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Postoperative Chylothorax After Cardiothoracic Surgery in Children

Emily H. Chan, BS, Jennifer L. Russell, MD, William G. Williams, MD,
Glen S. Van Arsdell, MD, John G. Coles, MD, and Brian W. McCrindle, MD, MPH

Department of Pediatrics, Division of Pediatric Cardiology, and Department of Surgery, Division of Cardiovascular Surgery, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada

Background. The purpose of this study is to determine the incidence, risk factors, and outcomes for chylothorax in children undergoing cardiothoracic surgery.

Methods. Hospital databases were used to identify chylothorax cases. Surgical databases were used to identify all patients undergoing cardiothoracic surgery. Medical records were reviewed, including daily records of drainage volumes and management.

Results. From September 2000 to December 2002, there were 48 cases of chylothorax in 1,257 surgeries—an incidence of 3.8% (95% confidence interval: 2.8% to 4.8%). Overall mortality rate was similar, but cases had longer postoperative hospital stays (median, 22 versus 8 days; $p < 0.001$). Incidence of chylothorax was significantly higher with heart transplantation and Fontan procedures. Diagnosis was made at a median of 6 days after surgery. Duration of drainage was a median of 15 days, with 11 patients draining more than 30 days. Longer duration of

drainage was associated with cavopulmonary anastomosis procedures and longer time to diagnosis of chylothorax. Nutritional management included low fat diet, enteral feeds enriched with medium-chain triglycerides, and parenteral nutrition. Five patients were treated with octreotide, 4 with thoracic duct ligation, and 1 with pleurodesis. Octreotide was associated with a variable effect on drainage. Thoracic duct ligation reduced, but did not stop drainage.

Conclusions. Chylothorax increases duration of hospitalization after cardiovascular surgery in children. Early diagnosis may reduce the duration of chylothorax. Nutritional strategies remain the cornerstone for management of postoperative chylothorax. The impact of octreotide and surgical intervention is limited when reserved for patients with severe or prolonged drainage.

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In recent years, many advances in surgery for patients with congenital heart disease, including earlier intervention, have improved patient survival. However, important morbidity continues to complicate the postoperative care of these patients. Chylous pleural effusion, or chylothorax, is an early postoperative complication [1–3]. The postoperative leakage of lymphatic fluid into the pleural space may result from the surgical disruption of the thoracic duct or one of its main tributaries, or increased pressure within the intrathoracic lymph system [1]. Patients usually remain asymptomatic until a large volume of chyle accumulates [4, 5]. Therefore, fluid accumulations may remain unrecognized for an important period of time. Loss of this fluid by therapeutic drainage can lead to nutritional depletion, fluid and electrolyte loss, hypolipemia, and lymphocytopenia of T cells, which can contribute to immunodeficiency [5–7].

Previous studies of chylothorax in children have been limited to issues regarding conservative versus surgical management and have not adequately determined the risk factors for postoperative chylothorax and factors affecting clinical course [1, 2, 5, 8, 9]. We sought to determine the incidence, risk factors, clinical spectrum, and

impact on outcomes of chylothorax in children undergoing cardiothoracic surgery, while further describing our experiences with treatment.

Patients and Methods

Study Population

The study population included all children under the age of 18 years diagnosed with chylothorax after cardiothoracic surgery at the Hospital for Sick Children, Toronto, over a 28-month period beginning September 2000. All patients with the diagnosis of chylothorax and chylopericardium were identified using a search of the databases from the Division of Cardiology and the hospital medical records. The diagnosis was verified by reviewing information recorded in the medical records for all patients. Data from all other patients undergoing cardiac surgery during the same time period were obtained from the database of the Division of Cardiovascular Surgery for comparison. Specific types of surgery were excluded that did not involve intrathoracic manipulations, such as wound drainage or closure, sternal reopening or closure, isolated lung biopsy, and placement on extracorporeal membrane oxygenation or other support.

Measurements

The medical records for all patients were reviewed. Data collected included demographics, clinical history, surgi-

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Address correspondence to Dr McCrindle, The Hospital for Sick Children, 555 University Ave, Toronto, ON M5G 1X8, Canada; e-mail: brian.mccrindle@sickkids.ca.

