Original Article

Treatment and outcomes of chylothorax in children: 20-year experience of a single institute

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Background: Chylothorax is an uncommon cause of pleural effusion in children. This study aimed to determine the characteristics, treatment strategies, and outcomes of chylothorax in children from a single institute.

Methods: The 65 episodes of chylothorax in patients aged 0–15 years who were diagnosed and received treatment in Songklanagarind Hospital between January 2001 and December 2020 were retrospectively review and analyzed.

Results: Of the 65 episodes, 80% were postoperative chylothorax, and were mostly related to cardiac surgery. The most common treatment strategy employed was dietary modification (64.6%). Octreotide was used as adjunctive therapy in 33.8%. Most cases of chylothorax were successfully treated by conservative treatment, while 10.7% required surgical therapy. The median time to resolution of chylothorax was 21 days [interquartile range (IQR): 8–33 days]. Young children aged <1 year were more likely to require mechanical ventilation and develop ventilator-associated pneumonia and catheter-related complications. The factors associated with death or prolonged hospitalization (>28 days) were non-postoperative chylothorax, use of total parental nutrition (TPN) >14 days, hypoalbuminemia, and ventilator-associated pneumonia.

Conclusions: Most (89.2%) cases of chylothorax were successfully treated conservatively using dietary modification and octreotide therapy. The modifiable risk factors for death or prolonged hospitalization were use of TPN >14 days and hypoalbuminemia.

Keywords: Chylothorax; dietary modification; octreotide therapy; pediatrics; pleural effusion

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Introduction

Chylothorax is characterized by the accumulation of chyle in the pleural space mostly due to damage or blockage of the thoracic duct (1). Other uncommon causes of chylothorax are abnormal pulmonary lymphatic flow/malformation or translocation of chylous ascites following the major abdominal or retroperitoneal surgery. In the pediatric population, chylothorax is considered an uncommon cause of pleural effusion and is still difficult to manage (2). Since chyle represents the lymph from the gastrointestinal system, the principal treatment of chylothorax is eliminating long-chain triglycerides from the diet to decrease the flow of chyle and allow spontaneous healing of the lymphatic

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leakage. In the pediatric population, dietary modification is the mainstay of the initial treatment of chylothorax from various etiologies. There are many nutritional options and protocols such as total parental nutrition (TPN) or specialized enteral feeding, e.g., fat-free (FF) or medium-chain triglyceride (MCT)-based diet, or low-fat (LF) diet. However, the nutrition of neonates and young infants is dependent on milk products, either breastmilk or infant formula, which are rich in long-chain triglycerides. Hence, dietary modification in this age group is very challenging. Other non-operative management options successfully used in the pediatric population include somatostatin analogs (1-3), glucocorticoids (4), and medical pleurodesis (1,2). Surgical intervention is reserved for specific cases of refractory and prolonged drainage of chyle that are resistant to conservative treatment.

Since there are various treatment options to manage chylothorax, variation among these methods may affect outcomes and complications. Lengthy hospitalization of pediatric patients with chylothorax is associated with mortality rates ranging from 3–12% (5,6). However, few studies have reported the complications from chylothorax itself and those associated with the assigned therapies. This study therefore aims to describe the etiologies, treatment strategies as well as outcomes and complications of patients with chylothorax in a single institute over two decades. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-474/rc).

Methods

We retrospectively reviewed patient medical records (both paper-based and electronic) of all patients aged under 15 years who were diagnosed and treated for chylothorax between January 2001 and December 2020 across all pediatrics service lines in Songklanagarind Hospital in southern Thailand. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Songklanagarind Hospital (No. REC-64-027-1-1) prior to the initiation of the study and informed consent was obtained from all the patients. A diagnosis of chylothorax was made based on one of the following observations: pleural triglyceride level >110 mg/dL, postoperative milky pleural drainage, especially after enteral feeding, or exudative pleural effusion with lymphocytic predominance (>80%) without evidence of respiratory infection or malignancy.

Data collection

The etiology of chylothorax was divided into the following four groups: "postoperative chylothorax"—developing within 30 days of thoracic surgery; "congenital chylothorax"—presenting within 48 hours after birth; "malignant-related chylothorax"—associated with malignancy conditions; and "spontaneous chylothorax"—conditions met none of the other groups. In our hospital, all patients diagnosed with chylothorax had a chest tube or intercostal drainage (ICD) for monitoring whether the condition was ongoing or resolving. Removal of the chest tube drain was considered the resolution point of chylothorax. The time to resolution of chylothorax was defined as the time between diagnosis of chylothorax and the resolution point. Dietary modification after the resolution point was not counted as chylothorax treatment.

