



Non-traumatic chylothorax: diagnostic and therapeutic strategies

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Non-traumatic chylothorax is associated with a myriad of medical disorders. Lipid analysis of pleural fluid is required to confirm the diagnosis. A multidisciplinary approach is recommended for the effective management of non-traumatic chylothorax. <https://bit.ly/3Nssb7n>

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Abstract

Non-traumatic chylothorax refers to accumulation of chyle in the pleural space in the absence of any traumatic disruption to the thoracic duct. Chyle originates from the intestines and is transported *via* the thoracic duct into systemic circulation. The anatomical course of the thoracic duct is complex with considerable variation; therefore, development of chylothorax is dependent on the site and level of the thoracic duct defect. Non-traumatic chylothorax is associated with a wide range of medical disorders, but malignancy accounts for three-quarters of cases. In up to 9% of cases, the aetiology remains unknown (termed idiopathic chylothorax). Gross appearance of pleural fluid is neither sensitive nor specific enough to diagnose chylothorax; therefore, biochemical analysis of the pleural fluid is required. Pleural fluid triglyceride level $>1.24 \text{ mmol}\cdot\text{L}^{-1}$ ($110 \text{ mg}\cdot\text{dL}^{-1}$) with a cholesterol level $<5.18 \text{ mmol}\cdot\text{L}^{-1}$ ($200 \text{ mg}\cdot\text{dL}^{-1}$) is diagnostic of chylothorax. In borderline cases, lipoprotein electrophoresis can help confirm the diagnosis by detecting chylomicrons in the pleural fluid.

Once the diagnosis of chylothorax is confirmed, the next step is to find the cause and identify the leakage point, for which various lymphatic specific radiological investigations may have an important role. There is paucity of data on the most suitable approach to manage non-traumatic chylothoraces and treatment often depends on the underlying cause. In general, conservative treatment is tried first, usually for a limited time, before considering more invasive measures. A multidisciplinary approach is recommended with close liaison among the respiratory physicians, thoracic surgeons, oncologists, interventional radiologists, dietitians and pharmacists.

Educational aims

- To review the pathophysiology, aetiology, and epidemiology of non-traumatic chylothorax.
- To discuss diagnostic and therapeutic strategies in the management of non-traumatic chylothorax.

Introduction

Non-traumatic chylothorax is defined as the pathological accumulation of chyle in the pleural space in the absence of trauma or injury to the thoracic duct (TD). Chyle is composed of lymph and chylomicrons absorbed from the intestinal system.

A wide array of medical disorders may be associated with the development of non-traumatic chylothorax; which compared with traumatic cases, makes its diagnosis and treatment more difficult. This review focuses on non-traumatic chylothorax, discussing its causes, pathophysiology, investigations and treatment strategies.



Chyle formation

Chyle originates from the intestines. It is composed of lipids, electrolytes, proteins, and lymphocytes (primarily T-lymphocytes) [1]. Humans require dietary triglycerides, which are triesters consisting of glycerol bound to three fatty acid molecules and are a major constituent of human body fat. Triglycerides are classified as small-, medium- or long-chained, dependant on the length of the fatty acid ester compounds.

Small- and medium-chained triglycerides are broken down into free fatty acids by the intestinal lipases and then absorbed into the portal circulation. The long-chain triglycerides combine with phospholipids, cholesterol and cholesterol esters to form chylomicrons within enterocytes in the jejunum. Chylomicrons are taken up by small lymphatic channels, lacteals within villi that line the small intestine. These lacteals coalesce to form larger lymphatic vessels that transport the chyle into the bloodstream *via* the TD at the subclavian vein. Figure 1 illustrates diffusion of triglycerides into the lacteal.

Anatomy of the thoracic duct

Lymphatic vessels originating from the intestine coalesce into the cisterna chyli, a lymphatic sac located anterior to the second lumbar vertebra and posterolateral to the abdominal aorta, which gives origin to TD that is ~36–45 cm long and 2–3 mm wide [2, 3].

The TD, after its origin from the upper end of cisterna chyli, runs along the right side of hemithorax between the aorta and the azygous vein at the level of the diaphragm. It then passes along the distal oesophagus, on the right side, but at the level of the fifth or sixth vertebra it crosses the midline to follow its course on the left. The TD exits the thoracic cavity through the superior thoracic aperture to form an arch at the level of seventh cervical vertebra. It then turns downwards and laterally before terminating at the junction of the left subclavian and internal jugular veins (figure 2) [2].

