ORIGINAL ARTICLE

Management and outcomes of congenital chylothorax in the neonatal intensive care unit: A case series

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Abstract

Importance: Congenital chylothorax is a rare condition with pulmonary and multiorgan system effects, for which there are no standardized treatment recommendations. Collective review of known cases offers some conclusions and suggestions for treatment.

Objective: The aim of this study was to present a case series of 5 patients who were treated in the neonatal intensive care unit with chylothorax.

Methods: We describe 5 infants who were diagnosed prenatally with hydrops fetalis and postnatally had clinically significant congenital chylothorax.

Results: Treatment guidelines specific to congenital forms of chylothorax have not yet been developed, although there are consistent trends across our cases. Four of the 5 infants in this study have survived to date. Chylothorax was treated with chest tube placement and chylous fluid drainage, scrupulous attention to fluid balance, mechanical ventilation, and nutritional management and, in 3 cases, with octreotide infusions. Some of the infants also required treatment for immunodeficiency and altered coagulation pathways. None of the infants underwent surgical thoracic duct ligation.

Interpretation: Aided by the advantage of prenatal diagnosis, many cases of congenital chylothorax can be successfully treated by a combination of nutritional and medical management as well as careful attention to fluid and electrolyte balance and avoidance of infection, thereby avoiding the need for surgical ligation of the thoracic duct.

KEYWORDS
congenital malformation, evidence-based medicine & outcomes, neonatal pulmonary medicine

1 | INTRODUCTION

Congenital chylothorax (CCT) is a condition in which chylous (lymphocytic predominant) fluid accumulates in the pleural space during fetal development. The affected fetus and neonate often present with non-immune hydrops fetalis, excess fluid accumulation in the extravascular spaces of the developing fetus.[1,2] Persistent chylous pleural effusions may impede lung development in the fetus and ventilation in the neonate, leading to severe respiratory disease. Beyond the pulmonary system, complications of CCT include poor nutrition, electrolyte and fluid imbalance, loss of anticoagulation factors, and immunodeficiency.[2,3] Due to a low incidence rate, randomized controlled studies are lacking. Treatment recommendations exist for infants and children with chylothorax, but these are not specific to congenital cases.

2 | METHODS

We present a case series of 5 neonates diagnosed prenatally with hydrops fetalis and postnatally with congenital chylothorax, born between 2009 and 2015 at our hospital. In all cases, the diagnosis of chylothorax was made based upon cell count analysis of pleural fluid collected on day of life (DOL) 1-2. In all cases, other fluid collections included ascites and/or tissue edema that did not require intervention. The authors were involved in and have focused on postnatal management; however, prenatal interventions were noted below if they occurred. Patients with pertinent genetic results or known syndromes were identified; a genetic condition was not confirmed at the time of data collection unless specified below. This was a retrospective chart review approved by the Institutional Review Board of Partners Healthcare.

3 | RESULTS

3.1 | Case 1

A female infant delivered vaginally after induction at 31 6/7 weeks gestational age (GA) and birth weight (BW) of 2190 g was diagnosed prenatally with bilateral chylothoraces and early hydrops fetalis on a 21-week ultrasound. In utero, thoracentesis was performed twice and pleurodesis was attempted. Delivery was induced due to maternal chorioamnionitis and prolonged rupture of membranes. Pleural effusions persisted postnatally. The patient was intubated in the delivery room for lack of spontaneous respirations. The patient developed respiratory failure, which required the use of high-frequency ventilation on day of life (DOL) 1. Bilateral chest tubes were in place from DOL 1 to DOL 8. The patient's course was complicated by pulmonary hypertension (PH), diagnosed by elevated right ventricular pressure (RVP) on echocardiogram on DOL 2, and a patent ductus arteriosus (PDA). Dopamine was initiated for hypotension, and inhaled nitric oxide was used to treat PH from DOL 3 through 6. The PDA closed spontaneously during the first 6 days of life. PH improved, although still present, on echocardiogram on DOL 6 when inhaled nitric oxide was discontinued. Reduced long-chain fatty acid (LCFA) formula was started on DOL 8. She was transitioned to breast milk and tolerated full-volume feeds by DOL 25 without re-accumulation of chylous pleural fluid. She was discharged on DOL 60 and had no readmissions through 1 year of age. At the time of data collection, the patient was 6 years old and was followed and treated for reactive airway disease (RAD).

