Cardiology in the Young

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Current practices for refractory chylothorax following congenital heart surgery

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Original Article

Cite this article: Adamson GT, Winder MM, Catton KG, Dewitt AG, Kozyak BW, Glenn ET, and Bailly DK (2023). Current practices for refractory chylothorax following congenital heart surgery. *Cardiology in the Young*, page 1 of 5. doi: 10.1017/S1047951123003918

Received: 25 April 2023
Revised: 7 September 2023
Accepted: 27 October 2023

Keywords:
Lymphatic dysfunction; survey; practice variation; paediatric cardiac surgery; pleural effusion

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Abstract

Introduction: Chylothorax following paediatric cardiac surgery is associated with significant morbidity, particularly those that are refractory to conservative therapy. It is our impression that there is important variability in the medical, surgical, and interventional therapies used to manage refractory chylothorax between congenital heart programmes. We therefore conducted a survey study of current practices for managing refractory chylothorax. *Methods:* The Chylothorax Work Group, formed with the support of the Pediatric Cardiac Critical Care Consortium, designed this multi-centre survey study with a focus on the timing and indication for utilising known therapies for refractory chylothorax. The survey was sent to one chylothorax expert from each Work Group centre, and results were summarised and reported as the frequency of given responses. *Results:* Of the 20 centres invited to participate, 17 (85%) submitted complete responses. Octreotide (13/17, 76%) and sildenafil (8/17, 47%) were the most utilised medications. Presently, 9 (53%) centres perform pleurodesis, 15 (88%) perform surgical thoracic duct ligation, 8 (47%) perform percutaneous lymphatic interventions, 6 (35%) utilise thoracic duct decompression procedures, and 3 (18%) perform pleuroperitoneal shunts. Diagnostic lymphatic imaging is performed prior to surgical thoracic duct ligation in only 7 of the 15 (47%) centres that perform the procedure. Respondents identified barriers to referring and transporting patients to centres with expertise in lymphatic interventions. *Conclusions:* There is variability in the treatment of refractory post-operative chylothorax across a large group of academic heart centres. Few surveyed heart centres have replaced surgical thoracic duct ligation or pleurodesis with image-guided selective lymphatic interventions.

Chylothorax is a common complication of paediatric cardiac surgery and is associated with significant morbidities and mortality.[1,2] Post-operative chylothorax can be secondary to mechanical trauma to lymphatic vessels, haemodynamic disturbances, and/or intrinsic lymphatic malformations. The diagnosis and treatment of chylothorax vary between congenital heart programmes, prompting the formation of a Chylothorax Work Group. We recently developed a consensus algorithm for the diagnosis and acute conservative management of paediatric post-operative chylothorax, which focuses on the timing and duration of fat-modified and nil-per-os feeding strategies according to the volume of chest tube output.[3] Currently, consensus guidelines do not exist around the medical, surgical, or interventional management of chylothorax that is refractory to conservative management. Through discussions in Chylothorax Work Group meetings, we recognised significant variability in the management of refractory chylothorax between participating centres. To better understand this variability, we conducted a survey study of current practices for managing refractory chylothorax at congenital heart programmes.

Materials and methods

The Chylothorax Work Group was formed in October 2020 with the support of the Pediatric Cardiac Critical Care Consortium (PC4) Quality Improvement Committee. Members of the work group represent 22 centres and consist of more than 60 multidisciplinary providers. The subgroup on refractory chylothorax, which included eight members of the Chylothorax Work Group, constructed a survey including known management strategies for chylothorax. The survey was revised according to feedback from the larger Work Group, and the final version is included in Supplementary File S1. The survey was administered to one representative from each centre in the Chylothorax Work Group. This representative was either the medical director of their ICU, the recognised institutional clinical expert in managing chylothorax, or an individual designated by the medical director to respond on behalf of the centre. The respondent

was instructed to discuss the survey with their practice group, including the ICU team, cardiologists, surgeons, and interventional cardiology and radiology teams, to achieve consensus on all answers. The respondent was encouraged to discuss the survey and answers with the refractory chylothorax subgroup prior to submitting the results. Survey results were summarised and reported as the percentage frequency of given responses.

