR pathway, decreasing inappropriate cell growth and angiogenesis. Phase II trials have demonstrated efficacy of sirolimus in vascular anomalies including complex lymphatic anomalies.[40] Despite a paucity of data, sirolimus is used as a first-line pharmacotherapy agent in symptomatic Gorham Stout, Kaposiform lymphangiomatosis, and generalized lymphatic anomaly. Sirolimus' efficacy in treating central conducting lymphatic anomaly is not known and is utilized as a secondary agent for refractory lymphatic leak. Although dosing practices vary, for use to treat pediatric vascular anomalies, we commonly initiate sirolimus at 0.8 mg/m^2/dose given twice daily by mouth and further titrated to a serum trough level of 10-15 ng/ml.[40] Caution should be taken to dose reduce sirolimus in the newborn and premature infant with presumed immature drug clearance (consider starting dose of 0.2 mg/m^2/dose given twice daily in

the newborn or premature infant).[41] Concurrent *Pneumocystis jiroveci pneumonia* prophylaxis is recommended. Side effects include neutropenia, mucositis, peripheral edema, hypertension, hypertriglyceridemia, hypercholesterolemia, headache, and elevation of liver transaminases.

CONCLUSIONS

Complex lymphatic anomalies can be debilitating, and complications of lymphatic leak can be life-threatening. Unfortunately, the field lacks basic natural history outcome trials and any prospective interventional trials dedicated to the treatment of symptomatic lymphatic anomalies or lymphatic leak. What is certain, however, is the need for a multidisciplinary, coordinated approach to the management of lymphatic leak. Management can be triaged based on the rate of lymphatic leak (low vs high flow) with aggressive nutritional support. Patience is mandatory as reduction in lymphatic flow can take weeks to achieve. Lymphatic imaging, surgical, and endolymphatic techniques continue to advance. The expanding identification of genetic variants that drive abnormal lymphatic disease has opened the door to new pharmacotherapy options to augment disease. With such advancements on many fronts coordinated prospective trials may be on the horizon.

Conflict of Interests: T.A.N. has consulted for Novartis phamaceuticals to develop consensus guidelines for PIK3CA-related overgrowth disorders. All additional authors have no financial/personal conflicts to disclose

REFERENCES

1. Lizaola, B., et al., *Review article: the diagnostic approach and current management of chylous ascites.* Aliment Pharmacol Ther, 2017. **46** (9): p. 816-824.

2. Bender, B., V. Murthy, and R.S. Chamberlain, *The changing management of chylothorax in the modern era.* Eur J Cardiothorac Surg, 2016. **49** (1): p. 18-24.

3. Bernet-Buettiker, V., et al., *Antithrombin activity in children with chylothorax.* Eur J Cardiothorac Surg, 2006. **29** (3): p. 406-9.

4. Vignes, S. and J. Bellanger, *Primary intestinal lymphangiectasia (Waldmann's disease).* Orphanet J Rare Dis, 2008.**3** : p. 5.

5. Bellini, C., et al., *Congenital fetal and neonatal visceral chylous effusions: neonatal chylothorax and chylous ascites revisited. A multicenter retrospective study.* Lymphology, 2012. **45** (3): p. 91-102.

6. Bialkowski, A., et al., *Congenital chylothorax: a prospective nationwide epidemiological study in Germany.* Arch Dis Child Fetal Neonatal Ed, 2015. **100** (2): p. F169-72.

7. Pinto, E., et al., *Neonatal lymphatic flow disorders: impact of lymphatic imaging and interventions on outcomes.* J Perinatol, 2020.

8. Steinemann, D.C., et al., *Atraumatic chylous ascites: systematic review on symptoms and causes.* J Am Coll Surg, 2011.**212** (5): p. 899-905 e1-4.

9. Hibbeln, J.F., M.D. Wehmueller, and A.C. Wilbur, *Chylous ascites: CT and ultrasound appearance.* Abdom Imaging, 1995.**20** (2): p. 138-40.

10. Dori, Y., *Novel Lymphatic Imaging Techniques.* Tech Vasc Interv Radiol, 2016. **19** (4): p. 255-261.

11. Notohamiprodjo, M., et al., *MR lymphangiography at 3.0 T: correlation with lymphoscintigraphy.* Radiology, 2012. **264** (1): p. 78-87.

12. Dori, Y., M.M. Zviman, and M. Itkin, *Dynamic contrast-enhanced MR lymphangiography: feasibility study in swine.* Radiology, 2014.**273** (2): p. 410-6.