3.2 | Case 2

A male infant delivered by emergency cesarean section at 30 1/7 weeks GA and BW of 2320 g was diagnosed prenatally with fetal hydrops and left-sided pulmonary sequestration at 18 weeks of gestation. Prior to delivery, prenatal pleurocentesis was performed on 4 separate occasions. A cesarean section was planned for the day of delivery following additional pleurocentesis; however, this was converted to emergent cesarean following fetal cardiac decelerations.

Neonatal resuscitation included intubation, chest compressions, line placement, fluid boluses, epinephrine, and placement of a pleural angiocatheter. Following transfer to the neonatal intensive care unit (NICU), bilateral pigtail catheters were placed and 35-160 mL of fluid/chest tube/day (15-69 mL/kg/tube/d) was drained. Fifty percentage of the volume lost by chest tubes was replaced using 5% albumin or blood products. He was not fed orally but did receive total parental nutrition (TPN). The infant died on DOL 3 after a pulmonary hypertensive crisis that did not respond to treatment with 100% oxygen, high-frequency ventilation, and inhaled nitric oxide. Placental pathology showed acute villous edema and intravillous hemorrhage, possibly due to vascular obstruction, but no clear etiology was identified.

3.3 | Case 3

A male infant delivered at 28 3/7 weeks GA and BW of 1350 g by urgent cesarean section because of progressive fetal hydrops, diagnosed at 27 weeks via ultrasound with bilateral pleural effusions and growing concern for fetal well-being. He required resuscitation including airway intubation and chest compressions. Bilateral thoracenteses were performed on DOL 2 and thoracenteses were repeated several times thereafter for re-accumulations of chylous fluid. A right-sided pigtail catheter was placed for a relatively short time from DOL 9-10, during which time chylous fluid drained at 40-100 mL/d (30-74 mL/kg/d), which was replaced with equal amounts of 5% albumin. He received TPN for the first 14 days of life, and then, oral feeds of long-chain fatty acid (LCFA)-free formula were commenced and advanced. He temporarily tolerated feeds of breast milk from DOL 34-52 but ultimately had to return to formula due to recurrence of chylothorax. On DOL 69, after having been extubated for nearly 2 months, the infant had a cardiopulmonary arrest and received 2 minutes of chest compressions. The patient was intubated and mechanical ventilation initiated. Inhaled nitric oxide was used for 4 days to treat suspected PH based upon challenges with oxygenation although this was not observed on echocardiogram at that time. A chest X-ray following the event showed stable bilateral pleural effusions, which were later drained via thoracenteses. He was treated with octreotide on DOL 69; however, he developed hematuria on day one of treatment and it was discontinued. Octreotide was restarted on DOL 93 because of persistent chylothoraces and then maintained at 4 μg/kg/h until DOL 116. Complications of chylous fluid loss included coagulopathy that was treated with blood product transfusions in the first 3 days of life and immunosuppression demonstrated by low levels of serum IgG, IgA, and IgM, but not to a degree necessitating intravenous immunoglobulin (IVIG) transfusions. The infant was discharged on DOL 144 with home oxygen. He had no readmissions through 1 year of age. He was 2 years old at the time of data collection and continues to be treated for RAD and chronic lung disease (CLD).

3.4 | Case 4

A male infant delivered by repeat cesarean section at 33 5/7 weeks GA and BW of 3200 g was diagnosed on a 19-week ultrasound with