Results

A total of 20 centres from the Chylothorax Work Group were invited to participate in the survey, and 17 (85%) submitted complete responses (Supplementary Table S1). The majority (10/17, 59%) of responding centres perform 350 or more congenital heart surgeries per year, whereas 3 (18%) perform 250 to 349, 1 (6%) performs 150 to 249 surgeries, and 3 (18%) perform < 150 surgeries per year. Geographically by US census region, four (12%) centres were Northeast, four (24%) Midwest, 7 (41%) South, and four (25%) West. There were six (35%) centres with an established lymphatic disorders team and three (18%) centres with a treatment protocol for refractory chylothorax. The definition of refractory chylothorax varied between centres (Supplementary Table S2).

Regarding feeding strategies for refractory chylothorax in patients who have not demonstrated improvement in chest tube output after a trial of nil-per-os, 10 (59%) centres routinely restart fat-modified feeds, whereas the remainder will continue nil-per-os management.

Regarding anticoagulation, 11 (65%) centres utilise prophylactic anticoagulation in some instances of refractory chylothorax, either in situations of particularly high chest tube output (5/17, 29%), history of prior thrombus (8/17, 47%), for specific cardiac lesions (8/17, 47%), or for all patients (1/17, 8%). Of these 11 centres, 9 (82%) use only enoxaparin or heparin, whereas two centres may use bivalirudin. No surveyed centres utilise prophylactic coumadin, apixaban, or other agents for refractory chylothorax.

The utilisation of medical therapies (octreotide, steroids, propranolol, midodrine, sildenafil, sirolimus, and MEK inhibitors) for the treatment of chylothorax is shown in Figure 1 and Supplementary Figure S1. Octreotide is used by most centres (13/17, 76%), though the timing of introducing the medication is variable. Sildenafil is the next most common medical therapy, given in 8 (47%) centres, half of whom utilise it in the first 10 days of chylothorax diagnosis. Six (35%) centres report using steroids, whereas propranolol, midodrine, and MEK inhibitors are used at only two (12%) centres each. One centre reported the use of sirolimus for the indication of refractory chylothorax.

The utilisation of more invasive therapies are shown in Figure 2. There are nine (53%) centres that use pleurodesis, all > 20 days after diagnosis, either by doxycycline (six respondents) or by mechanical means (three respondents). Two (12%) centres report utilising a blood patch (sterile injection of patient's blood into their chest tube); for one centre, this occurs 10–20 days after diagnosis, and for the other>20 days after diagnosis.

Surgical thoracic duct ligation is performed in 15 (88%) of the responding centres; 13 report that ligation typically occurs > 20 days after chylothorax diagnosis, whereas at 2 centres it more commonly occurs 10–20 days after diagnosis. Diagnostic lymphatic imaging is performed prior to surgical thoracic duct ligation in only 7 of the 15 centres (47%) that perform the procedure. Thoracic duct decompression is performed at 6 (35%) of the surveyed centres. At two centres, it is performed only via surgery (innominate vein turndown), at three centres only via transcatheter methods, and at one centre has been done by both methods depending on the clinical scenario. Pleuroperitoneal shunts are performed at three (18%) centres (all > 20 days after diagnosis), lymphovenous anastomoses at one (6%) centre (>20 days after diagnosis), and no surveyed centres report performing peritoneovenous shunts.

Percutaneous lymphatic interventions are performed at eight (47%) centres, in most cases (6/8, 75%) >20 days after chylothorax diagnosis. These interventions include lipiodol embolisation, total thoracic duct embolisation, and selective lymphatic channel embolisation. The interventions are performed by interventional radiologists at four centres, interventional cardiologists at two centres, and a team consisting of both interventional radiologists and cardiologists at two centres.

Prior to percutaneous lymphatic interventions, 7 of 8 (88%) centres routinely perform a delayed-contrast magnetic resonance lymphangiogram, with or without a standard lymphangiogram, whereas one centre reports utilising only a standard lymphangiogram to plan the intervention. Of the seven centres performing percutaneous lymphatic interventions with a delayed-contrast magnetic resonance lymphangiogram, five (71%) routinely utilise hepatic and/or mesenteric access points in addition to inguinal lymph nodes.

