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HEMATOLOGY: RESEARCH ARTICLE

Sirolimus efficacy in the treatment of critically ill infants with congenital primary chylous effusions

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Abstract

Background: Chylothorax can be a presenting symptom of complex lymphatic anomaly in children and is associated with significant respiratory morbidity. Historically, the traditional pharmacological treatment has been octreotide. There are several treatments that have been utilized in the past few years including sirolimus; however, data regarding their efficacy and outcomes is limited. Furthermore, sirolimus has proven efficacy in complex vascular malformations, and hence, its utility/efficacy in infantile primary chylous effusions warrants further investigation.

Methods: In this retrospective study at Texas Children's Hospital, data were extracted for all infants with chylothorax who were treated with sirolimus between 2009 and 2020. Details regarding underlying diagnosis, comorbidities, and number of days from sirolimus initiation to resolution of effusion were collected.

Results: Initially a total of 12 infants were identified. Among them, seven patients had complete data and were included in the study. Reasons for chylous effusions include presumed complex lymphatic anomaly, generalized lymphatic anomaly, and complex congenital lymphatic anomaly. The mean duration of sirolimus treatment needed for chest tube removal was 16 days, with a median of 19 days and range of 7–22 days. No patients had progression of effusions while on sirolimus.

Conclusion: With close monitoring, sirolimus appears to be an effective therapy for pediatric lymphatic effusions even in critically ill infants. The study also demonstrates shorter duration of chest tube requirement after initiation of sirolimus compared to previous studies. Larger multi-institutional studies are needed to further support our findings.

KEYWORDS
chest tube, chylous effusions, infants, pleural effusion, sirolimus

Abbreviations: NG, nasogastric; PO, per oral.

1 | INTRODUCTION

Chylothorax is the accumulation of chyle or lymphatic fluid in the pleural space. While rare in children, chylothorax is a significant cause of respiratory morbidity and can lead to depletion of fluids, proteins, immunoglobulins, and lymphocytes, eventually leading to malnutrition and immunodeficiency.[1,2] Chylothorax in newborn period may be primary (due to a disruption in the normal circulation of lymphatic fluid resulting in accumulation in the pleural space) or secondary to infection, malignancy, increased central venous pressure, or trauma. Primary chylous effusions occur in complex lymphatic anomalies (CLAs): rare conditions that appear due to errors in lymphangiogenesis (abnormal structure and connections of the lymphatic tree) or due to increased permeability of lymphatic vessel wall leading to leakage of lymphatic fluid or ineffective peripheral drainage.[3] CLAs include four known clinical entities: Gorham–Stout disease (GSD), kaposiform lymphangiomatosis (KLA), generalized lymphatic anomaly (GLA), and central conducting lymphatic anomaly (CCLA). Common characteristics include bone lytic lesions, micro/macrocystic lymphatic malformations, lymphatic effusions, and progressive clinical course. Due to the progressive nature, not all clinical criteria are present at birth. In some cases, patient has no symptoms until late childhood, whereas in others, nonimmune anasarca of lymphatic origin may be the first presentation at birth. After all secondary potential causes of chylothorax have been excluded, the infant will remain with a diagnosis of primary chylothorax or CLA *not otherwise specified* (not meeting the diagnostic criteria yet for any of the four described entities of CLA) until later in life when definitive imaging can be performed or disease declares itself.

Traditionally, octreotide has been the first-line pharmacologic treatment. However, new alternatives such as sirolimus are now increasingly being utilized. Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor derived from *Streptomyces hygroscopicus*. Because of the role of mTOR in cell proliferation and angiogenesis, an overactive mTOR pathway due to activating mutations of its components has been implicated in diabetes, cancer, neurological diseases, genetic disorders, vascular anomalies, and lymphatic anomalies.[4,5] Sirolimus is considered a strong agent against lymphatic anomalies, given its part in cell growth regulation and in the vascular endothelial growth factor (VEGF) pathway.[1] A recent systematic review of sirolimus as a treatment for lymphatic malformations found that treatment with sirolimus led to a partial remission of disease in 60 of 71 patients studied (three patients had progressive disease and eight patient outcomes were not reported).[6] An analysis of patients with GLA and GSD showed improvement of pleural and pericardial effusions in 72% and 50% of affected patients, but no infants were included in this study.[7] While sirolimus is currently being used in treatment of chylothorax in older children and adults, its use and efficacy need continued studying in critically ill infants to create better treatment guidelines.