chylothorax, ascites, and a muscular ventricular septal defect (VSD), and had a prenatal genetic diagnosis of a 16p gene deletion. Resuscitation after delivery included intubation, chest compressions, line placement, administration of epinephrine and fluid boluses, and bilateral pleural fluid drainage via angiocatheters. Bilateral chest tubes were placed on DOL 1 and remained in place until DOL 38 (right side) and 39 (left side). Maximum noted chest tube output was nearly 500 mL of chylous fluid per day. Volume loss from chest tubes was replaced at a 1:1 ratio with 5% albumin. TPN alone was used for nutritional support until DOL 15, when enteral nutrition with LCFA-free formula was begun. Treatment using octreotide was started on DOL 6 at a dose of 1 μg/kg/h and titrated to maximum dosing of 10 μg/kg/h on DOL 13. The dose of octreotide was weaned and discontinued on DOL 34, 4 days prior to removal of the right-sided chest tube. He was extubated on DOL 40. Full enteral nutrition was reached prior to discontinuation of octreotide or removal of chest tubes. The albumin replacement ratio was titrated and stopped as output decreased. An echocardiogram on DOL 1 demonstrated PH based upon elevated RVP; however, he did not require inhaled nitric oxide and later echocardiogram demonstrated normal RVP. The patient had additional complications of chylothorax including hypercoagulability leading to a right atrial thrombosis requiring anticoagulation. It was hypothesized that this was secondary to loss of anticoagulopathic proteins C and S and antithrombin in chylous fluid. Evaluation of coagulopathy was otherwise unrevealing. He also developed hypogammaglobulinemia with IgG levels measured at a nadir of 34.7% of the laboratory's lower threshold of normal. He was treated with IVIG infusions on 4 occasions from DOL 12-30. Initially, when chest tubes were in place, cefazolin was used as prophylactic antibiotic coverage. Once hypogammaglobulinemia was diagnosed, ampicillin alone was used for prophylaxis until DOL 29 when prophylactic dosing of trimethoprim-sulfamethoxazole was started, which continued after discharge. He was transferred to a level II NICU on DOL 69 without need for oxygen, receiving diuretics and a steroid taper. He was discharged at 4 months of age. The patient remained on LCFA-free formula after discharge. Final results of postnatal microarray revealed a 16p13.11 microdeletion syndrome concerning for Noonan syndrome. However, available records do not indicate that this diagnosis has yet been definitively made. He was 8 months of age at the time of data collection and not had any readmissions.

3.5 | Case 5

A female infant delivered by planned cesarean section at 33 5/7 weeks GA and BW of 2860 g was diagnosed with hydrops fetalis 3 days prior on prenatal ultrasound. After delivery, her resuscitation included endotracheal intubation and chest compressions. After transport to the NICU, a right-sided pigtail catheter was placed, yielding drainage of chylous fluid with resultant improvement in respiratory status. She received TPN until DOL 3, when she started slowly advancing feeds of LCFA-free formula. Chylous fluid continued to accumulate in the pleural space with a pigtail catheter output

of 700-1000 mL/d (244-350 mL/kg/d) between DOL 5 and DOL 9. Fluid losses from the pleural space were replaced at a 1:1 ratio with 5% albumin. The pigtail catheter had to be replaced with standard chest tubes multiple times due to repeated clogging of tubing and inadequate drainage leading to respiratory distress. Octreotide was initiated on DOL 9, at 4 μg/kg/h, and increased to reach 10 μg/kg/hron DOL 21. Chest tube drainage declined until the chest tube could be removed on DOL 33; octreotide was discontinued that same day. The albumin replacement ratio was titrated and stopped as output decreased. Additional complications of chylothorax affecting this patient included coagulopathy, as evidenced by elevated coagulation factors. The coagulopathy was treated with transfusions of fresh-frozen plasma. She developed immune dysfunction with persistently low IgG levels. The patient received one infusion of IVIG. She received cefazolin for prophylaxis while the chest tube was in place and a one-time dose of pentamidine as prophylaxis against pneumocystis pneumonia. The patient was discharged on DOL 53 after successfully transitioning to breast milk. She was too young at the time of data collection for readmission data to be available.

3.6 | Analysis of the 5 cases

We present a case series of 5 neonates born between 2009 and 2015 and diagnosed with congenital chylothorax. All had prenatal diagnosis of hydrops fetalis (Table 1). One infant died at 3 days of life, and the remaining 4 infants were alive at the time of this report. Gestational age ranged from 28 3/7 to 33 5/7 weeks. All of the infants had unilateral or bilateral chest tubes placed. Analysis of pleural fluid confirmed the diagnosis of chylothorax in each case. Percentage of lymphocytes in fluid samples obtained DOL 1-DOL 2 ranged from 78% to 98% with a mean of 88.6% (95% CI 79.0-98.2). Of the 4 surviving infants, 3 received treatment with octreotide for chylous pleural effusions; all 4 had enteral feeding initiated with formulas free of long-chain fatty acids. We did not find significant side effects of octreotide. Two infants were successfully transitioned to breast milk before discharge. Additional commonalities among congenital chylothorax patients included loss of immunoglobulins necessitating IVIG transfusion and varied effects on coagulation. The length of hospital stay of the 4 surviving infants ranged from 53 to 144 days (mean of 95 days).