Regarding referral patterns, 11 (65%) of respondents had referred patients to a lymphatic centre or outside hospital for a lymphatic intervention. Of these, seven (64%) experienced significant barriers to referral, including issues with insurance authorisation (4/11, 36%), long wait times at the receiving centre (3/11, 27%), distance from a lymphatic centre (3/11, 27%), and patient stability for transport (2/11, 18%), and/or disagreements between medical and surgical providers regarding the benefits of transfer to a lymphatic centre (2/11, 18%).

Discussion

Over the past decade, much has been learned about the anatomy and physiology of the lymphatic system as it relates to CHD and heart failure.[2,4,5] Congenital lymphatic anatomic abnormalities have been reported in over half of patients with CHDs,[6] and most patients with post-operative chylothorax have no evidence of surgical trauma to the thoracic duct.[2] Rather, post-operative chylothorax appears to be a manifestation of a congenitally abnormal lymphatic system unmasked by inflammation and haemodynamic perturbations. Obtaining a complete understanding of the unique lymphatic anatomy and physiology of each patient is advisable before proceeding to surgical or interventional procedures.[2,4,7]

Though much has been learned about post-operative chylothorax, the impact of this knowledge on clinical practice has not been previously evaluated. In this study, we report the current practice for the treatment of refractory post-operative chylothorax at a selection of paediatric heart centres across the United States of America. A strength of the survey lies in the targeting of one dedicated stakeholder per centre who is specifically interested in chylothorax research and clinical care to be responsible for reporting an institutional consensus on each survey answer. The intention is for the survey to seek facts from an institution rather than the opinion or recollection of an individual. We report significant heterogeneity in the type and timing of all therapies: medications, surgical procedures, and transcatheter interventions.

https://doi.org/10.1017/S1047951123003918 Published online by Cambridge University Press