2 | OBJECTIVE

The purpose of this study is to describe our center's experience with sirolimus for the treatment of primary congenital chylous effusions in critically ill infants, and determine the duration of treatment needed to resolve chylous effusions.

3 | METHODS

3.1 | Study design

This study was a retrospective chart review of all infants with a diagnosis of chylothorax at Texas Children's Hospital (TCH) who received sirolimus as treatment between January 1, 2009 and December 31, 2020. Institutional review board approval was obtained through the Baylor College of Medicine prior to undertaking this study. Informed consent and authorization were waived as the chart review was completed retrospectively and no direct patient contact was required for study completion.

3.2 | Study population

Data were extracted for all eligible patients. Inclusion criteria included patients less than 1 year of age who received sirolimus treatment primarily for the management of chylous effusion and required chest tube for the management of effusion due to respiratory distress. Patients of both genders and all races/ethnicities were included. Patients were excluded from the study if they did not have a chest tube at the time of treatment initiation with sirolimus, or had incomplete documentation of chest tube output after sirolimus was started.

While chest X-ray maybe useful, the primary method of objectively quantifying the chylous effusion in this case series was by quantifying chest tube output. We elected to use chest tube output only because the improvement in some patients by serial chest radiographs and in others by chest tube output cannot be compared objectively.

3.3 | Chart review protocol

Data were collected from the patients' electronic medical records. Charts were reviewed for demographic information, including age and gender, volume of chest tube output, sirolimus blood level, duration of chest tube placement, other medical and dietary interventions, lymphatic anomaly diagnosis, and comorbidities. Day 0/Hour 0 was the time of first sirolimus dose.

Chylous effusion was diagnosed by pleural fluid analysis findings consistent with lymphocyte content of >80%, pleural fluid triglyceride level >110 mg/dl, and ratio of pleural fluid to serum cholesterol <1.0. The vascular anomalies team was involved in the care of all these

patients. Our institutional guidelines for use of sirolimus are as follows. The starting dose of sirolimus is based on age (0.4 mg/m^2/dose for patients younger than 6 months and 0.8 mg/m^2/dose per oral (PO) or nasogastric (NG)/gastric (G) tube q12h). As per our institutional guidelines, sirolimus trough levels of 8–12 ng/ml are considered therapeutic, although the level needed to treat chylous effusions has not been determined. A trough level is checked after 72 hours to evaluate for toxicity as some newborns can reach the upper level of the range or even toxic troughs very early. In this case, the sirolimus is held and levels checked until they are back in range and the dose adjusted/decreased as needed until reaching goal. If the level is low or within range, it is checked again at 1 week and adjusted at that point. During hospitalization, all patients had sirolimus levels checked at least weekly. Administration was interrupted during proven or suspected infections and restarted immediately afterwards.

3.4 | Data analysis

Mean, median, and range of sirolimus duration of treatment required for chest tube removal were calculated. The rate of chest tube output after initiation of sirolimus treatment was also recorded and plotted.

4 | RESULTS

4.1 | Demographics

The preliminary database consisted of 12 infant charts identified as eligible patients. Of those patients, seven met the inclusion criteria and were included in the final analysis. The remaining patients did not have chest tube output data available post sirolimus initiation and therefore were excluded. Age at diagnosis ranged from 3 days to 8 weeks old. There were five males (71.4%) and two females (28.6%). Patient A had a CCLA. Patient C had a suspected RASopathy syndrome. The other five patients had clinical diagnosis of generalized lymphatic anomalies, but due to their critical state, no lymphangiogram was performed to fully investigate the integrity of the lymphatic central system. The cohort of patients described have a very high morbidity index, were newborns (some premature), and the prognosis was poor from diagnosis. Three patients (2, 3, and 4 weeks old at sirolimus initiation) have since died at 2, 8, and 3.5 months of age, respectively, due to severe comorbidities. Other four patients are alive at the time of writing this manuscript.