Nearly 2.4 L of chyle is transported from the intestines to the systemic circulation each day. Therefore, any damage to, or rupture or dysfunction of, the TD can manifest as chylothorax due excessive accumulation of fluid in the pleural space [4].

Although there are significant variations in the anatomy of the TD, its course explains the preferential development of unilateral chylous effusion (right or left sided) based on the level of the TD disruption [1]. Chylothoraces are unilateral in 83.3% (50% right sided, 33.3% left sided) and bilateral in 16.66% of cases [4, 5].

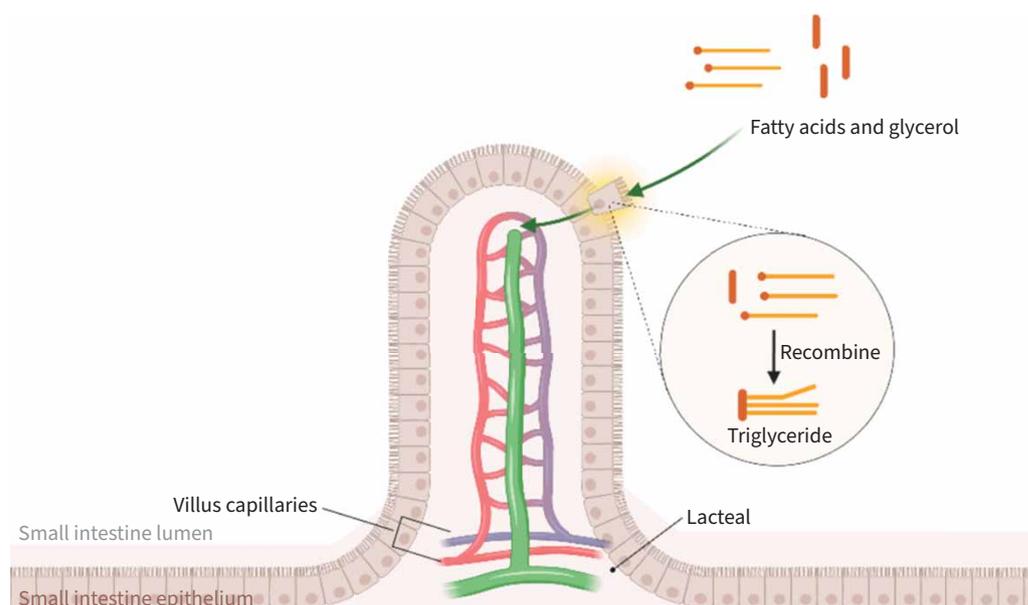


FIGURE 1 Diffusion of triglycerides into lacteals. Fatty acids and glycerol molecules diffuse into the intestinal cells. Once in the cell, fatty acids and glycerol molecules can recombine into triglycerides and then diffuse into the lacteal. Adapted from “*Absorption of Nutrients in the Small Intestine*”, by BioRender.com (2021). Retrieved from <https://app.biorender.com/biorender-templates>.