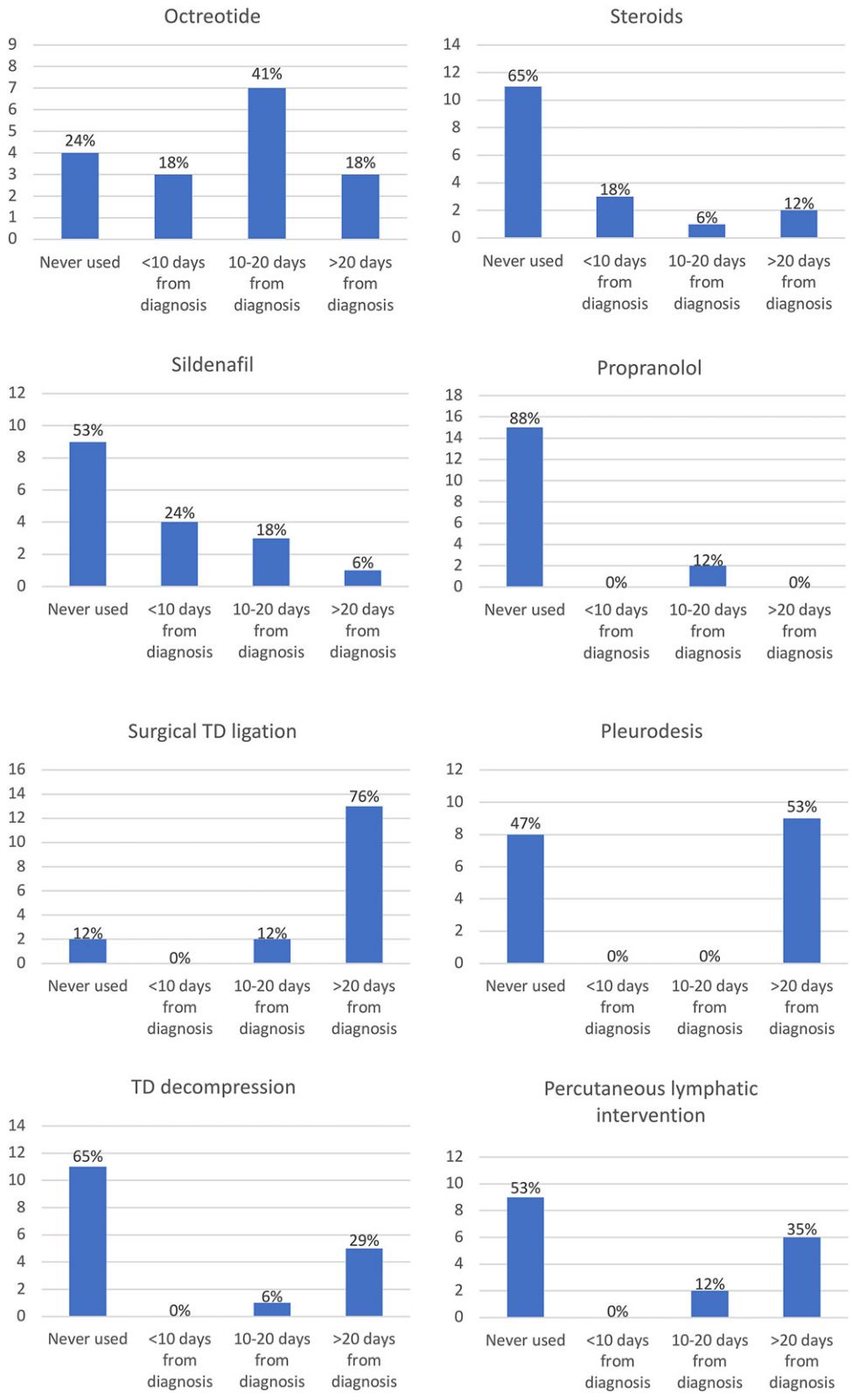

Figure 1. Utilisation of medical therapies for refractory chylothorax, with y-axis showing the frequency of responses, out of 17 survey respondents.

Figure 2. Utilisation of surgical or interventional therapies for refractory chylothorax, with y-axis showing the frequency of responses, out of 17 survey respondents.

Medications

Early medical treatment of chylothorax has historically been aimed at decreasing chyle production to promote healing of lymphatic channels, addressing residual haemodynamic and anatomic lesions, and treating or removing clot near the common locations of lymphatic drainage.[2,8,9] Numerous adjuvant medical therapies have been reported, though often with little data supporting their use. The more recent understanding that post-operative chylothorax is most commonly atraumatic may inspire more interest in utilising medications known to treat inflammation and/or modulate lymphatic tissue, such as those used for congenital

https://doi.org/10.1017/S1047951123003918 Published online by Cambridge University Press

lymphatic disorders. The more commonly used medications from the present survey are discussed below.

Octreotide, a somatostatin analogue, can reduce the hepatic, portal, and splanchnic blood flow and thereby decrease lymph production.[10] The rationale for its use is therefore similar to the nil-pre-os or low-fat feeding strategies, which is to decrease the amount of lymphatic fluid to promote healing of injured or inflamed lymphatic channels. There have been no randomised trials on its use, and attempts at systemic reviews have instead been summaries of case reports in primarily congenital neonatal chylothorax patients.[10,11] Though there is limited data supporting its use, octreotide is the most frequently utilised medication in this survey, used by three-quarters of responding centres. It is not clear whether this practice represents a belief in the efficacy of octreotide or whether its use is due to a lack of alternative therapies.

Just under half of the surveyed centres report using the phosphodiesterase-5 inhibitor sildenafil in the treatment of refractory chylothorax, typically within 20 days of diagnosis. There is a particular haemodynamic rationale to utilise sildenafil in patients with a cavopulmonary anastomosis and lymphatic dysfunction, where relatively small decreases in pulmonary vascular resistance can result in significant decreases in the systemic venous (and therefore lymphatic) pressure.[12] In addition to causing pulmonary vasodilation, the release of nitric oxide induced by sildenafil may directly induce relaxation of the lymphatic vasculature.[13,14] However, there are no data linking the use of sildenafil with improved outcomes in post-operative chylothorax.

Though there is early compelling data for the use of propranolol in the treatment of chylothorax, only two centres report its use in current practice for post-operative chylothorax. Researchers at Columbia showed significant similarities between the lymphatic endothelial cells of patients with congenital lymphatic abnormalities and those with post-operative chylothorax[15–17], prompting clinical study of the utility of propranolol in refractory post-operative chylothorax.[18] Corda and colleagues reported a retrospective cohort of 25 patients with high-volume post-operative chest tube output who received propranolol, and when compared to matched controls, there was an association with clinical improvement.[18]