Of note, none of the patients described below underwent any surgical, interventional radiology, or cardiac intervention while on sirolimus.

Each patient's clinical course on sirolimus has been briefly detailed (Table 1).

4.2 | Patient A

This patient was a term female infant with trisomy 21, who had a history of transient myeloproliferative disorder (TMD) in the first couple of weeks of life and had atrial septal defect. Shortly after the TMD resolved, she was found to have a chylous pleural and pericardial effusion and CCLA was diagnosed by MR lymphangiogram. Patient was started on low-fat diet (Enfaport formula). Sirolimus was initiated at 3 weeks of age. The initial dose of sirolimus was 1.6 mg/m^2/day via NG tube. This patient had three chest tubes at the beginning of sirolimus therapy. Chest Tube #1 had initial drainage of 102 ml (40 ml/kg/day) noted on day 8, which decreased to 33 ml by day 13 (12.9 ml/kg/day), and further minimized until chest tube removal on day 17. Chest Tube #2 had initial output of 130 ml on day 12 (50.6 ml/kg/day). Drainage was minimal by days 17–20, with eventual removal on day 20. Chest Tube #3 had 8 ml (3.1 ml/kg/day) output on day 17 and tube was removed the next day (Figure 1). Adjustments were made to sirolimus dose based on trough levels. She was discharged home on sirolimus without chest tubes and was clinically stable almost 1 month later. The patient was re-admitted at 8 months of age due to acute respiratory failure secondary to human metapneumovirus pneumonia and passed away. She did not have any chylous effusions at that time.

4.3 | Patient B

This patient was a 6-week-old male baby born at 37 weeks gestational age, diagnosed in utero with prune belly syndrome and urinary tract obstruction s/p placement of vesico-amniotic shunts ×3. At birth, he was found to have bilateral pneumothoraces, pneumomediastinum and pneumopericardium, and bilateral chylous effusions, necessitating bilateral pigtail placement, and concerning for GLA chylous effusions. Additionally, he required hemodialysis three to four times/week. He was started on low-fat diet with Enfaport formula. Due to significant chylous effusion and inability to clamp or remove the chest tubes, the vascular team was involved and treatment with sirolimus was initiated at 6 weeks of age. The initial dose of sirolimus was 0.6 mg/m^2/day PO, comparatively lower due to poor renal function. He had two chest tubes. Chest Tube #1 had initial output of 2 ml (0.6 ml/kg/day) on day 5, 34 ml (11 ml/kg/day) on day 6, and 28 ml (8.75 ml/kg/day) on day 8. Chest Tube #2 had drainage of 14 ml (4.5 ml/kg/day) on day 12, 14 ml (4.5 ml/kg/day) on day 14, and minimal drainage on days 15–19. Chest Tube #1 was removed on day 12 and Chest Tube #2 on day 19 (Figure 1). By day 20, sirolimus levels were therapeutic (longer time than usual due to renal dosing limitations). Sirolimus was continued for 5 more weeks without reaccumulation of pleural effusion or without need to replace chest tubes.

4.4 | Patient C

This patient was a 2-week-old critically ill, 32-week preemie with multiple medical complications including congenital heart block, hydrops, respiratory distress syndrome, chylothorax, and chyloperitoneum. Clinical presentation was concerning for RASopathy syndrome (genetic studies not completed) where chylous effusions may be encountered as a mark of abnormal lymphatic vasculature.

