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REVIEW

Chylothorax: Aetiology, diagnosis and therapeutic options

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Summary
Chylothorax is a rare condition that results from thoracic duct damage with chyle leakage from the lymphatic system into the pleural space, usually on the right side. It has multiple aetiologies and is usually discovered after it manifests itself as a pleural effusion. Diagnosis involves cholesterol and triglyceride measurement in the pleural fluid. Complications include malnutrition, immunosuppression and respiratory distress. Treatment may be either conservative or aggressive depending on the clinical scenario. In this review, we discuss the aetiology, diagnosis and treatment of chylothorax. English language publications in MEDLINE and references from relevant articles from January 1, 1980 to February 28, 2008 were reviewed. Keywords searched were *chylothorax*, *aetiology*, *diagnosis* and *treatment*.

Contents

Abbreviations: CT, (computed tomography); LAM, (Lymphangioleiomyomatosis); LDH, (lactate dehydrogenase); TB, (tuberculosis); VATS, (Video assisted thoracoscopic surery).

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Introduction

As approximately 2.4 l of chyle is transported through the lymphatic system every day, damage to, or rupture of the thoracic duct can give rise to a large and rapid accumulation of fluid in the pleural space.[1]

Lymph vessels arising in the peritoneal cavity form the thoracic duct by coalescing at the posterior aspect of the aorta, inferior to the diaphragm. The thoracic duct is approximately 36—45 cm long and 2—3 mm wide. From here the duct follows the course of the aorta superiorly through the diaphragm before continuing upwards on the right side of the thoracic vertebrae. At the level of the third or fourth vertebrae, the duct turns left, moves across the midline and follows the course upwards medially behind the oesophagus.[2] It proceeds often as far as the cervical region turning laterally before terminating in the subclavian vein. This typical pathway occurs in only 65% of the population due to embryological variation which may include multiple thoracic duct branches.[3] This is one of the main reasons the thoracic duct is damaged during surgery despite the surgeon's vigilance. The duct has numerous valves which maintain the unidirectional flow of chyle and normal respiration helps pump the chyle towards the venous circulation.

The primary role of the thoracic duct is to carry 60—70% of ingested fat at a concentration of 0.4—6 g/dl from the intestine to the circulatory system.[4] As a result chyle contains large amounts of cholesterol, triglycerides, chylomicrons and fat soluble vitamins. Lymph is the other main constituent of chyle and is made up of immunoglobulins, enzymes, digestive products and between 400 and 6800 white blood cells/ml, the majority of which are lymphocytes.[4] Chyle transportation is maximal after a high fat meal and minimal with starvation where flow is reduced to almost a trickle.[2]

Classically, a chyloma, a collection of chyle below the pleura develops when the thoracic duct first leaks. This, although rarely detected, manifests itself clinically as a swelling in the supraclavicular fossa which may be associated with severe chest pain, dyspnoea and tachycardia.[5] Chylomas can also manifest themselves at other sites of the pleura without causing supraclavicular swelling. Eventually the chyloma bursts through the pleura where the chyle accumulates in the pleural space. Very rarely, the chyle leak may lead to chylomediastinum[6] or chylopericardium.[7]

Aetiology

Chylothorax can be classified as traumatic or non traumatic [3] (Fig. 1).

Traumatic cases can be further sub-classified as iatrogenic or non-iatrogenic (20% of traumatic cases) with rupture even described after coughing or vomiting episodes.[2,3] Trauma directly damages the duct or leads to tissue damage close by, which results in swelling and blockage of the duct with eventual rupture.