Table 1. Factors Associated With Chylothorax

Variable	No Chylothorax (n = 1,209)	Chylothorax (n = 48)	p Value
Sex (male:female)	702:554	31:17	0.22
Age at surgery	5.8 months (birth, 20 years)	5.0 months (2 days, 18 years)	0.42
Weight at surgery (kg)	5.78 (0.56, 116)	5.44 (1.7, 49)	0.61
Body surface area (m ²)	0.37 (0.11, 2.37) (n = 933)	0.33 (0.13, 1.34) (n = 46)	0.16
Deaths during admission	54/1209 (4.5%)	3/48 (6.3%)	0.48
Duration of postoperative hospital stay for survivors (days)	8 (0, 236) (n = 1,153)	22 (7, 85) (n = 45)	<0.001

Data presented as frequency or median with range.

cal course, complications, and postoperative medical and surgical interventions. Serial data from their hospital stay were gathered from daily records, and included weight, fluid intake and output, dietary intake, laboratory investigations, medications, and chest tube drainage. Diagnostic criteria for chylothorax were applied as described by Buttiker and colleagues [4].

Data Analysis

Data are described as frequencies and medians with ranges as appropriate. The incidence of chylothorax was calculated together with 95% confidence limits (CL), and characteristics between patients with and without chylothorax were compared using χ^2 and Kruskal-Wallis analysis of variance testing. Factors associated with duration and volume of chylous drainage were sought using mixed linear regression analysis for repeated or serial measurements.

Results

Incidence and Risk Factors

From September 2000 to December 2002, 48 patients with postoperative chylothorax were identified from a total of 1,257 cardiothoracic surgeries, giving an incidence of 3.8% (95% CI: 2.8% to 4.8%). There were no significant differences between those with versus without chylothorax regarding sex, age, weight, or body surface area at surgery (Table 1). Deaths before hospital discharge were similar, although postoperative length of stay in survivors was significantly longer for those with versus without chylothorax (median, 22 versus 8 days; $p < 0.001$). Of the three surgeons operating during the study period, the incidence of chylothorax per surgeon was 2.8%, 4.3%, and 5.8% ($p = 0.07$).

Patient Characteristics

The primary diagnoses for the 48 patients with chylothorax included tetralogy of Fallot or double-outlet right ventricle in 12, hypoplastic left heart syndrome in 10, atrioventricular septal defect in 7, ventricular septal defect in 6, transposition of the great arteries in 3, with other simple lesions in 3, and complex lesions in 7 patients. Previous interventional cardiac catheterization procedures had been performed in 18 patients and previous surgical procedures, in 17 patients.

The incidence relative to the surgical procedure for those procedures performed more than 20 times during the study interval are shown in Table 2, and represent procedures performed in 45 of the chylothorax patients. The remaining 3 patients had rare procedures, including repair of total anomalous venous return, mitral valve replacement and mitral valve replacement with Konno procedure. Surgical approach was by median sternotomy in 47 patients, with 1 having a thoracotomy. Median duration of cardiopulmonary bypass was 126 minutes (range, 0 to 369) and median aortic cross-clamp time was 61 minutes (range, 0 to 469).

Excluding 3 patients who died, median initial duration of stay in intensive care was 6 days (range, 1 to 50), with 4 patients requiring readmission. The median total postoper-

Table 2. Incidence of Chylothorax by Type of Operation^a

Type of Operation	Incidence (%)	p Value ^b
Below overall incidence of 3.8%		
PDA ligation	0/88 (0%)	0.04
Aortic coarctation repair	1/65 (1.5%)	0.51
Arterial switch	1/54 (1.9%)	0.72
Secundum ASD repair	0/37 (0%)	0.40
Systemic-PA shunt	0.30 (0%)	0.63
Subaortic myectomy or fibromyectomy	0/27 (0%)	0.62
RV to PA conduit	0.23 (0%)	1.00
Primum ASD repair	0.22 (0%)	1.00
Mitral valvuloplasty	0/21 (0%)	1.00
Above overall incidence of 3.8%		
VSD repair	8/200 (4.0%)	0.84
Cavopulmonary shunt	4/58 (5.9%)	0.32
AVSD repair	5/84 (6.0%)	0.25
Tetralogy of Fallot repair	9/78 (11.5%)	0.002
Norwood 1	4/56 (7.1%)	0.16
Fontan procedure	6/52 (11.5%)	0.001
Heart transplantation	4/36 (11.1%)	0.04
Aortic valve replacement	2/28 (7.1%)	0.29
Double-outlet RV repair	1/20 (5.0%)	0.54

^a For only those operations performed in at least 20 patients; ^b p Value for specific procedure versus all other procedures.