TABLE 1 Summary of patients on sirolimus for chylous effusions

Patient	Age at sirolimus initiation	Clinical history	Underlying vascular diagnosis	Nonpharmacologic intervention	Pharmacologic treatment prior to sirolimus	Sirolimus initial dose and route of administration	Sirolimus-related toxicity	Duration of chest tube with sirolimus (days)	Length of sirolimus therapy after chest tube removal	Outcome
A	3 weeks	Late preterm, trisomy 21, moderate-sized ASD, transient myeloproliferative disorder, initially admitted to the PICU for acute respiratory failure secondary to viral bronchiolitis with superimposed bacterial pneumonia	CCLA	Low-fat diet (Enfaport)	None	1.6 mg/m^2/dayNGT	None	20	4 months	Died at 8 months of age
B	6 weeks	Late preterm with LUTO, prune belly syndrome, pulmonary hypoplasia, pulmonary hypertension s/p nitric oxide, presented with pericardial effusion and bilateral pleural effusions requiring chest tubes	GLA vs. iatrogenic	Low-fat diet (Enfaport)	None	0.6 mg/m^2/dayPO	None	19	5 weeks	Alive at 4 years
C	2 weeks	Critically ill 32-week preemie with bradycardia/heart block, hydrops, respiratory distress syndrome, left pleural effusion, suspected RASopathy syndrome	Suspected RASopathy syndrome, CLA	Low-fat diet (Enfaport)	Octreotide	1 mg/m^2/dayNGT	None	7	7 weeks	Died at 2 months of age
D	4 weeks	Trisomy 21, hydrops, persistent pleural effusions	Suspected CLA	Low-fat diet (Enfaport)	Octreotide	0.8 mg/m^2/dayPO	None	20	8 weeks	Died at 3.5 months of age

(Continues)

TABLE 1 (Continued)

Patient	Age at sirolimus initiation	Clinical history	Underlying vascular diagnosis	Nonpharmacologic intervention	Pharmacologic treatment prior to sirolimus	Sirolimus initial dose and route of administration	Sirolimus-related toxicity	Duration of chest tube with sirolimus (days)	Length of sirolimus therapy after chest tube removal	Outcome
E	1 week	35-Week preemie, left pleural effusion, right hydronephrosis with hydroureter	Congenital pleural effusion, suspected CLA	Low-fat diet (Enfaport)	None	0.8 mg/m^2/dayPO	None	13	5.5 months	Alive at 11 months
F	8 weeks	Former 25-week preemie, history of intestinal perforation s/p ileostomy and resection, ESBL sepsis, severe anasarca post op, with worsening pleural effusion requiring chest tube placement	Suspected CLA	Low-fat diet (Enfaport)	None	0.8 mg/m^2/dayPO	None	14	3.5 months	Alive at 10 months
G	3 days	Former 34-week preemie born with hydrops fetalis causing respiratory failure, bilateral pleural effusion and ascites, pericardial effusion	Suspected CLA	Low-fat diet (Enfaport)	None	0.4 mg/m^2/dayNGT	None	22	2 weeks	Alive at 8 months

Abbreviations: CCLA, complex congenital lymphatic anomaly; CLA, complex lymphatic anomaly; ESBL, extended spectrum beta lactamase; GLA, generalized lymphatic anomaly.