Thoracic surgery has now replaced physical injury as the leading cause of trauma with oesophageal surgery having an incidence of 4%.[8] A transhiatal approach rather than a thoracic approach to the surgery increases the risk.[9] Other iatrogenic traumatic causes include thoracic duct damage following subclavian vein catheterisation and duct blockage due to central venous catheterisation related venous thrombosis.[10]

Non-iatrogenic traumatic cases include thoracic duct damage following fracture—dislocation of the spine, childbirth and penetrating trauma from knife or gun shot injuries.[11—13]

Non-traumatic aetiologies include malignancy, sarcoidosis, retrosternal goitre, amyloidosis, superior vena cava thrombosis, benign tumours, congenital duct abnormalities and diseases of the lymph vessels such as yellow nail syndrome, LAM and haemagiomatosis.[2] Thoracic duct obstruction due to malignancy is the commonest cause of non-traumatic chylothorax. Lymphoma is found in 70% of cases (non-Hodgkin's>Hodgkin's).[8] Rarely metastatic tumour can give rise to duct obstruction.[2]

Disease of the lymph vessels is extremely uncommon. Lymphangioleiomyomatosis tends to occur in females of child bearing age where proliferation of the smooth muscle in the lungs, lymph nodes and thoracic duct occurs, with two-thirds of patients experiencing chylothorax.[14,15] In the case of haemagiomatosis (Gorham's disease), vasculature (blood or lymph) within bone proliferates destroying it. Seventeen percent of patients experience life threatening leakage from the lymphatic vessels.[16]

Yellow nail syndrome due to hypoplastic lymphatics, is a rare condition where patients have yellow nails (due to slow growth), lymphoedema, particularly of the lower limbs and pleural effusions (generally non-chylous). The effusions have a high content of protein, lactate dehydrogenase and white blood cells, predominantly lymphocytes.[17] Patients may also have a history of bronchiectasis and sinusitis with defective intestinal lymphatics also described.

Mediastinal lymphadenopathy may compress the lymphatic vessels preventing drainage of lymph from the lung periphery resulting in extravasion of chyle in to the pleural space.[3]

Congenital chylothorax occurs more so due to congenital malformations than trauma during delivery.[18] Chylothorax has also been described as an early and late complication of radiotherapy.[19]

Clinical features of chylothorax

Clinical features of chylothorax depend on the rate of chyle loss as well as the concomitant effect of the aetiology.