4 | DISCUSSION

Although diagnostic and treatment algorithms for children and infants with chylothorax exist, management recommendations for infants specifically with CCT have not yet been developed. Two of the largest accounts of CCT, retrospective studies—of 28 cases in Germany and of 29 infants in Taiwan—also concluded that there is no consensus on optimal treatment.[4,5] Infants with CCT affecting in utero development require a unique approach to those who develop chylothorax secondary to cardiac surgery or other postnatal illness, in part due to compromised fetal lung development. Care of infants

TABLE 1 Demographic, treatment, and outcome data of infants with CCT

	n	%
N = 5		
Male sex	3	60
Prenatal intervention	2	40
Chest tube placement	5	100
Mortality	1	20
Known or suspected underlying genetic anomaly	1	20
Mode of delivery		
Vaginal delivery	1	25
Planned cesarean	2	50
Urgent/emergent cesarean	2	50
Delivery room intervention		
Intubation	5	100
Chest compressions	4	80
Fluid bolus	4	80
Epinephrine	2	40
Pleural fluid drainage	2	40
Of infants surviving beyond 3 days		
N = 4		
Infusion of IVIG	2	50
Coagulopathy	2	50
Hypercoagulability	1	25
Pulmonary hypertension	3	75
	Mean (range)	**SD**
Gestational age at diagnosis (wk)	23 4/7 (18-33)	6.3 d
Gestational age at birth (wk)	31 4/7 (28 3/7-33 5/7)	16 d
Birth weight (g)	2384 (1350-3200)	707.7
Length of hospital stay[a] (d)	94.25 (53-144)	44.8

Data above are presented in units conventionally used for each variable.
[a]For infants surviving to discharge.

with CCT will ideally begin with prenatal diagnosis. Delivery should occur in a tertiary care facility with NICU and pediatric surgical services available. Delivery attendants should be prepared to perform endotracheal intubation, chest compressions, line placement, administer fluid boluses, and epinephrine and to drain pleural fluid in the delivery room.

Three of the 5 infants had PH requiring treatment with inhaled nitric oxide. Notably, PH has also been noted as a side effect of octreotide in this population, but octreotide use did not precede PH in any of the infants in this case series.[6] To the authors' knowledge, PH is not often described with chylothoraces. Although pulmonary hypertension can result due to a multitude of factors including prematurity and hypoxia, we hypothesize those infants specifically affected by hydrops fetalis and large CCT are at risk for PH by similar mechanisms to those in congenital diaphragmatic hernia (CDH),

which are also not well understood. In CDH, the hypoplastic lung has a small vascular bed and thickened pulmonary arterial walls. It is not clear whether the vascular abnormalities are the etiology or the result of the hypoplastic lung. Although the role of mass effect alone in CDH is also not known, it is, however, interesting to consider how the development of fetal lungs affected by CCT may display similarities.