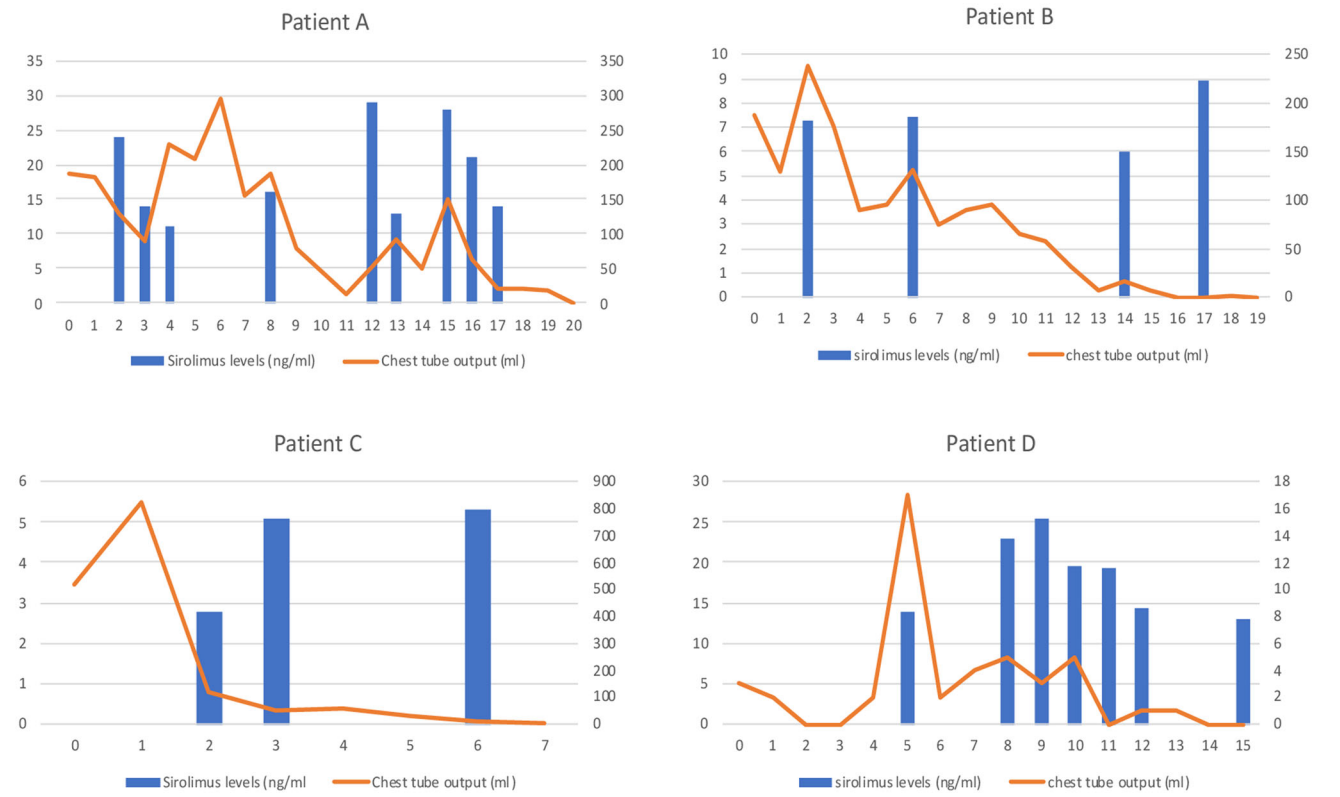

FIGURE 1 Graphs showing sirolimus levels and chest tube drainage in patients A–D

Serum cholesterol was less than 50 mg/dl. He was started initially on octreotide and low-fat diet (Enfaport). After a week's trial of octreotide, vascular team was consulted and patient was switched to sirolimus due to persistent significant chylous effusions. The initial dose of sirolimus was 1 mg/m^2/day via NGT. Patient had extensive chest tube output initially 220 ml (55 ml/kg/day), 860 ml (215 ml/kg/day), and 300 ml (75 ml/kg/day) on days 0, 1, and 2, respectively. Chest tube drainage markedly decreased by day 3 with 39 ml (9.75 ml/kg/day) and was minimal by day 6 at 8 ml (2 ml/kg/day), and the chest tube was removed on day 7. The sirolimus level remained subtherapeutic on day 6; however, by day 9 reached therapeutic levels (Figure 1). The patient passed away at 2 months of age due to deteriorating cardiac function.

4.5 | Patient D

This patient was a 4-week-old infant with trisomy 21, born at 32 weeks at an outside hospital due to hydrops fetalis and bilateral primary chylous pleural effusion; there was concern for CLA. Serum cholesterol was 85 mg/dl. She was initially treated with octreotide at the outside facility but due to significant persistent chylous effusions even after 2 weeks, she was transferred to our center and transitioned to sirolimus at a starting dose of 0.8 mg/m^2/day PO, along with Enfaport for low-fat diet. There was large volume of chest tube output of 550 ml (157 ml/kg/day) on day 0, which gradually decreased to 300 ml (86 ml/kg/day) a week later, less than 100 ml (25 ml/kg/day) by day 15, and ultimately 10 ml (2.3 ml/kg/day) on day 19, and the chest tube was removed on day 20 (Figure 1). Levels were supratherapeutic at the time of chest tube removal at 23 ng/ml, but no sirolimus-related toxicity was noted. The patient was transitioned to comfort care measures only due to respiratory failure, and passed away at 3.5 months of age.