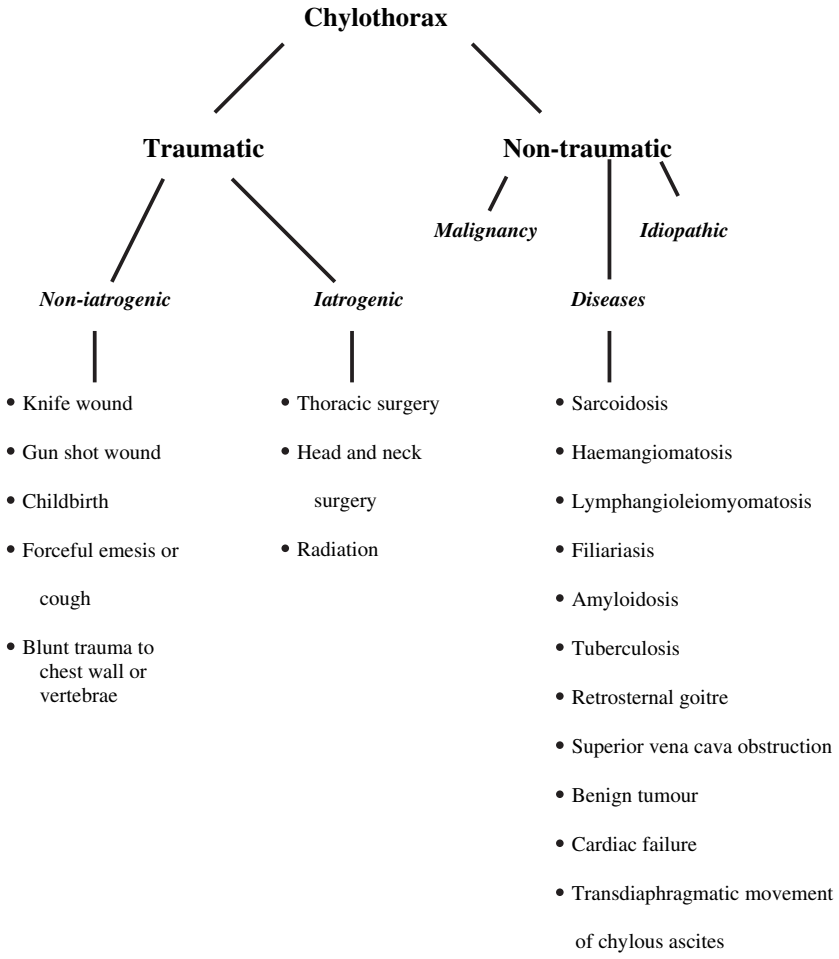

Figure 1 Multiple aetiologies of chylothorax.

Rapid loss is associated with hypovolaemia and respiratory difficulty as the pleural space fills with fluid. Patients may experience malnutrition due to the loss of protein, fats and vitamins. Electrolyte loss can result in hyponatraemia and hypocalcaemia.[20]

Significant loss of immunoglobulins, T lymphocytes and proteins into the pleural space results in immunosuppression.[21,22] This immunosuppression predisposes the patient to opportunistic infections although this almost never occurs in the effusion itself as chyle is bacteriostatic.[23] Drugs such as digoxin and amiodarone may become sub therapeutic as they are lost through the leaking chyle.[3]

Clinically, dyspnoea, chest pain and cough may occur as in any pleural effusion. In certain diseases such as lymphoma, the chylothorax may be the first manifestation of the illness often discovered by an incidental X-ray.

The effusion may be unilateral, either right (50%) or left sided (33.3%), or bilateral (16.66%) and is dependent on the location of the leak. Damage to the duct above the fifth thoracic vertebra results in a left sided effusion whereas damage to the duct below this level leads to a right sided effusion.[24]

In chronic cases where the leak goes unchecked or unnoticed, malnutrition ensues with weight loss and muscle wasting.

The mortality rate from chylothorax has improved considerably from a rate of approximately 50% described in 1948. This is attributed to the more aggressive management plans implemented since then. Currently malignant and bilateral chylothoraces have the worst prognosis.[25]

Investigation

Investigation of suspected chylothorax begins with the confirmation of the diagnosis by fluid analysis, followed by the identification of the leakage point where possible. Investigation should continue until the aetiology is discovered.

Clinical suspicion is important in the diagnostic process. Patients with post operative or post-traumatic effusions should be monitored carefully, particularly those with persistent drainage via a chest drain. The fluid will not always be milky or white and may for example be blood stained after trauma or even serious in appearance if the patient is fasting.

In non-traumatic cases CT abdomen and thorax should be performed given the strong association with malignancy (Fig. 2). This may demonstrate evidence of tumour or lymphadenopathy. Lymphangiography may be used to demonstrate the site of leakage or blockage.[26]

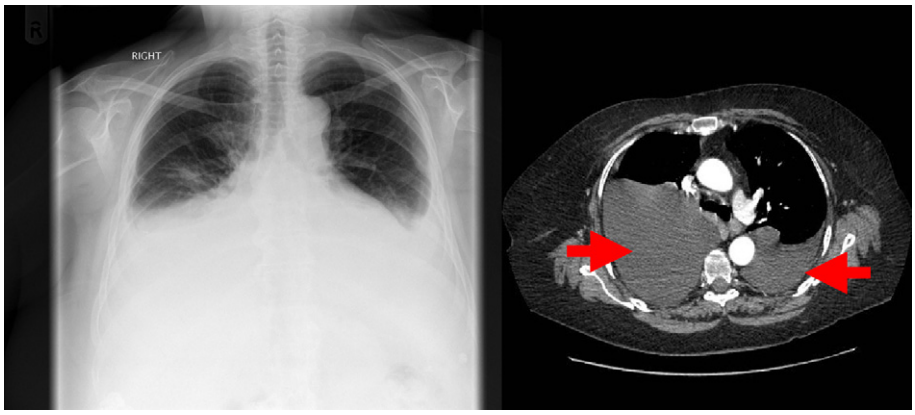

Figure 2 Chest X-ray and CT thorax demonstrating bilateral chylothorax.