About two-thirds of surveyed centres start anticoagulation for refractory chylothorax patients, even in the absence of known thrombus. The rationale for anticoagulation may be as a therapy (i.e. to treat venous thrombus that is obstructing major lymphatic drainage points) or as prophylaxis, since protein losses including antithrombin III and other coagulation factors place patients in a prothrombotic state[19]. Only one-third of surveyed centres report using steroids in the treatment of post-operative chylothorax. In addition to anti-inflammatory effects, the rationale for their use in chylothorax is to increase the rate of extrahepatic protein degradation, thereby increasing the production of plasma proteins by the liver and increasing the oncotic pressure.[20] Loomba et al., in a Pediatric Health Information System (PHIS) database study, found that the use of steroids in paediatric cardiac surgery admissions with chylothorax was associated with shortened lengths of stay, decreased cost, fewer surgical interventions for chylothorax, and decreased mortality.[21]

Surgical and interventional therapies

Historically, surgical thoracic duct ligation, pleurodesis, and pleuroperitoneal shunts were some of the only interventional options for the treatment of refractory post-operative chylothorax.[22] More recently, there is compelling evidence that these practices should be replaced by dynamic lymphatic imaging and consideration of image-directed lymphatic interventions.[2,4,5] Depending on the individual anatomy and patient's genetic substrate, empirically embolising or ligating the thoracic duct may result in resolution of the chylothorax, have no impact, or could make the clinical problem worse. Many patients with isolated chylothorax, for example, have congenital substrate for abnormal perfusion to the abdomen, and removing normal central lymphatic vessels will alter the haemodynamics of the lymphatic system and cause leakage to other compartments.[2,23,24] In a subset of patients with chylothorax, the leak to the pleural space originates directly from the liver lymphatics and will never resolve from the removal of the thoracic duct.[24] In all instances, ligating or embolising the thoracic duct significantly complicates the management of future lymphatic dysfunction, which is especially important in patients who require repeat surgeries or who have chronically elevated central venous pressure (i.e. cavopulmonary connections).

However, in this contemporary survey, over 75% of the surveyed centres perform surgical thoracic duct ligation for refractory chylothorax and over half proceed without first imaging the lymphatic system. Additionally, over 50% of the surveyed centres are performing pleurodesis and 18% are performing pleuroperitoneal shunts. Since this survey is directed at centres with a self-identified interest in studying and improving outcomes in post-operative chylothorax, it is conceivable that the survey underestimates the incidence of each of these interventions.

The survey therefore identified a significant gap between the advances in our understanding of post-operative chylothorax and resultant changes in clinical practice. Effectively imaging the lymphatic system can be technically and administratively challenging, involving collaboration with an anaesthesiologist or ICU provider to transport and manage an ill patient in an MRI scanner, a proceduralist to access lymphatic channels and keep needles secure for patient transfers, and a radiologist skilled in protocolising and interpreting the images. Selective lymphatic channel embolisation procedures can present similar technical challenges. However, about half of centres have performed at least one percutaneous lymphatic intervention, suggesting that procedural expertise may be growing. If imaging or interventional expertise is not available at a centre, significant barriers exist when referring patients to hospitals with the appropriate infrastructure. Survey respondents highlighted insurance authorisation disputes, long wait times at recipient centres, and patient inability to medically tolerate a transport. Even in clinical settings where imaging can be obtained, the clinical expertise in cardiac lymphatics is not widespread, and obtaining input from experts at other centres is not immediate. Further study is required to understand the rationale for the current widespread practice elucidated in this study.

Limitations

There are several inherent limitations to this survey study. This is a study only of the Chylothorax Work Group and does not represent the majority of congenital heart centres nationwide. Furthermore, 15% of the surveyed centres did not respond. Though respondents from each heart centre were identified as the medical director or leading clinician interested in lymphatic disorders, there is a possibility that inaccurate responses were given.

https://doi.org/10.1017/S1047951123003918 Published online by Cambridge University Press

Conclusions

There is significant variability in the medical and interventional treatment of refractory post-operative chylothorax across a large group of major academic heart centres. Few surveyed centres have supplanted thoracic duct ligation with image-directed lymphatic interventions, and there are important barriers to referral for the transfer of patients to centres with expertise in lymphatic imaging and intervention.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951123003918.

Acknowledgements. We wish to acknowledge the efforts of every participating member of the Chylothorax Work Group for their time and enthusiasm. We also thank the Pediatric Cardiac Critical Care Consortium Quality Improvement Committee for supporting this Work Group.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Competing interests. None.

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