13. Krishnamurthy, R., et al., *Imaging the central conducting lymphatics: initial experience with dynamic MR lymphangiography.*Radiology, 2015. **274** (3): p. 871-8.

14. Biko, D.M., et al., *Intrahepatic dynamic contrast MR lymphangiography: initial experience with a new technique for the assessment of liver lymphatics.* Eur Radiol, 2019. **29** (10): p. 5190-5196.

15. Dori, Y., et al., *Intramesenteric dynamic contrast pediatric MR lymphangiography: initial experience and comparison with intranodal and intrahepatic MR lymphangiography.* Eur Radiol, 2020.**30** (10): p. 5777-5784.

16. Bellini, C., et al., *Congenital Chylothorax of the Newborn: Diagnosis and Treatment in Three Pictures.* Lymphology, 2016.**49** (3): p. 150-6.

17. Dorsi, M., et al., *Prenatal factors associated with neonatal survival of infants with congenital chylothorax.* J Perinatol, 2018.**38** (1): p. 31-34.

18. Zabeck, H., et al., *Management of chylothorax in adults: when is surgery indicated?* Thorac Cardiovasc Surg, 2011. **59** (4): p. 243-6.

19. Giefer, M.J., K.F. Murray, and R.B. Colletti, *Pathophysiology, diagnosis, and management of pediatric ascites.* J Pediatr Gastroenterol Nutr, 2011. **52** (5): p. 503-13.

20. Bellini, C., et al., *Octreotide for congenital and acquired chylothorax in newborns: A systematic review.* J Paediatr Child Health, 2018. **54** (8): p. 840-847.

21. Fishman, S., *Truncal, Visceral, and Genital Vascular Malformations* , in *Mulliken and Young's Vascular Anomalies: Hemangiomas and Malformations* , J. Mulliken, P. Burrows, and S. Fishman, Editors. 2013, Oxford University Press: New York, New York. p. 966-1016.

22. Lopez-Gutierrez, J.C. and J.A. Tovar, *Chylothorax and chylous ascites: management and pitfalls.* Semin Pediatr Surg, 2014.**23** (5): p. 298-302.

23. Epaud, R., et al., *Therapeutic strategies for idiopathic chylothorax.* J Pediatr Surg, 2008. **43** (3): p. 461-5.

24. Camoglio, F.S., et al., *Treatment of neonatal chylous ascites using a modified Denver peritoneovenous shunt: a case report.* Pediatr Med Chir, 2003. **25** (2): p. 145-7.

25. Huang, Y., et al., *Management of refractory chylous ascites with peritoneovenous shunts.* J Vasc Surg Venous Lymphat Disord, 2017.**5** (4): p. 538-546.

26. Hodges MM, C.T., Meyers M, Kulungowski A, Marwan AI, Nakano T, Behrendt N, Liechty KL, *Massive fetal chylothorax successfuly treated with postnatal talc pleurodesis: a case report and review of the literature.* Journal of Pediatric Surgery Case Reports, 2016.**9** : p. 1-4.

27. Brissaud, O., et al., *Congenital idiopathic chylothorax in neonates: chemical pleurodesis with povidone-iodine (Betadine).* Arch Dis Child Fetal Neonatal Ed, 2003. **88** (6): p. F531-3.

28. Nissen A, T.F., Edwards M, *Thoracoscopically-assisted doxycycline sclerotherapy for a microcystic thoracoabdominal lymphatic malformation in a 3-month old patient.* Journal of Pediatric Surgery Case Reports, 2016. **5** : p. 12-14.

29. Spagnol, L., et al., *Preoperative administration of Sudan III and successful treatment of persistent chylous ascites in a neonate.* J Pediatr Surg, 2011. **46** (5): p. 994-7.

30. Mitsunaga, T., et al., *Successful surgical treatment of two cases of congenital chylous ascites.* J Pediatr Surg, 2001.**36** (11): p. 1717-9.

31. Kuroiwa, M., et al., *Successful laparoscopic ligation of the lymphatic trunk for refractory chylous ascites.* J Pediatr Surg, 2007.**42** (5): p. E15-8.

32. Hayashida, K., S. Yamakawa, and E. Shirakami, *Lymphovenous anastomosis for the treatment of persistent congenital chylothorax in a low-birth-weight infant: A case report.* Medicine (Baltimore), 2019.**98** (43): p. e17575.