High fat content feed mixed with methylene blue can also demonstrate the site of damage at surgery.

The definitive tests come with thoracentesis and laboratory analysis of the pleural fluid. The colour of the fluid can be misleading as only 50% of cases show the classical milky white appearance (Fig. 3) (also seen in pseudochylothorax) while others demonstrate serous, serosanguinous, yellow, green and bloody appearances.[27] Therefore laboratory analysis is necessary to make a diagnosis.

Chylothorax can be differentiated from empyema by performing centrifugation where the fluid remains uniform unlike the clear supernatant that develops in empyema. Chylothorax can be differentiated from pseudochylothorax by adding 1—2 ml of ethylether. The milky appearance disappears in pseudochylothorax.[28]

The exact diagnosis of chylothorax is based on the presence of chylomicrons in the pleural fluid. Chylomicrons are molecular complexes of proteins and lipids that are synthesised in the jejunum and transported via the thoracic duct to the circulation. They are only found in the circulation postprandially with a peak 3 h after eating.[28] On occasion chylomicrons have been demonstrated in haemothorax directly after a meal but repeated thoracentesis sampling over hours will help demonstrate a true chylothorax.[28]

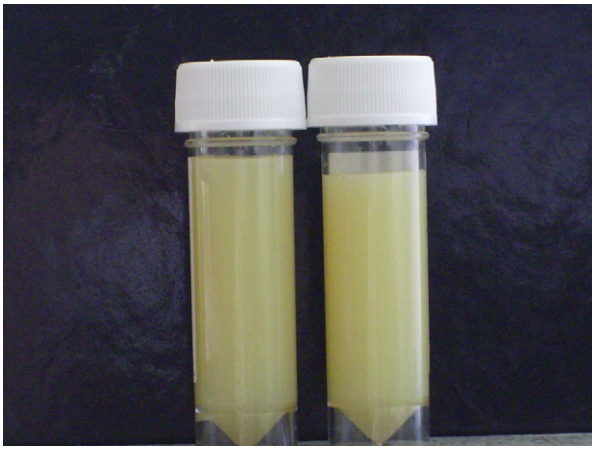

Figure 3 Chylous pleural fluid.

Cytological analysis of fluid stained with Sudan III will demonstrate chylomicrons, which although sensitive, is not specific and therefore should be combined with complementary fluid analysis. In centres with available facilities, lipoprotein analysis demonstrating chylomicrons is the gold standard. Where this facility is not available, institutions rely on the measurement of fluid cholesterol and triglyceride levels. Staats et al. introduced criteria for the biochemical diagnosis of chylothorax in 1980.[29] They noted that a pleural fluid triglyceride of $>$110 mg/dl had a 1% chance of being non-chylous and that a triglyceride of $<$50 mg/dl had a 5% chance of being chylous.[29] As a result, pleural fluid triglyceride levels $>$1.24 mmol/l (110 mg/dl) with a cholesterol $<$5.18 mmol/l (200 mg/dl) is diagnostic of chylothorax.

A triglyceride level $<$0.56 mmol/l (50 mg/dl) with a cholesterol $>$5.18 mmol/l (200 mg/dl) is found in pseudochylothorax. Cholesterol crystals are also often seen in this condition (Table 1).

However the results must be interpreted in conjunction with the clinical scenario as was demonstrated recently by Maldonado et al. Their retrospective analysis of 74 patients with chylomicron positive pleural fluid demonstrated that 14% of the chylous effusions had triglyceride levels less than 110 mg/dl. Four of the effusions occurred after surgery, three after central venous line placement complications and one was in a patient with pancreatic cancer. The low triglyceride level in all these cases was attributed to fasting preoperatively or malnutrition and therefore care should be taken in relying solely on the fluid criteria for diagnosis in these types of patients.[30]

Pseudochylothorax develops when an exudative effusion remains in the pleural space for a long period of time (often years) gradually becoming enriched with cholesterol. The most common aetiologies include tuberculous pleurisy, chronic pneumothorax, rheumatoid pleurisy, poorly evacuated empyema and chronic haemothorax.