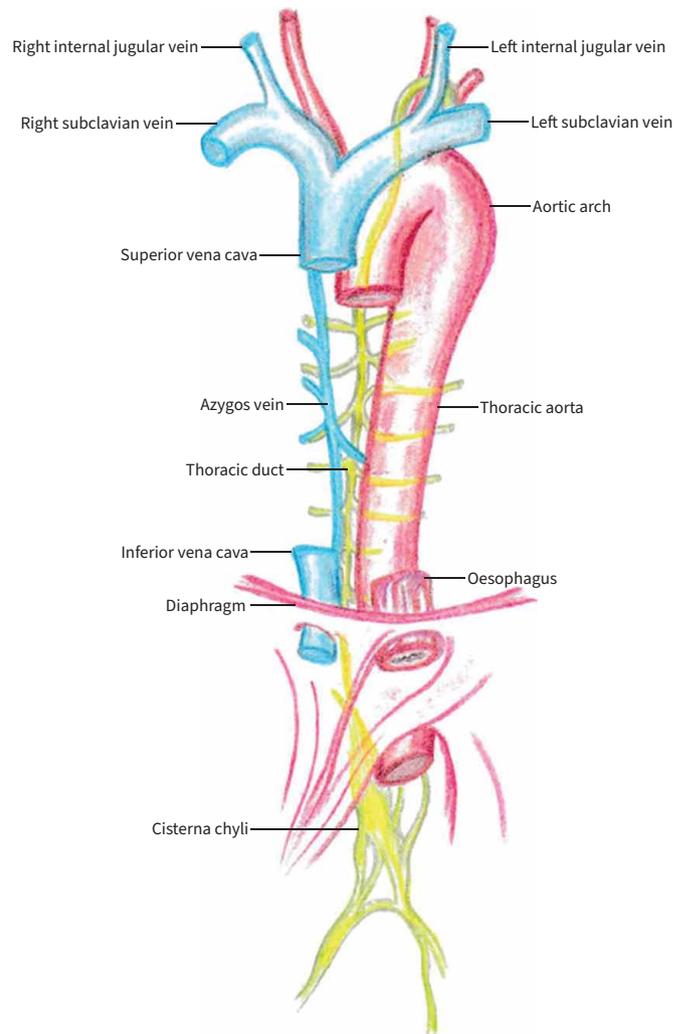


FIGURE 2 Anatomical course of the thoracic duct.

Epidemiology and aetiology

Chylothorax, traumatic or non-traumatic, is a rare condition accounting for up to 3% of cases of all pleural effusions [6], with traumatic cases outnumbering all non-traumatic aetiologies combined. Amongst traumatic cases, the leading cause is iatrogenic, because of damage to the TD during thoracic operations especially oesophageal surgery [7]. Incidence of iatrogenic chylothorax in oesophageal resections can be up to 4% owing to close association of the TD to the oesophagus and its inconsistent course [3].

The causes of non-traumatic chylothorax are outlined in table 1 [1–10].

The commonest cause of a non-traumatic chylothorax is malignancy, accounting for almost a third of all cases. Lymphoma is responsible for 70–75% of cases of malignant chylothorax, with non-Hodgkin lymphoma being the most prevalent cause [2–4]. Metastatic epithelial tumours may also cause chylothorax, but this is relatively rare. Other causes of non-traumatic chylothorax, combined, constitute nearly one-fifth of all cases [2].

Primary lymphatic disorders including lymphangiectasia syndromes are relatively rare. Lymphangioliomyomatosis (LAM), characterised by the pathological proliferation of smooth-muscle cells, typically affects women of childbearing age. Chylothorax may affect up to 40% of LAM patients in their lifetime [2]. Yellow nail syndrome, also a form of lymphangiectasia, can present with chylothorax; however, more often the effusion is non-chylous. Other features of this syndrome are slow-growing brittle nails and lymphoedema especially of the lower extremities [2, 11, 12]. Gorham's disease, a rare form of congenital haemangiomas, can also be associated with development of chylothorax [3].

TABLE 1 Causes of non-traumatic chylothorax

	Diseases
Malignancy	Lymphoma, Kaposi sarcoma, thyroid cancer, oesophageal cancer
Congenital duct abnormalities and diseases of the lymph vessels	Congenital thoracic duct absence or atresia, yellow nail syndrome, lymphangiomyomatosis (LAM), congenital haemangiomas (e.g. Gorham's disease)
Infections	Tuberculosis, histoplasmosis, filariasis
Systemic disorders	Systemic lupus erythematosus, Behçet's disease, sarcoidosis, amyloidosis
Miscellaneous	Cirrhosis, congestive heart failure, superior vena cava thrombosis, mediastinal lymph node enlargement, retrosternal goitre
Idiopathic	Up to 9% of non-traumatic chylothorax

Rarely, chylothorax may develop in the setting of transudative pleural effusions with common causes being congestive heart failure, cirrhosis with chylous ascites, and nephrotic syndrome [2, 13, 14]. Lastly, in 9% of cases, the cause remains unknown, termed as idiopathic non-traumatic chylothorax [7].

Pathophysiology of chylothorax

Mechanisms implicated in the development of non-traumatic chylothorax include direct malignant disruption of the TD, transdiaphragmatic flow of chylous ascites into the pleural space, raised hydrostatic pressure and hyperpermeability of the lymphatic system [6].

Both in malignancy and primary lymphatic disorders, chyle leak may occur in the retroperitoneum but due to negative intrathoracic pressure, the chyle flows upstream into the pleural space through small transdiaphragmatic defects [9]. In LAM complicated with chylothorax, lymphangiographic studies may reveal chyle leak at multiple levels and in variable locations [2, 10, 15].