4.6 | Patient E

This patient was born at 35 weeks with a prenatally diagnosed congenital pleural effusion s/p pleural amniotic shunt. She required chest tube placement at birth and sirolimus 0.8 mg/m^2/day PO at 1 week of age due to persistent chylous effusion and inability to remove the chest tube; CLA was suspected. Initially chest output was low ranging from 0 to 3 ml/day (0–1.25 ml/kg/day), increased to maximum of 17 ml (7 ml/kg/day) in a day, and then decreased again to 0–5 ml/day. She was also on Enfaport for low-fat diet. Chest tube was ultimately removed on day 15 (Figure 2). Subsequent sirolimus levels were therapeutic.

4.7 | Patient F

This patient was an 8-week-old ex-25-week preemie who was admitted for *Escherichia coli* sepsis, presumed fungal sepsis, respiratory failure, and grade 4 intraventricular hemorrhage (IVH). She was noted

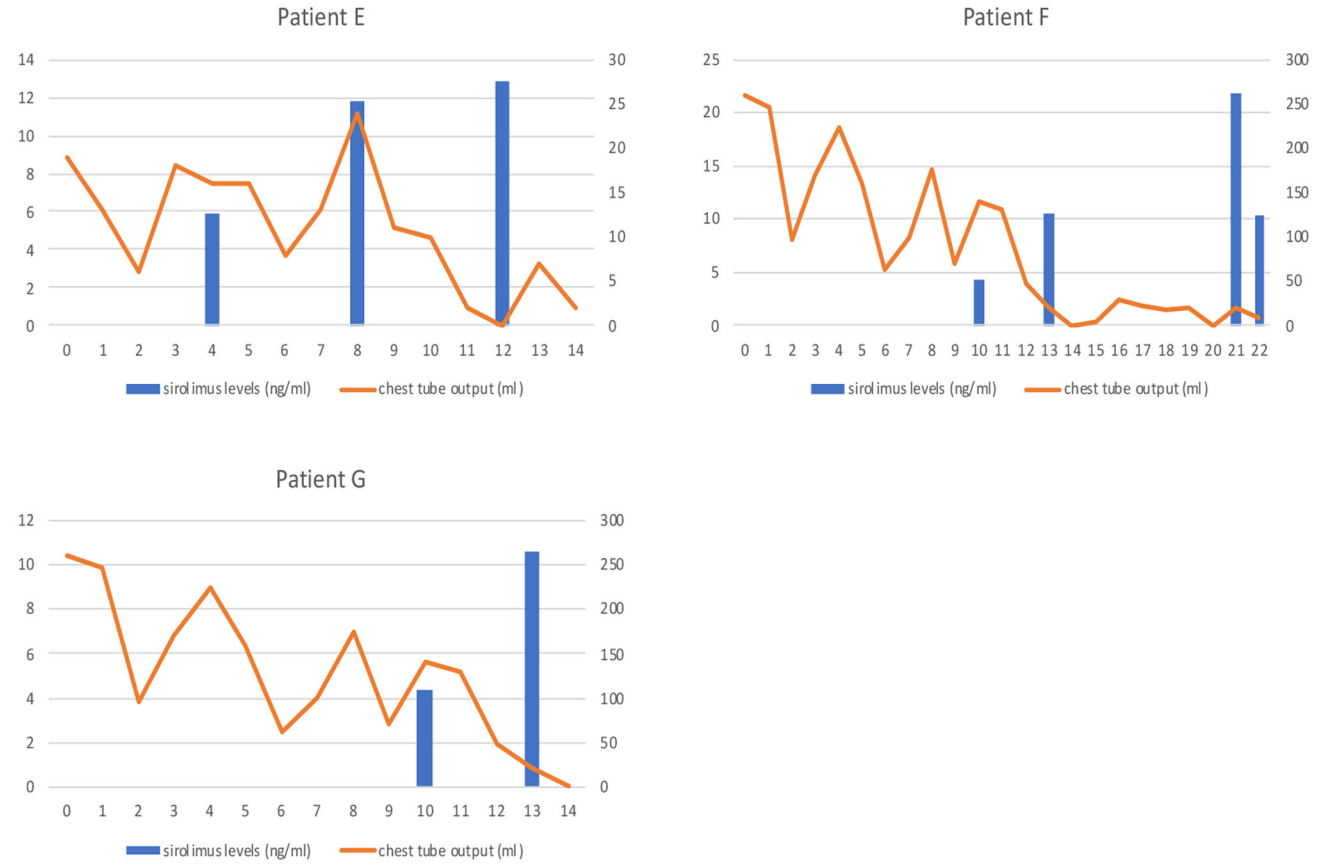

FIGURE 2 Graphs showing sirolimus levels and chest tube drainage in patients E–G

to have diffuse anasarca and bilateral pleural effusions, which were initially attributed to ongoing infections. However, due to persistent anasarca and pleural effusions even after finishing the course of antibiotics and antifungals and repeated failed attempts to clamp the chest tube, vascular team was consulted for concern for CLA. She was started on sirolimus and low-fat diet with Enfaport for CLA. Since initiation of sirolimus at a dose of 0.8 mg/m^2/day PO, chest tube output decreased ranging from 6 to 24 ml/day (3–13 ml/kg/day) and team was able to pull out the chest tube on day 14 (Figure 2). Sirolimus levels were therapeutic when checked on day 16.

4.8 | Patient G

Patient G was born emergently at 35 weeks due to decreased fetal movements and nonimmune fetal hydrops, and found to have bilateral pleural effusions at birth, concerning for CLA and requiring chest tube placements. Serum cholesterol was 95 mg/dl. The vascular team was involved on day 3 of life due to significant ongoing chest tube output concerning for suspected CLA. He was started on sirolimus at a dose of 0.4 mg/m^2/day via NGT along with Enfaport for low-fat diet. He had some interruptions to sirolimus in the beginning due to intermittent discontinuation in the setting of infectious concern - necrotizing enterocolitis (NEC). Hence, initially the chest tube output was high and ranged 60–260 ml/day (25–100 ml/kg/day). However, by day 13 sirolimus trough was therapeutic and chest tube output was noted to come down with eventual removal of chest tube on day 23 (Figure 2). Patient was ultimately taken off sirolimus 2 weeks post chest tube removal due to concern for another infection. He did not develop any subsequent effusions.