ASD = atrial septal defect; AVSD = atrioventricular septal defect; PA = pulmonary artery; PDA = patent ductus arteriosus; RV = right ventricle; VSD = ventricular septal defect.

Table 3. Characteristics of Clinical Course for Patients Who Underwent Cavopulmonary Connections^a Versus all Other Patients

Characteristic	Cavopulmonary (n = 10) Median (Range)	Other (n = 38) Median (Range)	p Value
Day diagnosed	6 (2, 30)	6 (1, 28)	0.70
Pleural fluid characteristics at diagnosis			
Triglyceride level (mmol/L)	1.56 (0.71, 6.24)	1.35 (0.33, 6.92)	0.88
White blood cell count (cells/mm ³)	2,100 (347, 21,500)	1,411 (204, 10,200)	0.55
Percent lymphocytes	88 (8, 96)	90 (14, 97)	0.64
Duration of drainage (days)	32 (13, 315)	13 (5, 57)	0.002
Maximum daily drainage (mL/kg)	48 (10, 115)	37 (14, 672)	0.25

^a Includes 4 patients with cavopulmonary shunt and 6 patients who had Fontan procedure.

ative duration of hospital stay of the 45 survivors was 22 days (range, 7 to 85), not including the subsequent readmission of 3 patients for persistence or recurrence of chylothorax.

Reoperations were required during hospital admission for 5 patients, and included 2 pacemaker insertions and 3 revision surgeries. Median duration of initial mechanical ventilation was 2 days (range, less than 1 to 38), with 14 patients requiring reintubation and 1 patient dying without ever being extubated.

Characteristics of Chylothorax

Chylous pleural effusions were bilateral in 26 patients (54%), with 7 patients (15%) having an additional pericardial effusion. Median time to diagnosis of chylothorax was 6 days (range, 1 to 30) after surgery. One patient did not have chest tubes in place at the time of diagnosis as fluid testing results were obtained by samples from pleurocentesis. This patient never required chest tube placement for chylous drainage. Median drainage on the day of diagnosis was 21 mL/kg (range, 2 to 314 mL/kg).

Diagnosis of the chylothorax was evident from laboratory testing of the fluid demonstrating the presence of chylomicrons in 43 patients (90%) and triglyceride concentration above 1.1 mmol/L in 33 (69%; median, 1.38 mmol/L; range, 0.33 to 6.92 mmol/L). Additional testing of fluid cell counts in 35 patients showed total white blood cell counts above 1,000 cells/mm³ in 22 (63%; median, 1,753 cells/mm³; range, 204 to 21,500 cells/mm³), with a percentage of lymphocytes above 80% in 21 patients (60%; median 89%; range, 8% to 97%). Overall, all but 1 of the 48 patients had at least one of the four fluid abnormalities. Although the fluid analysis for 1 patient did not reach any of the cutpoints and the fluid was negative for chylomicrons, the triglyceride level was 0.83 mmol/L and the white cell count was 700 cells/mm³ with 78% lymphocytes.

The characteristics of chylous drainage from patients after cavopulmonary connection procedures were not significantly different from those after other surgeries (Table 3).

Management of Chylothorax

Nutritional management included the use of a low fat diet for 7 patients and feeds enriched with medium-chain triglycerides for 40 patients. One remaining patient who

died was given parenteral nutrition with small volumes of expressed breast milk. Total parenteral nutrition was used for 11 patients. Octreotide was used in 5 patients, as shown in Table 4. Three of these patients also were treated with thoracic duct ligation, in 2 before and 1 after ligation. One additional patient had thoracic duct ligation without octreotide treatment. Thoracic duct ligation resulted in drainage cessation in only 1 of the 4 patients undergoing this procedure (Table 4).

Duration of Drainage

Duration of chylothorax from surgery to the time of final chest tube removal in 44 patients was a median of 15 days (range, 5 to 315), with 11 patients draining 30 days or more. Three patients died during their initial hospital stay at 30, 57, and 90 days after surgery owing to chronic lung disease, sepsis, and ischemic bowel, respectively, and all without resolution of their chylothorax. Another patient had an intraoperative complication leading to severe neurologic injury and was discharged after 33 postoperative days to his country of origin for palliative care with chest tube draining. No further follow-up information was available, but it was assumed that he died.