In cases where the triglyceride level is above the criteria set for pseudochylothorax but below those for chylothorax (0.56—1.24 mmol/l or 55—110 mg/dl), lipoprotein analysis is required to confirm or exclude a diagnosis of chylothorax.

A fluid to serum cholesterol ratio $<$1 and triglyceride ratio $>$1 are also found in chylothorax.[3]

Pleural fluid should also be analysed for protein and LDH. The protein content in chyle is in the region of 2—3 g/dl

Table 1 Pleural fluid criteria for the diagnosis of chylothorax and pseudochylothorax.

	Triglyceride	Cholesterol	Chylomicrons	Cholesterol crystals
Chylothorax	> 1.24 mmol/l (110 mg/dl)	<5.18 mmol/l (200 mg/dl)	Present	Not seen
Pseudo-chylothorax	< 0.56 mmol/l (50 mg/dl)	>5.18 mmol/l (200 mg/dl)	Absent	Often seen

giving a projected effusion protein level in the transudate range.[31] Agrawal et al. postulate that there is resorption of water and some solute from the chylous effusion that renders it, typically, exudative.[32] Nonetheless transudative chylothoraces have been described and reviewed by Diaz-Guzman et al. They found that cirrhosis and nephrotic syndrome were the commonest causes of the 15 transudate cases they described.[33] Cirrhosis related chylothorax results from ascites induced raised intra-abdominal pressure leading to functional obstruction of the thoracic duct.[30]

Other well described causes of transudative chylous effusion include mantle radiotherapy for Hodgkin's disease, cardiac failure and constrictive pericarditis.[32]

Maldonado et al.'s previously described retrospective study also analysed pleural fluid protein and found that pleural effusion were exudative in 86% of cases and transudative in 14%.[30] The transudative chylothoraces were found in patients with cirrhosis, lymphoproliferative disorder, surgery, pancreatic cancer, radiation injury and in patients with no identifiable cause (idiopathic).[30]

The LDH level in chyle is quite low relative to total protein and Agarawal et al. have speculated that this is due to the relatively decreased filtration of the larger LDH molecule out of the capillary compared to the smaller plasma protein.[32] Chylothoraces with high LDH levels should provoke consideration of an additional diagnosis such as cirrhosis.[32]

On the same theme, Agarawal et al. retrospectively analysed the pleural fluid of 876 consecutive thoracenteses. Twenty-two of these had chylomicrons or a triglyceride concentration >110 mg/dl. They then classified the effusions as transudate, concordant exudate, protein discordant exudate (where protein is in exudative range but LDH is not), LDH-discordant exudate (where LDH is in exudative range but protein is not) and lymphocyte predominant (>50% lymphocytes).[32] Eleven effusions were lymphocyte predominant-protein discordant exudates and all were attributed solely to chyle leakage. Seven were transudates and 4 were concordant exudates; all of which were associated with conditions that were known to cause pleural effusion apart from chyle leakage.[32] Agrawal et al. concluded that chylous effusions caused solely by conditions known to cause chylothorax were lymphocyte predominant-protein discordant exudates. Protein concentrations in the transudative range or elevated LDH concentrations were associated with a co-existing condition that may impact on the management of the chylothorax.[32] They proposed that effusions that fail to meet the lymphocyte predominant-discordant exudate classification should be considered for additional effusion related pathologies and investigated and treated appropriately.[32]