In decompensated liver cirrhosis, in addition to transdiaphragmatic flow of chylous ascites from the peritoneum into the thorax through small defects, ascites may also cause functional obstruction of the TD due to raised intra-abdominal pressure [4, 13]. In heart failure, it is postulated that raised venous pressure, secondary to increased capillary filtration, results in an increase in TD flow (up to 12-fold the normal rate), but the stiffness of the veno-lymphatic junction in the neck limits lymphatic flow. Additionally, lymphatic venous collaterals are formed due to restricted lymphatic drainage caused by increased pressure in the left subclavian vein. These collaterals may not handle the normal lymph flow leading to chyle leakage into the peritoneal or pleural cavity [16].

Clinical features of non-traumatic chylothorax

There may be significant variability in the clinical presentation of non-traumatic chylothorax since its causes are many and the rate of accumulation of chyle in the pleural space can also vary. It may remain asymptomatic, especially at the initial stage when the volume of chylothorax is low. Nevertheless, the most common symptoms are breathlessness and cough [2]. This mostly occurs insidiously in non-traumatic chylothorax due to sluggish accumulation of chyle in the pleural space as opposed to traumatic cases. Chest pain and fever are rare owing to the noninflammatory composition of chylous fluid [2, 8]. Cases of malignant chylothorax may also present with other features of underlying malignancy, such as weight loss, night sweats and asthenia.

Investigating non-traumatic chylothorax

Investigations for non-traumatic chylothorax can broadly be divided into two categories.

- 1) Investigations that are required to confirm the diagnosis of chylothorax. This always requires analysis of the pleural fluid. A suggested diagnostic algorithm for chylothorax is illustrated in figure 3.
- 2) Investigations that are performed to identify the underlying cause, e.g. malignancy, and locate site(s) of the TD leak.

Pleural fluid analysis

Macroscopic appearance

The gross appearance of the fluid is neither sensitive nor specific enough to diagnose a chylothorax. Less than half of chylous pleural effusions have the characteristic milky appearance (figure 4), while the others demonstrate different appearances such as serous, serosanguinous, yellow, green, and heavily blood