At our institute, the following three modalities were used for chylothorax treatment: (I) dietary modification: fasting with TPN, FF, LF, or MCT-enriched diet. These were usually prescribed in stepwise manner, beginning with the most intense restriction on enteral fats either via fasting with TPN or FF diet. Gradually, long-chain triglycerides (MCT-enriched or LF diet) were started; (II) octreotide: a synthetic somatostatin analog as adjunctive therapy to dietary modification. Octreotide was administered as a continuous intravenous infusion, with a starting dose of 0.2–2.0 μg/kg/min and gradual titration to a maximum dose of 20 μg/kg/min; and (III) surgical correction: thoracic duct ligation, with or without pleurodesis. There was no standard protocol for dietary modification or criteria for initiation of adjunctive therapy, and the treatment decisions depended on the attending physicians. The failure of conservative treatment was defined as cases wherein surgical corrections were required after dietary modifications or octreotide administration.

The data from mortality and morbidity occurring during treatment for chylothorax were collected. The following morbidities occurring after diagnosis of chylothorax were included for analysis: sepsis, hypoalbuminemia (serum albumin <3.5 g/dL), ventilator-associated pneumonia (pneumonia diagnosed in intubated-patients with prolonged ventilator use >48 h or patients within 48 h after extubation), hospital-acquired pneumonia (pneumonia diagnosed after >48 h hospitalization), ICD-related complications (consists of pneumothorax, pleural infection, chest tube wound infection), TPN-related metabolic disturbances (significant electrolyte abnormalities which

Table 1 Etiology of chylothorax in each age group

Etiology	Age group, n (%)			Total (N=65)
	<1 month (N=18)	1–12 months (N=18)	>12 months (N=29)	
Congenital	6 (33.3)	0 (0.0)	0 (0.0)	6 (9.2)
Malignant-related	1 (5.6)	0 (0.0)	4 (13.8)	5 (7.7)
Spontaneous	0 (0.0)	1 (5.6)	1 (3.4)	2 (3.1)
Postoperative	11 (61.1)	17 (94.5)	24 (82.7)	52 (80.0)
Systemic to pulmonary artery shunt	6 (33.3)	6 (33.3)	6 (20.7)	18 (27.7)
Isolated PDA repair or ligation	3 (16.7)	7 (38.9)	1 (3.4)	11 (16.9)
TOF correction	0 (0.0)	0 (0.0)	7 (24.1)	7 (10.8)
ASD/VSD repair	0 (0.0)	1 (5.6)	4 (13.8)	5 (7.8)
Bidirectional cavopulmonary shunt	0 (0.0)	0 (0.0)	2 (6.9)	2 (3.1)
Pulmonary artery banding	0 (0.0)	2 (11.1)	0 (0.0)	2 (3.1)
Fontan operation	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.5)
TAPVR repair	1 (5.6)	0 (0.0)	0 (0.0)	1 (1.5)
Arterial switch operation	1 (5.6)	0 (0.0)	0 (0.0)	1 (1.5)
Non-cardiac surgery	0 (0.0)	1 (5.6)	3 (10.3)	4 (6.1)

PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; ASD, atrial septal defect; VSD, ventricular septal defect; TAPVR, total anomalous pulmonary venous connection.

required medical intervention during TPN administration), TPN-related liver diseases (elevation of liver enzyme and/or alkaline phosphatase 1.5–3 times the upper limit of normal values within 1–3 weeks of initiation of TPN), catheter-related complications (consists of catheter-related blood stream infection, catheter exit site infection, displacement and significant leakage or malfunction of catheter, which required removal/replacement). The length of hospitalization was defined as the total duration of each patient's stay in the hospital after chylothorax was diagnosed. In-hospital death and prolonged hospitalization (>28 days) were defined as unfavorable treatment outcomes.

Statistical analysis

Data were analyzed using R program (open source) with R studio. Descriptive data are presented as a percentile, mean [standard deviation (SD)], and median [interquartile range; (IQR)]. Categorical data were analyzed by chi-squared or Fisher's exact test, as appropriate. An independent t-test was used for continuous data with a normal distribution and the Wilcoxon rank sum test was used for skewed data. A two-sided P value <0.05 was considered statistically significant. For the exploratory analysis, multivariable logistic regression with significant factors for unfavorable treatment outcome (P<0.05) in univariate was used. The collinearity was assessed, and the model was sequentially reduced by eliminating non-significant predictors, yielding the final reduced model. The results are reported as adjusted odds ratios (aOR) with their 95% confidence intervals (CI).