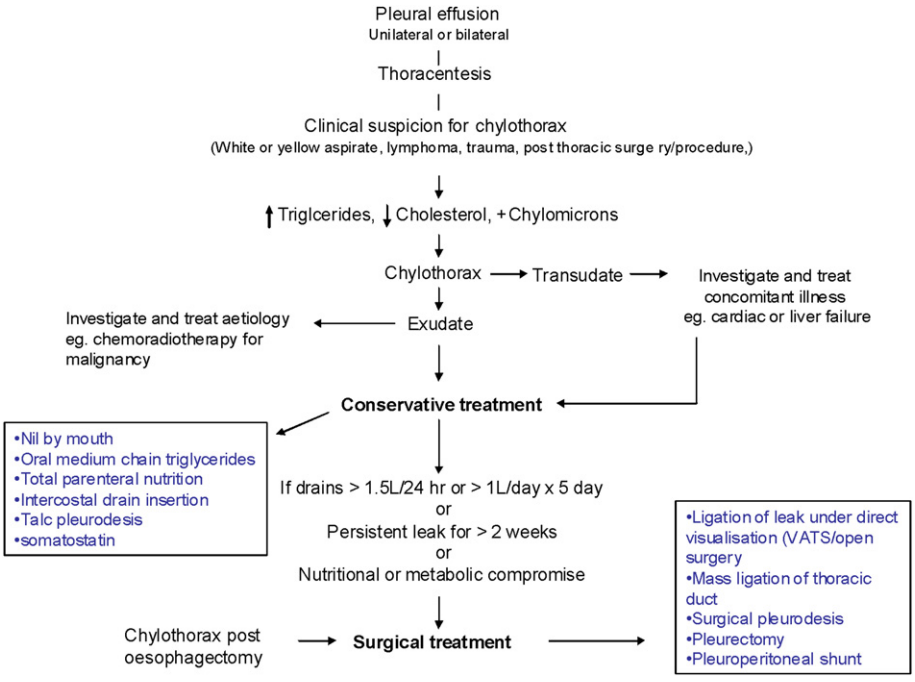

Figure 4 Recommended treatment pathway for chylothorax.

In these cases the proportional contribution of the chyle leak to the overall effusion is difficult to determine until the other conditions are treated.

Treatment

Treatment can be classified under 3 categories[1] treatment of the underlying condition,[2] conservative management and[3] surgical management[2] (Fig. 4).

Treatment of the underlying condition, for example treating sarcoidosis with steroids[34] or cardiac failure with diuretics, can have important benefits for the patient overall as well as leading to an improvement in the chylothorax and in some cases to its resolution. On the other hand treatment of the underlying condition may lead to improvement in the disease burden (e.g. lymphoma) without necessarily improving the chylothorax.[35]

Conservative treatment initially involves replacing the nutrients lost in the chyle and draining large chylothoraces using chest drain insertion if necessary, to ensure complete lung expansion. Nil by mouth or the administration of low fat medium chain triglycerides by mouth resolves approximately 50% of congenital or traumatic chylothoraces.[36] Medium chain triglycerides are directly absorbed in to the portal system, bypassing the intestinal lymph system. This reduces the flow of chyle in the thoracic duct allowing it the opportunity to heal.[28] If the chyle leak does not stop following the use of medium chain triglycerides, then total parenteral feeding to reduce the chyle flow even further should be considered.[28,36] Monitoring of serum electrolytes, lymphocyte count, albumin and total protein as well as weight is recommended.[28]

Somatostatin and octreotide have proved to be useful in the conservative treatment of chylothorax. These agents reduce intestinal chyle production, thereby reducing the volume flowing through the injured thoracic duct.[37–39]

In malignancy where radiotherapy or chemotherapy have not led to improvement in the chylothorax, chemical pleurodesis is an alternative option in the majority of patients that are too unwell for surgical closure of the chyle leak.[40] Mares et al. demonstrated that medical thoracoscopic talc pleurodesis was a safe and 100% effective method of palliation in lymphoma related chylothorax refractory to chemotherapy or radiotherapy in their series of 19 patients.[41] Other pleurodesis agents including tetracycline, bleomycin, povidone and elemene have been successfully used.[3,42,43]