4.9 | Chest tube outcomes with sirolimus use

Duration of chest tube after initiation of sirolimus ranged from 7 to 20 days, with a mean of 16 days and median duration of 19 days. There were some interruptions in treatment due to infections, but no other sirolimus-related toxicity. The number of infections was considered similar to patients in NICU of same age and comorbidities and not a side effect of sirolimus. The medication was held during all episodes of proven or suspected infections and/or neutropenia.

5 | DISCUSSION

Our study focuses on pleural lymphatic effusions caused by CLAs. The average duration of sirolimus treatment needed for chest tube removal

was 16 days in our patient cohort. This is shorter than what has been reported in previous studies with other interventions.

The two most common CLAs that present with lymphatic effusions are GLA and CCLA. KLA and GSD, the other two forms of CLA are almost never present during newborn period. GLA is characterized by multifocal lymphatic malformation involving the bones, visceral, thoracic, and abdominal cavities.[3] It may present at birth or later in life, and clinical course is related to the areas affected by the disease. Bone involvement is represented by lytic lesions, predominantly of the appendicular skeleton.[3] CCLA is characterized by defects in thoracic duct and/or cisterna chylae causing leakage of chylous fluid, most commonly resulting in chylothorax or chylous ascites.[3] Differential diagnosis between the two entities is mainly made by imaging including MR lymphangiogram. In our cohort, we did not have definitive diagnosis in a majority of patients as they were critically ill at the time of presentation and not stable to undergo lymphatic imaging. Additionally, bone lesions (commonly seen with GLA) are hardly noticed in neonatal period and usually evolve over time. We continue to follow these patients in the outpatient setting and will perform MR lymphangiogram when appropriate. Of note, none of these patients had micro- or macrocystic malformations noted during newborn period.