Results

Overall, 65 episodes of with chylothorax were diagnosed among 63 patients (two patients with Down syndrome each underwent two cardiac surgeries) Forty-two patients (64.6%) were male. The median (IQR) age and body weights were 7.2 (0.9–37.0) months and 6.1 (3.0–12.4) kg, respectively. Seven episodes (10.8%) of chylothorax occurred bilaterally.

Eighty percent of the cases developed postoperatively. Of 52 postoperative episodes, 48 (92.3%) occurred after surgical repair of congenital heart disease. The three most common operations were systemic to pulmonary artery shunt (27.7%), isolated patent ductus arteriosus repair (16.9%), and total correction of tetralogy of Fallot (10.8%) (*Table 1*). On average, postoperative chylothorax was

Table 2 Treatment strategies and time to resolution of chylothorax

Treatment strategies	Total, N=65 (%)	Age ≤1 y, N=36 (%)	Age >1 y, N=29 (%)	Time to resolution (d), median [IQR]	Hospitalization (d), median [IQR]
Fasting + total parenteral nutrition	9 (13.8)	9 (25.0)	0 (0.0)	14 [14–15]	21 [15–43]
Dietary modification (diet)	33 (50.8)	14 (38.9)	19 (65.5)	19 [10–29]	25 [13–43]
Diet + octreotide	16 (24.6)	12 (33.3)	4 (13.8)	25 [21.2–48.5]	30 [25–54.2]
Diet + octreotide + surgery	6 (9.2)	1 (2.8)	5 (17.2)	37 [21–69]	39 [25–73]
Diet + surgery	1 (1.5)	0 (0.0)	1 (3.4)	19 [–]	20 [–]

IQR, interquartile range.

diagnosed 8 days (±5.9 days) postoperatively. Congenital chylothorax was diagnosed in six patients, while four cases (66.7%) were associated with hydrops fetalis. The other remaining seven cases of chylothorax were malignant-related and spontaneous.

The typical milky appearance of pleural fluid was found in 44.6% cases, which was equal to the number of cases with a hazy or cloudy appearance. Others were bloody (6.2%) or had a clear effusion (4.6%). Forty out of 65 episodes (61.5%) had a pleural triglyceride level >110 mg/dL, whereas others were diagnosed with lymphocytic exudative pleural profile lacking evidence of respiratory infection.

Treatment of chylothorax

All episodes of chylothorax were drained by a chest tube (either use of a newly inserted tube or continued use of the pre-existing chest tube especially in postoperative cases). The median volume of chyle leakage in the first 24 hours was 8.3 (IQR 4.0–14.4) mL/kg/day. The treatment strategies and time to resolution of chylothorax are presented in *Table 2*. The most common strategy to treat chylothorax was dietary modification (50.8%), which combined various types of nutritional therapy in a stepwise manner such as fasting with TPN, FF diet, MCT-rich diet, and LF diet. Nine neonates received fasting with TPN treatment until chylothorax resolved. Overall TPN prescription rate was 87.7% of all episodes, with median duration of TPN use of 14 (IQR 9–25) days. The time to resolution of chylothorax and hospitalization increased when multiple modalities of chylothorax treatment were used (*Table 2*).

Octreotide was prescribed as adjunctive therapy to dietary modification in 22 episodes (33.8%) of chylothorax. Octreotide was started a median of 8 (IQR 2–13.5) days after chylothorax was diagnosed. Cessation of chyle leak occurred in 16/22 episodes (72.8%) of octreotide treatment. The median duration of octreotide use was 9.5 (IQR 7–16) days. When starting octreotide treatment, the patients for whom treatment was successful had a significantly lower amount of chyle than the group in which treatment failed (13.6±9.2 *vs.* 26.1±10.1 mL/kg, P=0.015).

According to the secular trend of chylothorax treatment over two decades, there was no significant difference in modalities and time to resolution of chylothorax; however, there was significantly greater use of octreotide in the later decade [2011–2020] compared to that in the former decade [2001–2010] (88.9% *vs.* 24.0%, P=0.036). However, there was no difference in the success rate of octreotide treatment between the two decades.

Failure of conservative therapy, either dietary or octreotide, required surgical correction in seven episodes of chylothorax. The median duration between diagnosis and a surgical correction was 21 (IQR 10–33) days. All operations were able to resolve chyle leakage with a median time of 11 (IQR 8–30) days after surgery. None of the patients had postoperative complications.