A cannulation and embolisation technique used by Cope et al. prospectively to treat chylothorax was curative in patients with demonstratable duct leakage.[44] However reproducibility and success have varied in different centres. More recently Boffa et al. have used the technique of thoracic duct embolisation or disruption with very good effect in patients with chyle leak post thoracic surgery[45] and Litherland et al. described a case report where CT guided disruption of the lymphatics had good effect in the management of high output chylothorax.[46]

Matsumoto et al. performed lymphangiography on 9 patients that were unlikely to respond to conservative measures. They found that lymphangiography not only identified the site of the leak but led to the leak resolving in all cases. They recommend early lymphangiography in cases unlikely to be cured by conservative methods only.[47]

Surgical therapy is recommended in cases where despite conservative management the patient drains more than 1.5 l/day in an adult or >100 ml/kg body weight per day in a child,[48] leaks chyle at a rate of >1 l/day× 5 days[49] or has persistent chyle flow for more than 2 weeks.[50]

Surgery is also recommended if there has been a rapid decline in nutritional status despite conservative management.[3]

In certain situations urgent surgical intervention is advocated by a number of groups when the duct has been damaged as a complication of surgery, reducing the risk of electrolyte disturbance, malnutrition and immunological deficiency.[51,52] In particular, chylothorax post oesophageal surgery treated with surgical intervention is associated with a mortality of 10% compared to a mortality of 50% in conservatively managed cases.[9,53]

Cerfolio et al. recommend ligation or pleurodesis if the thoracic duct is suspected to be damaged during surgery.[54] Dougenis et al. recommend prophylactic thoracic duct ligation in all cases of extensive oesophageal resection. In their series of 255 patients, elective ligation of the thoracic duct reduced the incidence of chylothorax from 9% to 2.1%.[55]

Thoracic duct ligation can be performed during thoracotomy or by thoracoscopic intervention.[56,57] The main problem is identifying the chyle leak.

Ligation of the thoracic duct is successful in 90% of patients when performed just above the right hemi-diaphragm.[58] Ligating here, also has the advantage of halting flow from any unidentified accessory ducts.[59,60] Collateral circulation redirects the chyle around the ligation point ensuring that the chyle still completes its journey to the circulation. If the leak is in the region of the neck or upper thorax, the thoracic duct is ligated in the area known as Poirier's triangle between the arch of the aorta, internal carotid and vertebral column.[31]

In thoracoscopic ligation, thoracoscopy is performed after enteral feeding of approximately 50 ml of cream. Up to 3 ports are inserted strategically between different ribs and the thoracic duct is sought. A short segment of the duct is excised before clipping the remaining ends.[3]

If the leak is not identifiable in either thoracoscopy or thoracotomy, then mass ligation of all the tissue between aorta, spine, oesophagus and pericardium is performed.[3] Extensive dissection to find the duct is discouraged reducing the risk of further trauma and leak.

Pleurectomy or pleurodesis with talc or glue is an alternative and effective option in cases where the thoracic duct is unidentifiable.[61] In cases of loculated or complicated chylothorax pleural decortication with pleurodesis may be performed.[3]

In patients that are too unfit for major surgery or have malignancy, a pleuroperitoneal shunt may be useful. This is a subcutaneous or external unidirectional communication between the pleura and the peritoneum that is connected to a pump, activated by light pressure. It minimises the nutritional or immunological deficits seen in chylothorax. In cases where the chyle leak ceases, the shunt can be removed.[58]

Conclusion

Chylothorax is a rare condition with multiple aetiologies. Pleural fluid analysis can identify this condition when clinical suspicion exists. Conservative management is generally recommended in most non-iatrogenic cases with surgery being reserved for those that have a large or persistent leak or in those who become immunologically challenged or malnourished. Given the wide variety of treatment options and opinions, future randomised control trials would greatly assist with the evaluation of conservative and surgical management assisting with the development of treatment guidelines.

Conflict of interest

We have no financial or conflict of interest.

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