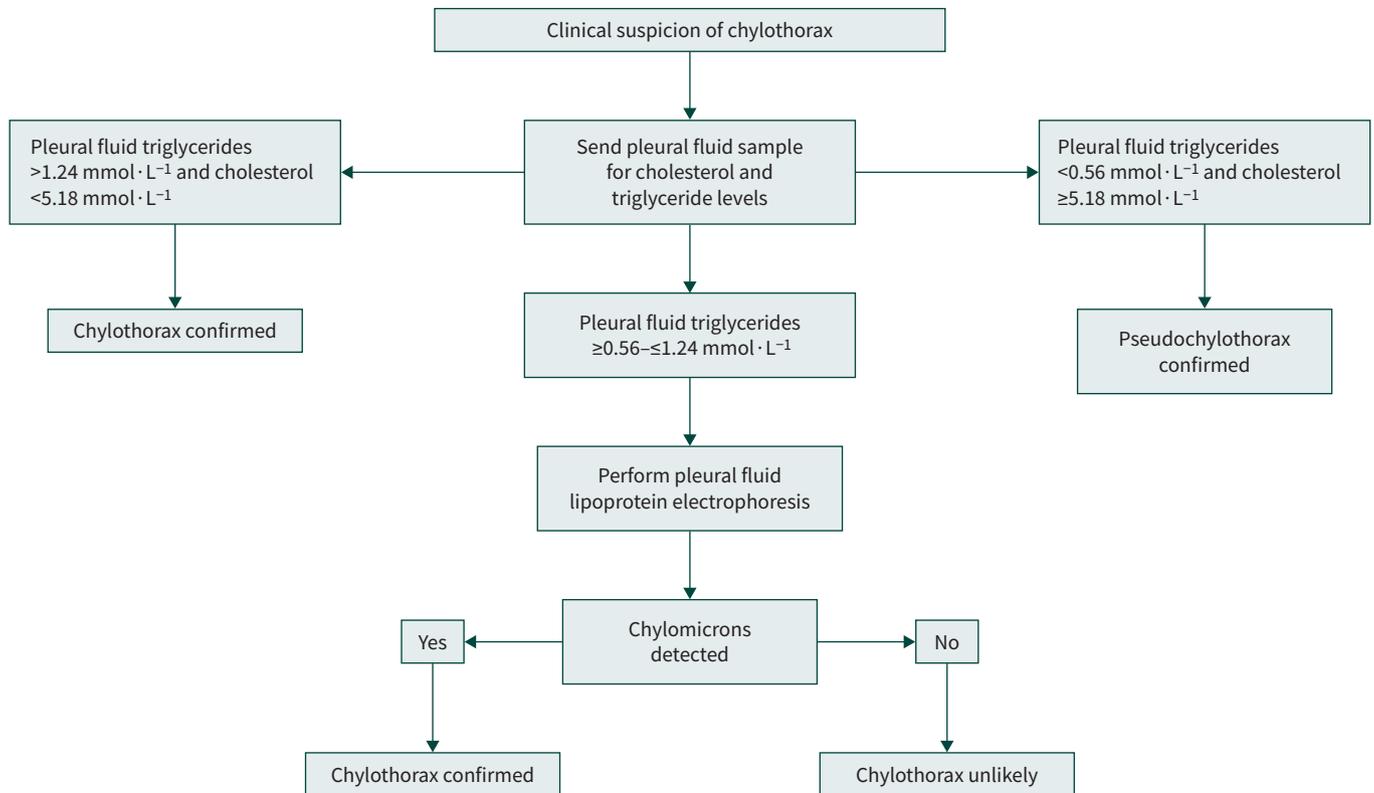


FIGURE 3 Diagnostic algorithm of chylothorax.

stained [4, 17]. The exact mechanism of this heterogeneity in colour of chylous effusions is unknown, but it is plausible that it is related to underlying disorders or the nutritional status of the patient with variable lipid ingestion, *i.e.* less triglyceride intake leads to a less turbid effusion [2].

The milky appearance of fluid is not an exclusive phenomenon in chylothorax, as similar appearances may also be observed in conditions such as pseudochylothorax, pleural infection, and displacement of a central venous line with lipid accumulation [2].

Pseudochylothorax, an important differential diagnosis with milky appearance, results from persistence of exudative pleural effusion for a long time which slowly becomes enriched with cholesterol, hence it is also termed cholesterol effusion. Tuberculous effusion, chronic pneumothorax, rheumatoid effusion, chronic haemothorax and poorly drained empyema are among the common causes of pseudochylothorax or cholesterol effusion [4].

In the past, the ether clearance test was used to distinguish pseudochyle from chyle. The addition of 1–2 mL of ethyl ether will dissolve the lipid component of a chylothorax, clearing its milky appearance, whereas the appearance of pseudochyle will remain unchanged [18]. However, given the variability in the macroscopic appearances of chyle, it is no longer considered a reliable test for chylous effusions.

Centrifugation may help in differentiating chylothorax from empyema as, unlike chylothorax, a clear supernatant develops in empyema [18]. The milky appearance of pleural fluid in empyema is due to suspended leukocytes and debris, which clears following centrifugation.

Sudan III or IV stain may be used to demonstrate the presence of chylomicrons in pleural fluid, but this test is not specific enough to reach a definitive diagnosis of chylothorax alone [18].

Lipid analysis

Measurement of pleural fluid cholesterol and triglyceride levels is often used as a first-line investigation to diagnose chylothorax. Pleural fluid triglyceride levels $>1.24 \text{ mmol}\cdot\text{L}^{-1}$ ($>110 \text{ mg}\cdot\text{dL}^{-1}$) with a cholesterol

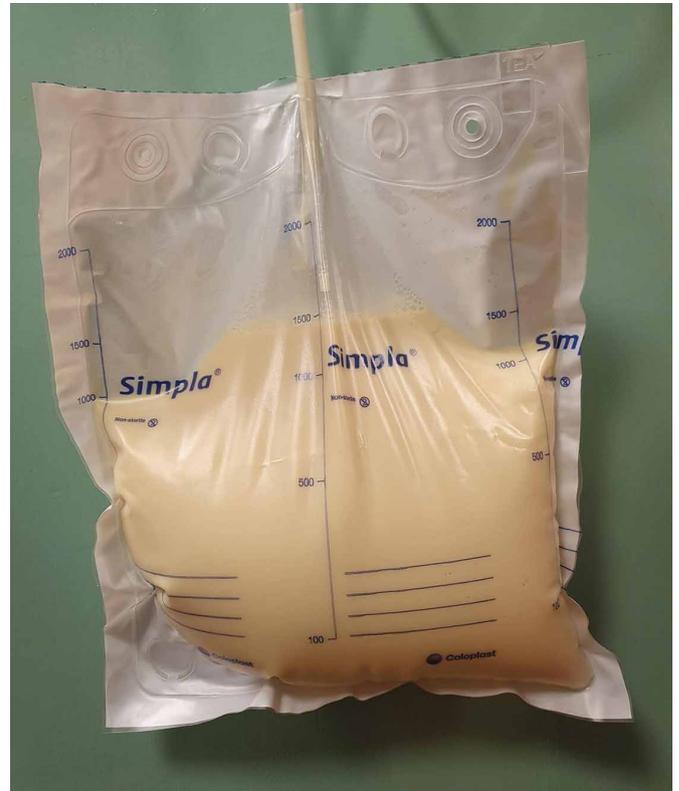


FIGURE 4 Milky appearance of pleural fluid in a patient with chylothorax.