Outcomes and complications

The median time to resolution of chylothorax was 21 (IQR 14–30) days, and the median length of hospitalization was 27 (IQR 18–47) days. There were eight in-hospital deaths (12.3%) in which two patients died before chylothorax resolved, one death was due to severe sepsis, and the other due to multiple congenital anomalies. The other six patients did not survive despite complete resolution of chylothorax; four had sepsis, one had hypoxic arrest, and one had congenital heart defect with cardiogenic shock. The time to resolution of chylothorax, hospitalization, and in-hospital death rate were not significantly different between age groups (*Table 3*). The rate of mechanical ventilation requirement, ventilator-associated pneumonia,

Table 3 Outcomes and complications in each age group

Outcomes and complications	Age ≤1 y, N=36	Age >1 y, N=29	P value
Time to chylothorax resolution (days), median [IQR]	21 [14–31]	21 [11–27]	0.517
Length of hospital stay (days), median [IQR]	34 [21–53]	23 [16–38]	0.060
Death (in-hospital death), n (%)	7 (19.4)	1 (3.4)	0.066
Mechanical ventilation required, n (%)	17 (47.2)	4 (13.8)	0.009
Complications during treatment, n (%)			
Sepsis	15 (42.9)	7 (24.1)	0.192
Hypoalbuminemia	27 (75.0)	19 (65.5)	0.575
Ventilator-associated pneumonia	14 (38.9)	2 (6.9)	0.007
Hospital-acquired pneumonia	5 (13.9)	4 (13.8)	1.000
ICD-related complication	17 (47.2)	12 (41.4)	0.826
Catheter-related complication	19 (52.8)	6 (20.7)	0.017
TPN-related metabolic disturbance	31 (86.1)	20 (69.0)	0.171
TPN-related liver disease	4 (11.1)	2 (6.9)	0.684

IQR, interquartile range; ICD, intercostal drainage; TPN, total parenteral nutrition.

Table 4 Factors associated in-hospital death or prolonged hospitalization (>28 days)

Variables	Univariate			Multivariate		
	Crude OR	95% CI	P value	Adjust OR	95% CI	P value
Age ≤1 year	3.8	1.3–10.7	0.009	–	–	–
Non-postoperative chylothorax	6.9	1.4–34.5	0.006	4.4	0.6–32.5	0.127
Total TPN used >14 days	12.4	3.5–43.8	<0.001	11.9	2.3–59.9	<0.001
Mechanical ventilator required	6.7	1.9–23.5	0.001	–	–	–
Sepsis	5.5	1.7–17.9	0.002	–	–	–
Hypoalbuminemia	11.0	2.8–43.7	<0.001	13.0	1.9–89.8	0.009
Ventilator-associated pneumonia	23.7	2.9–194.2	<0.001	41.2	3.1–542.4	<0.001
ICD-related complication	12.5	3.7–41.8	<0.001	–	–	–

OR, odds ratio; CI, confidence interval; TPN, total parenteral nutrition; ICD, intercostal drainage.

and catheter-related complication were significantly higher in the younger group aged <1 year.

Unfavorable treatment outcomes were observed in 34 episodes of chylothorax (52.3%). *Table 4* shows the multivariate regression analysis conducted to predict the unfavorable treatment outcome. The independent risk factors were non-postoperative chylothorax (aOR 4.4), use of TPN >14 days (aOR 11.9), hypoalbuminemia (aOR 13.0), and ventilator-associated pneumonia (aOR 41.2). However, the confidence intervals were relatively wide for all these factors.

Discussion

Chylothorax treatment is challenging, especially in young children. Our study found that 80% of chylothorax cases were due to a complication of thoracic surgery, especially cardiac surgery. The overall incidence of chylothorax after cardiac surgery in our institute was almost 2%, which is comparable to a previous study that reported an incidence

rate ranging from 1.9% to 4.8% (7-9).

Most dietary modification treatments at our institute began with fasting, resulting in a higher rate of TPN use (87.7%) than in other reports from developed countries, which range from 30–60% (6,7,9). Furthermore, age is the main factor that influenced treatment options for chylothorax in our study. Fasting with TPN was used as a single therapeutic option only in the <1-year-old group, reflecting the limitation of choice for young infants of our institute. Further, newborns were associated with increased risk of complications, including catheter-related complications. Dietary modification among neonates and young infants, for whom nutrition mostly comes from milk products, remains a major challenge in chylothorax treatment. The MCT-rich infant formula was used to treat postoperative chylothorax in neonates and infants with a favorable outcome (71% success rate) (10). However, the total substitution of breast milk with MCT-rich infant formula removes the benefit of the immunoprotective effects of human milk. Modified-fat human milk, either defatted with fortification (11) or LF human milk (12,13) has been advocated for chylothorax treatment in neonates and offers comparable efficacy and duration of chylothorax resolution to an MCT formula. The critical barrier to these nutritional options in many centers, including in our institute, is the availability and affordability of these special neonatal formulas.