Chest tube reinsertion was required in 23 patients, in 9 after drainage supposedly stopped for a median of 7 days (range, 1 to 24); these included 1 patient who had a cardiac arrest as a result of reaccumulation.

Patient and surgical characteristics independently associated with duration of drainage (after logarithmic transformation to normalize the distribution) included cavopulmonary anastomosis procedures (cavopulmonary shunt or Fontan procedure; parameter estimate 0.97; $p < 0.001$) and greater time to diagnosis of chylous drainage (after logarithmic transformation; parameter estimate 0.37; $p = 0.009$). Patients who drained more than 30 days included all 4 patients who had Norwood I procedure, 3 of the 6 Fontan patients, 2 of the 4 heart transplantation patients, 2 of the 4 cavopulmonary shunt patients, 1 patient who had repair of ventricular septal defect, and 1 patient who had tetralogy of Fallot repair. Furthermore, the duration of chylothorax after cavopulmonary connection procedure was longer than after other surgeries (Table 3).

Table 4. Outcomes for Patients Treated With Octreotide or Surgical Intervention

Patient No.	Surgery Type	Treatment Attempted	Treatment Summary			Short-Term Outcomes			Long-Term Outcomes		
			Started Postoperative Day	Octreotide Duration (Days)	Maximum Dose ($\mu\text{g}/\text{h}$)	Pretreatment Drainage (ml/kg/day)	Posttreatment Drainage (ml/kg/day)	Change in Drainage	Drainage Duration (Days)	Died	
1	Fontan	Octreotide	16	8	60	51	50	—	85	No	
2	Transplant	Octreotide	15	6	22	141	236	↑	57	No	
3	Norwood 1	Ligation	26	—	—	173	122	↓	57	Yes	
4	BT shunt	Ligation	15	—	—	30	126	↑	90	Yes	
5	BCPS	Octreotide	20	8	40	126	29	↓	314	No	
6	Fontan	Octreotide	25	—	—	58	39	—	62	No	
		Octreotide	143	5	50	39	58	→			
		Ligation	161	—	—	74	<1	→			
		Octreotide	185	23	45	56	16	→			
		Pleurodesis	247	—	—	4	<1	↑			
		Octreotide	266	40	55	60	4	→			
		Octreotide	22	5	13	6	—	—			

Pretreatment drainage is the average daily drainage for 5 days before treatment.

Posttreatment is the average daily drainage for the last 5 days on octreotide or the first 5 days after thoracic duct ligation.

BCPS = bidirectional cavopulmonary shunt; BT shunt = Blalock-Taussig shunt; h = hour; PO = oral or enteral.

Table 5. Factors Associated With Serial Measurements of Daily Volume of Drainage per Body Weight (mL/kg)

Variable	Parameter Estimate	p Value
Intercept	8.38	
Days since surgery ^a	19.28	<0.001
Duration of drainage ^b	10.89	0.02
Norwood I procedure	28.90	0.02
No use of octreotide ^c	-0.05	0.15
Use of octreotide ^c	-0.11	<0.001

^a After inverse transformation; ^b After logarithmic transformation; ^c Interaction term with days since surgery.

Amount of Drainage

The maximum amount of drainage occurred at a median of postoperative day 2 (range, 0 to 30) and with a median of 37 mL/kg (range, 11 to 672 mL/kg) on that day. Patient and surgical characteristics independently associated with greater maximum drainage (after logarithmic transformation) included only bilateral chest drainage (parameter estimate 0.7; $p = 0.003$); longer duration of drainage almost reached statistical significance ($p = 0.055$). The maximum amount of drainage for chylothorax after cavopulmonary connection procedure was not significantly different from other surgeries (Table 3).

Lower daily drainage was associated with an increased duration from surgery after inverse transformation, indicating an initially rapid then slower decrease in drainage amount. Higher daily drainage was associated with those with longer total duration of drainage (after logarithmic transformation) and patients who had the Norwood I procedure. The impact of therapy directed at reducing chylous drainage was sought using mixed linear regression analysis of daily drainage (Table 5). The use of octreotide was associated with a greater rate of decline in daily drainage.