level $<5.18 \text{ mmol}\cdot\text{L}^{-1}$ ($<200 \text{ mg}\cdot\text{dL}^{-1}$) is diagnostic of chylothorax, based on biochemical criteria proposed by STAATS *et al.* [19]. They reported that a pleural fluid triglyceride of $>1.24 \text{ mmol}\cdot\text{L}^{-1}$ ($>110 \text{ mg}\cdot\text{dL}^{-1}$) had a 1% chance of being non-chylous and that a triglyceride of $<0.56 \text{ mmol}\cdot\text{L}^{-1}$ ($<50 \text{ mg}\cdot\text{dL}^{-1}$) had a 5% chance of being chylous [18, 19].

Nutritional status is directly linked with pleural fluid triglyceride levels, which can make the diagnosis of chylothorax difficult in certain clinical situations, particularly if the fluid triglyceride level is used in isolation. MALDONADO *et al.* [13] demonstrated, in a retrospective study of 74 confirmed cases of chylothorax (chylomicron positive pleural effusion), that 14% of the chylous effusions had triglyceride levels less than the proposed diagnostic limit, *i.e.* $1.24 \text{ mmol}\cdot\text{L}^{-1}$ ($110 \text{ mg}\cdot\text{dL}^{-1}$). Subgroup analysis demonstrated that the low triglyceride level was secondary to poor nutrition status [13].

Despite the similar gross appearance of pleural fluid in both chylothorax and pseudochylothorax, biochemically they are very different. A triglyceride level $<0.56 \text{ mmol}\cdot\text{L}^{-1}$ ($<50 \text{ mg}\cdot\text{dL}^{-1}$) with a cholesterol level $>5.18 \text{ mmol}\cdot\text{L}^{-1}$ ($>200 \text{ mg}\cdot\text{dL}^{-1}$) is found in pseudochylothorax [3]. If there remains difficulty in distinguishing between pseudochylothorax and chylothorax, a fluid to serum cholesterol ratio <1 and triglyceride ratio >1 is found in chylothorax [3] and may be helpful in clinching the diagnosis in these cases.

Lipoprotein electrophoresis

The definitive diagnosis of chylothorax is based on demonstration of chylomicrons in pleural fluid [9]. This requires pleural fluid analysis by lipoprotein electrophoresis. Chylomicrons are found in the circulation postprandially reaching their peak concentration 3 h after a meal. Haemothorax occurring after a postprandial trauma can sometimes show presence of chylomicrons, but repeated thoracentesis may help differentiating such cases from a true chylothorax [18].

Lipoprotein electrophoresis of pleural fluid is an expensive test, and it is also not readily available; therefore, we recommend its use only when it is not possible to reliably diagnose or exclude chylothorax

on biochemical criteria, such as cases with an intermediate range of pleural fluid triglycerides levels, *i.e.* ≥ 0.56 – ≤ 1.24 mmol·L⁻¹ [20].

Lactate dehydrogenase and protein

We recommend analysing pleural fluid for protein and lactate dehydrogenase (LDH). Despite the low protein concentration of chyle (range: 2–3 g·dL⁻¹), most chylous effusions become protein-discordant exudates (where protein is in the exudative range, but LDH is not) owing to greater fluid/solute reabsorption from the pleural cavity into the intravascular space with resultant higher pleural fluid protein concentration [2, 13, 14, 20].

In chylothorax, protein concentration is comparatively higher than LDH concentration. AGRAWAL *et al.* [14] proposed that this is due to greater filtration of smaller sized plasma proteins than large sized LDH molecules [4, 14]. Therefore, a high concentration of LDH in a chylous effusion is an atypical feature needing work-up for an alternative diagnosis or an additional process such as infection [2].

Transudative pleural effusions are less common in the setting of chylothorax. A retrospective study by MALDONADO *et al.* [13], which involved analysis of biochemical characteristics of chylothorax reported that pleural effusion was exudative in 86% of cases and transudative in 14% [4, 13].

Investigating the cause

Once the diagnosis of chylothorax is confirmed, the next step is to find the cause and identify the cause of the leak where possible.