The prolonged use of TPN (>14 days), which was associated with unfavorable treatment outcomes, could be a result of the stepwise dietary modification at our institute. It is quite a liberal manner to step "back and forth" on the intensity of fat restriction without using a standard fixed protocol. Strategies that have been successful in shortening time to resolution of chylothorax and chest tube utilization in the pediatric population are specific steroids (hydrocortisone, dexamethasone, and methylprednisolone) and furosemide (14), thoracic duct embolization (9,15,16) and protocolized management (9,17). Most protocols categorized the severity of chylothorax by the volume of chyle output, using a cut-off of 20 mL/kg/day. It has been suggested that the high output group receive fasting and TPN combined with octreotide therapy as the initial treatment step (17). This strategy was observed only in some cases in the last few years of our study period.

The observation that chylothorax treatment evolved over time between decades (2001–2010 and 2011–2020) in our study was revealed by the significant increase of octreotide use from 19.3% to 47% of cases. We found no significant change in the therapeutic outcomes, time to resolution of chylothorax, hospitalization, or morbidity and mortality rate between the two periods. Octreotide treatment for neonatal and pediatric chylothorax cases is considered to have had a positive treatment effect over the last decade (3,18). Tatar *et al*. (19) reported the successful use of octreotide as initial conservative treatment along with diet modification for all 12 post-cardiac surgery-related chylothorax patients. They reported an average resolution of chyle of 10.3 days, using a dosage range of 4–10 μg/kg/hour. With this same dosage range, another retrospective study among 29 children with chylothorax due to cardiac surgery reported a success rate of 62% (20). However, because of the lack of a control group, it is difficult to conclude the true additional benefit and make a solid recommendation for this therapy. The efficacy of octreotide in this study could not be determined since there was no specific protocol, and octreotide was initiated at different stages of chylothorax. However, without a standard protocol for dosage titration, our median duration of octreotide therapy of 9.5 days and success rate of 72.8% is comparable to those in previous studies (3,20,21).

Although most of chylothorax episodes (89%) were successfully treated with conservative methods, the rate of thoracic duct ligation in our study (10.8%) was slightly higher than that in most recent studies (4–9%) (6-9,22). There is less variety of therapeutic options at our institute. The use of many non-surgical interventions reported in postoperative chylothorax, were hardly observed in our study including steroids, propranolol, chemical pleurodesis, and intravenous immunoglobulin (4,6,8,9,14,23). Further, the thoracic duct embolization, which was identified as another effective, less-invasive option for chylothorax in recent years (9,15,16), is not available at our institute. Therefore, at our institution, thoracic duct ligation was a safe option when available less-invasive treatment options failed.

The mechanical ventilation requirement and ventilator-associated pneumonia were observed more in younger patients (age <1 years). This may not be the consequence of chylothorax alone and may also influenced by cardiopulmonary compromise of infants especially after post-cardiac surgery. The recent systematic analysis of congenital chylothorax of newborns (24) also reported a high rate of mechanical ventilator use (56%), similar to our study. Other morbidities observed during chylothorax treatment in our study, including sepsis and hypoalbuminemia, were possibly the result of prolonged chyle loss, while few may be related to TPN administration,

ICD, and catheter placement. These factors have not been emphasized in previous studies in children (5-9). Non-operative chylothorax is one of the significant risk factors related to unfavorable outcomes, which has also been reported in previous study in adult patients (25). The potential modifiable risk factors are the use of TPN >14 days and hypoalbuminemia. With in-depth exploration, we also found that the initial prolonged fasting (>7 days) as an aggressive fat restriction strategy does not significantly shorten the time to resolution of chylothorax and hospitalization. This emphasizes the benefit of fat-modified diet as early as possible. Furthermore, the elimination of enteral feeding for chylothorax treatment should be discouraged.

This study was a retrospective study conducted over a 20-year period, and hence, the treatment strategies were dependent on the physician's practice preference and resource availability. The effectiveness of such modalities and outcomes should be interpreted with caution.

Conclusions

In our study, most (89.2%) of chylothorax were successfully treated conservatively, using dietary modification and octreotide therapy. Young children aged <1 year were challenging patients due to limitations of appropriate nutritional options and higher risk for specific complications. The potential modifiable risk factors for death or prolonged hospitalization were the use of TPN >14 days and hypoalbuminemia.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-474/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-474/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-474/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Approval was obtained from the ethics committee of Songklanagarind Hospital (No. REC-64-027-1-1), and informed consent was taken from all the patients.

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