Octreotide tended to be used for patients with higher or unchanged drainage patterns (Table 4). However, results of this therapy were variable. One patient had an important decrease in drainage, with recurrence when the octreotide was temporarily stopped. Thoracic duct ligation tended to reduce, but not stop drainage.

Comment

Incidence, Risk Factors, and Outcomes for Postsurgical Chylothorax

Incidence of chylothorax in our study population (3.8%) was similar to values reported from other recent studies with incidences of 2.5% [1] and 4.7% [10]. This is higher than older studies, reporting 1% from 1979 to 87 by Allen and coworkers [5] and 1.1% from 1961 to 1969 by Higgins and associates [11]. This change likely reflects differences in the characteristics of patients and types of surgical procedures.

A higher incidence of chylothorax was observed in heart transplantation and Fontan procedures in our study. Conceptually, heart transplantation is associated

with increased trauma to the chest cavity and Fontan or cavopulmonary anastomosis procedures will elevate superior vena cava pressure, both resulting in higher risk for chylothorax. The systemic venous hypertension can cause a backup of pressure into the thoracic duct, resulting in increased chyle loss. This loss is consistent with our observations of longer duration of chylous drainage after these procedures.

Knowing that cavopulmonary anastomosis procedures have a higher risk of prolonged pleural drainage may indicate that earlier, more aggressive therapy is indicated for these patients. Further studies should be conducted to evaluate whether earlier intervention can reduce hospitalization duration and improve prognosis.

Beghetti and associates [1] reported an increased incidence of chylothorax with Blalock-Taussig shunt procedures. In this study, isolated Blalock-Taussig shunt procedures were not evaluated because too few procedures were performed in the time interval studied. However, Norwood I procedures were associated with an increased risk of chylothorax and higher daily drainage (Table 5).

Four patients had postoperative complications of venous thrombus in the innominate, jugular, or superior vena cava, all related to central venous lines. Despite the theoretical increase in systemic venous hypertension, their drainage duration was not distinctly lengthened from other patients at 13, 20, 20, and 61 days, respectively. However, further study with clear documentation of central venous pressures is needed to clarify the importance of this risk factor in chylothorax patients.

Presentation and Diagnosis

Diagnostic criteria for pediatric chylothorax have been defined by Buttiker and coworkers [4]. In our study, 90% of patient samples had chylomicrons, but fewer met the other diagnostic criteria. In some patients, that was due to less consistent testing for these other criteria. Poor enteral nutrition at the time of diagnosis may have also played a role in decreasing chylomicron and triglyceride levels in the pleural fluid [4], thereby contributing to delays in diagnosis. As longer time to diagnosis is correlated with increased drainage duration, there may be a role for early retesting of pleural fluid after enteral fat challenge to reduce the time to diagnosis in cases with a high index of suspicion for chylothorax.

Treatment of Chylothorax

To date, there have been no randomized controlled clinical trials to provide evidence for best management of chylothorax. The primary modes of treatment include pleural space evacuation, low-fat diets, medium chain triglyceride enriched feeds, enteric rest, and parenteral alimentation [1, 2, 12-14]. The limited numbers of patients studied in each series precludes interpretations as to the protocol most effective for treatment [1, 4, 10, 12, 13].

Nutritional Management Strategies

The use of medium-chain triglyceride enriched diets is based upon the understanding that enterocytes directly

absorb medium chain fatty acids into the circulation. That would theoretically allow patients to be supplied with adequate nutrition while reducing lymphatic flow to allow healing of the damaged lymphatic vessels. In our series, most patients (34 of 48, 71%) had resolution of their drainage with only changes to enteral nutrition. Although spontaneous recovery is possible, these data help substantiate the use of low fat or medium chain triglyceride enriched diets as first-line therapy.

A more rigorous mode of management is the use of total parenteral nutrition. This strategy was attempted for short periods for 11 patients in our series who had previously been managed with enteral diet change in this study. However, 5 of the 11 patients eventually went on to require further interventions, including octreotide or thoracic duct ligation. From these results, it may be reasonable to start patients on total parenteral nutrition and octreotide therapy concurrently after abandoning enteral changes to more achieve rapid control of the drainage or to expedite the decision to undertake a surgical intervention.