Chest radiography

Chest radiography is an initial investigation which can confirm the presence of pleural effusion, but its role is very limited in differentiating chylothorax from other causes of pleural effusion [7]. It is, nevertheless, a useful initial screening tool for lung malignancy, gross hilar lymphadenopathy or chest wall trauma, *etc.*

Thoracic ultrasonography

Thoracic ultrasonography, due to its high sensitivity, has an important role in confirming presence of pleural fluid in the pleural space, but like chest radiography it may not differentiate chylothorax from the rest of the causes of pleural effusion [7].

Computed tomography

In appropriate settings, computed tomography (CT) scanning of the thorax and abdomen should be performed, given the strong association of non-traumatic chylothorax with malignancy. Although a CT scan, with or without contrast, cannot reliably study the lymphatic circulation, it can identify lymphadenopathy or solid tumours, thus narrowing down the differential diagnoses in the setting of chylothorax [6, 7].

Lymphatic specific investigations

In treatment-resistant cases or where no obvious cause is identified, lymphatic imaging may help guide management. These investigations allow study of the lymphatic system in detail to identify any focal or diffuse lymphatic vascular anomalies. Despite the nonspecific nature of findings in most cases of diffuse lymphatic disease, they can help in the diagnosis and/or guide therapeutic management [6, 7].

CT lymphangiography

CT lymphangiography, performed by CT-guided access of the cisterna chyli and direct administration of water-soluble contrast media, can demonstrate the TD anatomy [6] to identify site(s) of chyle leak. Thoracic high-resolution CT constructed from CT lymphangiography can also detect lung parenchymal abnormalities (*e.g.* LAM) [21].

Nuclear medicine studies

In those cases where CT is unable to identify a cause or site of chyle leak, nuclear medicine studies such as lymphoscintigraphy and single photon emission computed tomography (SPECT) may help, with SPECT the superior modality. Functional assessment provides valuable data on lymphatic flow and is therefore helpful in identifying primary lymphatic disorders [6]. However, access to these imaging techniques may be limited.

Magnetic resonance imaging

Use of magnetic resonance (MR) imaging, especially MR lymphangiography, may also be employed in suitable cases of non-traumatic chylothorax. Based on the technique used, MR lymphangiography can be divided into two subtypes [6] as follows.

- 1) Non-enhanced MR lymphangiography: this is a noninvasive study, performed without intravenous contrast, which can study lymphatic flow and is particularly useful in diagnosing primary lymphatic disorders. However, it does not offer much information about the site of lymphatic leak.
- 2) Dynamic contrast-enhanced MR lymphangiography: this invasive study requires intranodal administration of a contrast medium such as gadolinium after accessing the inguinal lymph node and acquisition of T1-weighted images. Whilst invasive, it can be used to identify the sites of lymphatic leak.

Conventional lymphangiography

This is the gold standard investigation in the study of the lymphatic system and hence in identification of lymphatic defects or anomalies [6, 7]. Conventional lymphangiography may also carry therapeutic value in some cases of chylothorax [6], especially where the TD defect is focal and/or identifiable. However, given its invasive nature, limited availability, and the risks of exposure to ionising radiation [6, 7], appropriate patient selection is important where conventional lymphangiography has potential to offer diagnostic and/or therapeutic benefit.

Treatment

Treatment strategies for non-traumatic chylothorax may vary and it is more difficult to treat than traumatic chylothorax due to its association with a wide range of medical conditions. Prospective data on the most suitable approach to manage this condition are lacking [1]. In general, conservative treatment is tried first, usually for a limited time, before more invasive measures are considered based on type/site of the chyle leak, local expertise, the patient's performance status and the underlying cause.

A multidisciplinary approach is recommended with close liaison among the respiratory physicians, oncologists, thoracic surgeons, interventional radiologists, dietitians and pharmacists.

Treatment of the underlying condition

For the definitive treatment of non-traumatic chylothorax, it is usually proposed to treat the underlying cause, but this strategy may not always be successful, and its usefulness is often related to the nature and extent of underlying pathology [1]. Treating sarcoidosis with steroids or cardiac failure with diuretics can lead to an improvement in the chylothorax and sometimes even its resolution [4, 22].

Similarly, where appropriate, anti-cancer therapy may be considered in cases of malignant chylothorax. Chylothorax secondary to lymphoma is managed with both a conservative approach and specific treatment of the lymphoma. Chemotherapy, radiotherapy, or both prove beneficial in most cases. Spontaneous resolution may also occur in some cases [6].