None of the infants in this case series underwent thoracic duct ligation. Bialkowski et al, similarly, found that of the 28 cases they reviewed, none underwent surgical ligation; Lee et al found that only one in a series of 29 infants had a ligation.[4,5] In combination with our review, this suggests that nutritional therapy and use of octreotide are most often successful and ligation is therefore infrequently needed. As demonstrated by case 5 mentioned above, medical and nutritional management should be considered even in the setting of very high chyle volume production, in that case over 300 mL/kg/d. This is a notable variation in management from available treatment algorithms for the broad population of children and infants with chylothorax (not specific to CCT), which suggest proceeding to ligation before medical management if the chyle volume is over 100 mL per year of life or over 10 mL/kg after 4 weeks of treatment and also suggest proceeding to surgery if chylothorax persists after 2-4 weeks of medical management. As a somatostatin analog, octreotide inhibits release of growth hormones, glucagon and insulin. Therefore, infants receiving octreotide must be closely monitored for alterations in blood glucose. Octreotide also causes vasoconstriction of splanchnic vessels and so there is a logical concern about the risk of necrotizing enterocolitis (NEC), which premature neonates are already at risk for. Fortunately, the incidence of NEC among neonates receiving octreotide has not been found to be different from that of the general neonatal population.[7] Of the 4 surviving infants in this series, 3 received octreotide; in 2 cases, the dose was gradually increased to a continuous infusion of 10 μg/kg/h without significant side effects noted. Length of medical treatment with octreotide ranged 3-5 weeks. This difference in practice between infants with CCT and the broader pediatric population with chylothorax may be because CCT patients are often born prematurely (in this series at GA 28 3/7-33 5/7 weeks) and the desire to avoid surgery due to their small size and a difficult-to-visualize thoracic duct.[8] Also unique to this population, most have undergone resuscitation after delivery and associated diagnoses are often yet to be made. A surgical case series has documented that 6 of 14 infants with CCT underwent thoracoscopic parietal pleural clipping, which was performed because visualization of the thoracic duct was not possible. Of the other 8 infants, 4 died and 4 had CCT resolved with medical management. In that series, 5 of 9 infants who received octreotide later underwent surgery. Of note, the authors of this series cite leukopenia and infection risk as a significant cause of morbidity and mortality in this population but do not report on immunoglobulin levels or prophylactic measures.[8] In our case series, we found that by monitoring of immunoglobulin levels and treatment with both IVIG and prophylactic antibiotics, we were able to mitigate this risk while allowing for a longer period of medical management.

A final unique observation of this case series is that 2 infants developed coagulopathy and another developed a hypercoagulable state. Each of these conditions has been attributed to chylous fluid loss. Hypercoagulability and thrombosis have been documented in prior studies of chylothorax, congenital, or otherwise. This has largely been attributed to the loss of antithrombin in chylous fluid.[3,4] The authors, however, have not found prior accounts of coagulopathy as developed in 2 of our patients. We propose that in these 2 patients, protein deficiency interfered with coagulation factor and fibrinogen synthesis. However, this study was not designed, and we do not have enough data, to suggest why some CCT patients develop hypercoagulability and some coagulopathy.

The small number of patients limits our study, and because it is a retrospective case series, patients were not randomized for types of management and results are subject to bias. Information was obtained by chart review and subject to error. It is, however, unlikely that a randomized controlled trial for the treatment of CCT will be possible, and our results add to other reports of CCT management with growing evidence in support of nutritional and medical management with careful attention to supportive care and management of sequelae of CCT.

In summary, congenital chylothorax is a rare condition for which there are no standardized treatment recommendations. However, the collective body of retrospective case series is growing, offering the potential to develop treatment guidelines. Review of prior cases and those at our own institution have led the authors to the following conclusions as well as the suggestions for treatment described above. Fluid, protein, and electrolyte losses in CCT can be quite extreme. Total body fluid balance must be carefully managed, and our patients responded well to replacing chylous fluid losses with colloid infusions. As a result of chylous fluid loss, CCT patients are at risk for immunodeficiency due to lymphopenia and immunoglobulin loss, putting them at high risk for infection. It is therefore prudent to serially measure serum immune cell levels and immunoglobulin levels and treat with IVIG if indicated. Prophylactic antibiotics, particularly if a chest tube is in place, are also warranted for patients with immunosuppression. Nutritional management remains critical, and these patients can transition to breast milk after resolution of CCT; therefore, mothers who desire to breastfeed should be sup-

ported in collecting and saving breast milk. Octreotide can be safely used in neonates with CCT. We found success by gradually increasing the dose to a maximum continuous infusion rate of 10 μg/kg/h and then weaning the dose prior to discontinuation. Our study demonstrates that octreotide is an important therapeutic approach in CCT even in the setting of chyle volume outputs greater than prior proposed thresholds for surgery.

CONFLICT OF INTEREST

None of the authors of this article have any conflicts of interest to disclose.

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