Octreotide, a somatostatin analog, was used in 5 patients in this series as a second-line therapy. Recently, successful treatment has been noted in some case reports for chylothoraces of various etiologies [15-19], but its mechanism of action is not well understood. It has been postulated that octreotide can reduce leakage by increasing lymphatic vessel contraction [15]. The patients that were given octreotide in our study had variable responses to the treatment, with no overall decreases in drainage over the treatment period in 4 of the 5 patients (Table 4). With the weak contractility of lymphatics, it has been thought that octreotide may be more beneficial for use with mild to moderate flow chylothoraces [15]. In our study, the variable efficacy may be due to the late application of octreotide in management of patients with relatively higher daily drainage of chyle, and perhaps other subtle differences in patient characteristics not yet understood.

Surgical Management Strategies

The surgical management for postoperative chylothorax most commonly involves ligation of the thoracic duct, commonly through thoracotomy. Three of the 4 patients undergoing duct ligation in this series subsequently died of other causes. Chest tubes were still draining in 2 patients, and the remaining patient had a pleurodesis and further octreotide therapy before drainage was stopped. The high mortality rate of these patients seems to indicate that thoracic duct ligation was reserved for patients with poor prognosis.

In summary, octreotide and surgical interventions were not applied effectively to stop drainage in this study population. When reserved for patients with severe or prolonged drainage, the usefulness of these more aggressive therapies appears to be limited. Further studies are needed to elaborate an evidence-based protocol for the management of unremitting chylothorax. Until such evidence is available, we have drafted and instituted a "care map" (Fig 1) to standardize the