33. Taghinia, A.H., et al., *Lymphaticovenous bypass of the thoracic duct for the treatment of chylous leak in central conducting lymphatic anomalies.* J Pediatr Surg, 2019. **54** (3): p. 562-568.

34. Srinivasa, R.N., et al., *Endolymphatic Interventions for the Treatment of Chylothorax and Chylous Ascites in Neonates: Technical and Clinical Success and Complications.* Ann Vasc Surg, 2018. **50** : p. 269-274.

35. Majdalany, B.S., et al., *Pediatric lymphangiography, thoracic duct embolization and thoracic duct disruption: a single-institution experience in 11 children with chylothorax.* Pediatr Radiol, 2018.**48** (2): p. 235-240.

36. Biko, D.M., et al., *Pediatric pulmonary lymphatic flow Disorders: Diagnosis and management.* Paediatr Respir Rev, 2019.

37. Greenlee, R., et al., *Developmental disorders of the lymphatic system.* Lymphology, 1993. **26** (4): p. 156-68.

38. Venot, Q., et al., *Targeted therapy in patients with PIK3CA-related overgrowth syndrome.* Nature, 2018. **558** (7711): p. 540-546.

39. Li, D., et al., *ARAF recurrent mutation causes central conducting lymphatic anomaly treatable with a MEK inhibitor.* Nat Med, 2019. **25** (7): p. 1116-1122.

40. Adams, D.M., et al., *Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies.* Pediatrics, 2016.**137** (2): p. e20153257.

41. Mizuno, T., et al., *Model-based precision dosing of sirolimus in pediatric patients with vascular anomalies.* Eur J Pharm Sci, 2017.**109S** : p. S124-S131.

42. Cho, S., et al., *Chylous Manifestations and Management of Gorham-Stout Syndrome.* Korean J Thorac Cardiovasc Surg, 2019.**52** (1): p. 44-46.

Figure 1: The lymphatic system is a unidirectional transport system to return fluid to the blood circulation **1a:** Intestinal lymphatics drain from mesenteric nodes to the cysterna chyli located around the aortic hiatus of the diaphragm and ascends cephalad through the thoracic duct to empty into the blood circulation via the subclavian to brachiocephalic veins. Pulmonary lymphatics drain from paratracheal and bronchopulmonary lymph nodes to right and left thoracic ducts to similarly empty into subclavian to brachiocephalic veins. The illustration depicts select lymphatics of the left lung and small intestine in a healthy neonate (1) thoracic duct (2) left brachiocephalic vein and branches (3) inferior vena cava (4) cysterna chyli. **1b:** The illustration depicts select abnormalities of the lymphatic system (5) idiopathic stenosis of the thoracic duct; results in impaired lymphatic drainage, increased trans-pleural filtration pressure (lymphatic hypertension), retrograde lymphatic flow and increased permeability that results in lymphatic leak (6) large region of pulmonary lymphangiomatosis (over proliferation of lymphatic vessels) and lymphangiectasia (inappropriately dilated lymphatic vessels) enveloping the ventral surface of the lung; results in failure of appropriate lymphatic drainage (7) chylothorax collecting in the left pleural cavity (8) chylous ascites collecting in peritoneum causing a distended abdomen.

Figure 2: 2a) Maximal intensity projection (MIP) coronal projection of intranodal DCMRL in patient with KLA showing massively dilated and tortuous thoracic duct (arrow) and bilateral pulmonary perfusion (arrowheads) as well as mediastinal perfusion. **2b)**MIP coronal projection of IN-DCMRL in patient with an EPHB4 mutation and lymphatic conduction disorder showing dermal backflow (arrowheads) and no flow into the thorax. **2c)** MIP coronal projection of intrahepatic DCMRL in the same patient showing peritoneal leak (arrow), retrograde mesenteric flow, and conduction up left sided paravertebral channels supplying the left sided posterior intercostal networks (arrowhead).

Figure 3: Management of a lymphatic leak

Hosted file

Table 1.pdf available at https://authorea.com/users/410125/articles/519608-how-we-approach-pediatric-congenital-chylous-effusions-and-ascites

Hosted file

Table 2.pdf available at https://authorea.com/users/410125/articles/519608-how-we-approach-pediatric-congenital-chylous-effusions-and-ascites

Hosted file

Table 3.pdf available at https://authorea.com/users/410125/articles/519608-how-we-approach-pediatric-congenital-chylous-effusions-and-ascites