Typically, management of large pleural effusions involves placement of a chest tube with quantification guiding therapy. Many hospitals use drainage output as a guide to quantify clinical improvement or failure (<10 ml/kg per day of pleural drainage is considered to be an indication that the chest tube can be discontinued; >10 ml/kg per day of pleural drainage is considered failure after 4 weeks of nonsurgical management).[8,9] Management for chylous effusion further includes dietary modifications to limit chyle-forming elements in the diet. This requires a fat-free diet with medium-chain triglycerides, available as enteral formulas or total enteric rest and parenteral nutrition, which is a more aggressive option.[1] Use of conservative enteral or complete parenteral feeding for 1–3 weeks may result in resolution of the chylothorax when the effusion is not due to a lymphatic anomaly.[9] However, in patients with significant chylothorax and associated respiratory compromise (such as the patients described in our study), especially if the patient is too clinically unstable to completely image the lymphatic vasculature, conservative treatment alone is not adequate. Additionally, chylous effusions can lead to malnutrition and immunodeficiency due to loss of proteins and immunoglobulins in the chylous fluid. Given the associated complications, it is imperative to reduce the amount of pleural effusion promptly to alleviate the resulting respiratory compromise.

Historic data regarding efficacy of octreotide for the pharmacologic treatment for chylothorax are debatable. In a 2017 study of 178 neonates with chylothorax, Church et al. found that the addition of octreotide to dietary management of chylothorax revealed no significant differences in any outcome including success.[10] Likewise, a 2010 Cochrane review of 20 case reports (no randomized controls identified) found no significant benefit of the addition of octreotide to treatment regimens.[11] In our study, there were two patients (28.6%) who failed octreotide treatment prior to sirolimus initiation. The other five patients were started on sirolimus from the beginning due to confirmed or presumed lymphatic etiology.

Our study validates previous studies that showed sirolimus may help in partial remission of lymphatic disease.[4,6] There are several case reports noting the reduction of lymphatic effusions post sirolimus treatment, with an average time of 25 days to chylothorax resolution.[1,7,12–15] Based on our limited study population, medical therapy with sirolimus appears to be an efficient consideration without significant reported side effects even during newborn period in critically ill patients.

As this is a single-center study, it is limited by the small size. While 12 patients were originally considered within the study criteria, inadequate chest tube drainage data and death prior to chest tube removal narrowed the study population to seven. All seven were critically ill infants with a multitude of comorbidities limiting our ability to perform diagnostic imaging at the time of presentation for complete description of the lymphatic vasculature. The clinical course for all these patients varied widely due to their disparities in comorbidities. The incongruency in patients limits the extendibility of the research. Additionally, the study was limited by the variable data points of both sirolimus level and chest tube output. Future studies could be improved by measuring sirolimus at regular intervals post initiation. Though efforts were made to quickly find appropriate dosing of sirolimus, the patients studied were at times subtherapeutic or supratherapeutic. It is difficult to draw conclusions regarding sirolimus levels and the impact on lymphatic drainage given the small numbers. The exact therapeutic levels are not established yet. While we have extrapolated dosage from lymphatic malformations management in general, it is possible that a lower range may also be effective. Tighter control of sirolimus levels would aid in finding the appropriate therapeutic range of sirolimus. Additionally, with more systematic or standardized approach to treatment with sirolimus, more patterns will be identified, and we can then individualize therapy based on findings. To better control the confounding factors of the study, exclusion factors could be added to exclude patients with previous medical interventions (such as octreotide).

In conclusion, our study shows that with close monitoring, sirolimus appears to be an effective therapy for pediatric chylous effusions even in critically ill infants. Due to the rare incidence of the condition, our conclusion is based on a small case series. Larger multi-institutional studies will be needed to further support and confirm these findings.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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