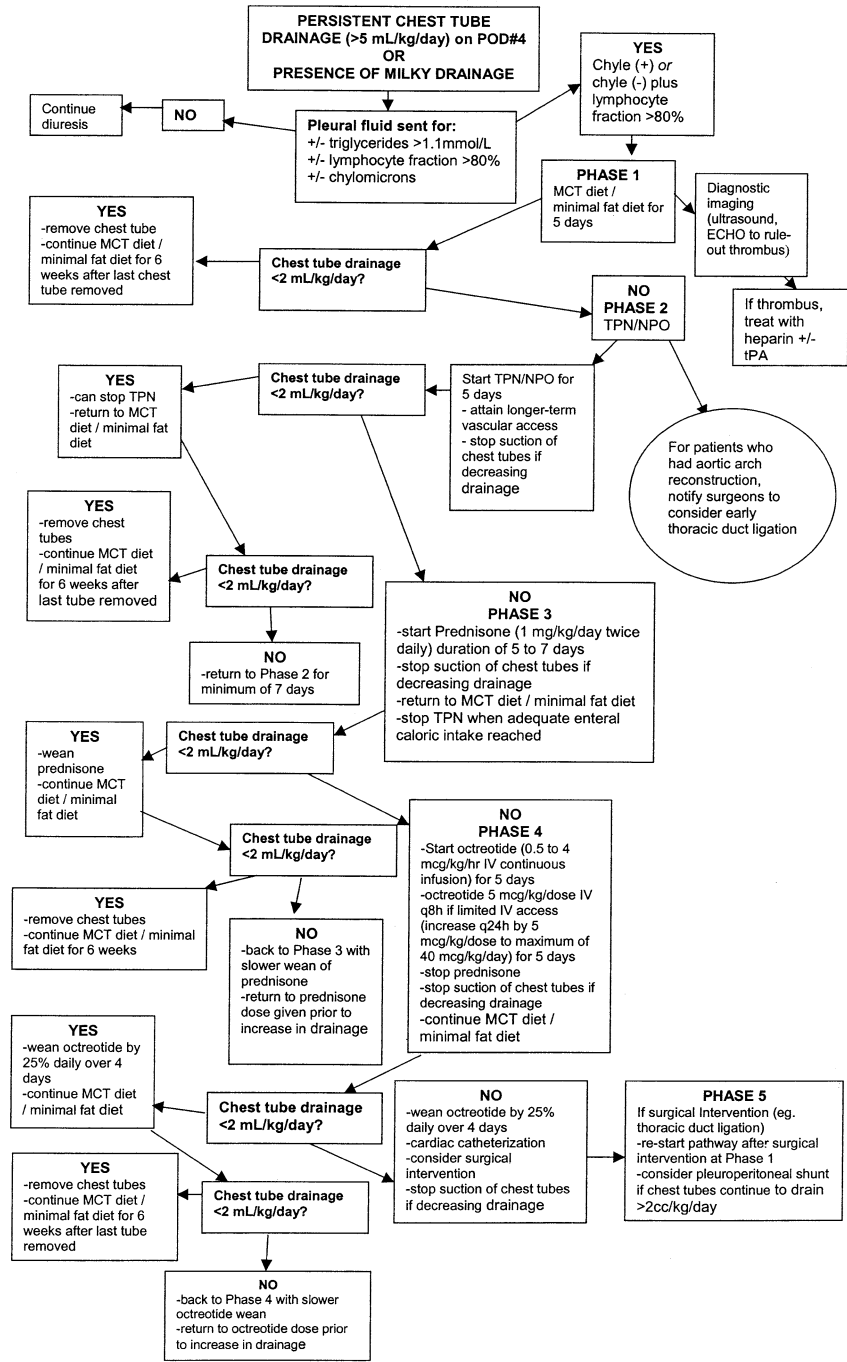


Fig 1. Care map flowsheet for diagnosis and management of chylothorax. (ECHO = echocardiogram; IV = intravenous; MCT = medium chain triglycerides formula or nutritional supplement; NPO = nothing by mouth; POD = postoperative day; q8h = every 8 hours; q24h = daily; tPA = tissue plasminogen activator; TPN = total parenteral nutrition.)

diagnosis and management of chylothorax within our institution.

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INVITED COMMENTARY

Chylothorax after repair of congenital heart defects is an infrequent complication, but one that can cause significant morbidity. One of the challenges of managing this complication, especially in neonates and small infants, is to maintain fluid, electrolyte, and nutritional homeostasis while trying to eliminate the lymphatic leak using therapies that are often lengthy. Chan and colleagues [1] in their relatively large, retrospective series report an incidence of 3.8% for chylothorax, which is comparable with other contemporary series. Treatment was determined by physician preference rather than a protocol that was later proposed. However, the median length of hospitalization for patients who had a postoperative chylothorax develop was 22 days compared with 8 days for patients without this complication. This prolonged hospitalization underscores the often protracted course from postoperative chylothorax and its morbidity potential.

A definitive treatment strategy for postoperative chylothorax is currently elusive. The therapeutic modalities include drainage of the pleural space, diets low in long chain triglycerides and enriched with medium chain triglycerides, or complete abstinence from enteral nutrition opting for parenteral calorie delivery. Surgical ligation of the thoracic duct, and recently octreotide administration, have been used when dietary restrictions fail. The authors report a 71% success rate for resolution of chylothorax using a low fat, medium chain triglycerides enriched diet. When total parenteral nutrition was used, only 6 of 11 patients had elimination of the chylothorax. Five patients received octreotide as second line therapy, but 4 showed no overall decrease in chylous drainage. Thoracic duct ligation was performed on 4 patients between 20 and 161 days after cardiac surgery. Three of

these patients demonstrated a decline in daily drainage, but survival in this group was 50%. In addition, patients were at risk for prolonged chylous drainage (50% drained longer than 30 days) after a cavopulmonary anastomosis, including the Fontan operation. Furthermore, increased duration of drainage was associated with delay in diagnosis of chylothorax, and a trend emerged between greater maximum daily drainage and longer duration of chylous drainage. These results support the principle of early diagnosis and expeditious resolution of chylothorax, especially in patients after having cavopulmonary anastomoses.

The algorithm for diagnosis and management of chylothorax offered by the authors is well organized and promotes specific criteria to govern therapy for this challenging problem. However the treatment goal for chylothorax should be rapid resolution to minimize the morbidity associated with lipid and protein losses, immunosuppression, long-term chest tube and intravenous access, and hospitalization. An additional therapeutic modality demonstrated to be effective in adults with chylothorax is percutaneous embolization of the thoracic duct. This technique may provide a means to quickly achieve early closure of the lymphatic fistula in children, particularly those patients believed to have a chylous leak secondary to elevated lymphatic pressures after cavopulmonary anastomosis.

The authors mention fluid and electrolyte losses and acquired immunodeficiency from lymphocyte depletion as consequences of chylothorax, but they discuss little about their replacement therapy. In cavopulmonary anastomosis or Fontan patients, in particular, we have practiced partial volume replacement with fresh frozen

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