Multiple strategies are employed for the treatment of chylothorax in the setting of LAM. These patients may benefit from mammalian target of rapamycin (mTOR) inhibitor therapy, such as everolimus, in addition to conservative and interventional treatment [6].

Conservative treatment

In a conservative approach, a combination of treatment modalities is considered based on the underlying cause of chylothorax, its symptomatology, and patient preference. If the patient is symptomatic, drainage of the effusion is almost always required. However, prolonged drainage should be avoided as this can lead to immunocompromise, malnutrition, and severe electrolyte disturbance with increased morbidity and mortality [1, 3].

Various conservative strategies may be employed to replace nutrients lost in chyle and prevent further chyle formation.

Dietary measures

Dietary measures such as a low-fat diet are an important facet to the conservative treatment of chylothorax, therefore, the involvement of dietitians at an early stage is invaluable. It has been observed that administration of low-fat medium-chain triglycerides may resolve nearly half of congenital or traumatic chylothoraces [4, 23]. Chyle flow in the TD reduces, allowing the leak to heal, since medium-chain triglycerides are directly absorbed into the portal circulation as they bypass the lymphatic system of the

intestines [18, 21]. Failing this intervention, total parenteral feeding may be considered to further reduce the chyle flow [4, 18, 23].

It is, however, important to note that strict dietary measures may not be a pragmatic approach in all non-traumatic cases since most of these patients have an underlying malignant disease and may already be very frail and malnourished due to the disease burden.

Pharmacological therapy

Pharmacological therapy may either be considered when chylothorax continues to recur despite an appropriately established dietary regimen or in conjunction with dietary measures.

Somatostatin and its analogues form a major part of medical therapy for the management of chylothorax. They exhibit many inhibitory actions in the gastrointestinal and hepatobiliary system, including reduction in absorption from the intestine and a decrease in splanchnic blood flow [24].

However, it is not clear how somatostatin helps resolve chyle leaks; it is speculated that reduction in lymph flow in the TD secondary to decreased absorption of triglycerides induced by the drug may play a part. Lymph flow in the TD is dependent on the splanchnic circulation and gastrointestinal motility, both of which are inhibited by somatostatin [24].

Their use needs to be combined with a low-fat diet to derive any major benefit. Successful use of subcutaneous octreotide and a fat-free diet has been reported in non-traumatic chylothorax due to malignancy [25, 26].

There is no consensus on the optimal dosing regimen, or route of administration for somatostatin or octreotide. In children the starting dose is $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ and then titrated as required. In adults, the usual starting dose is $50 \mu\text{g}$ every 8 h [24, 26]. The optimum duration of treatment in patients who will respond to octreotide or somatostatin is also not clear, but it is usually administered for 1 or 2 weeks before stopping treatment in non-responders [24].

Octreotide is a synthetic somatostatin analogue with anti-secretory properties similar to those of somatostatin but it has a longer duration of action [27]. It is important to be aware of the side-effects, which may include diarrhoea, dizziness, hepatotoxicity, and thrombocytopenia and cardiac arrhythmia [25]. Therefore, appropriate patient selection and thorough counselling about the side-effects prior to starting treatment are crucial.

Novel medical therapy

There are several case reports suggesting the successful use of α_1 -adrenergic agonists, such as midodrine and etilefrine, in the management of chylothorax [28–30]. However, the role of α_1 -adrenergic agonists in the treatment of chylothorax is currently limited and the appropriate dosing regimen is not clear.

Moreover, the exact mechanism of action of these agents is unknown. However, it is speculated that midodrine, by inducing splanchnic vasoconstriction, can modulate portal blood flow with a reduction in lymph production and its transport, which in turn leads to a decrease in chyle flow in the TD [29].

Interventional procedures

In many cases, if the chyle leak is large, conservative management may not be sufficient and an invasive procedure is required either as a definitive or palliative measure.

Non-traumatic chylothorax is technically more challenging to treat because there are host of disease processes directly or indirectly affecting the lymphatic system, the chyle leak may occur at unusual sites and/or the site of leak may not be easily identified. Therefore, the crucial challenge, prior to considering any suitable intervention, is to study the lymphatic system in detail on preplanning imaging work up to identify the leak [9].

Chemical pleurodesis

Chemical pleurodesis can be considered in cases where conservative management has failed and/or in patients who are not suitable candidates for surgical repair of the chyle leak.

Re-expansion of the lung and appropriate apposition of the visceral and parietal pleura is a prerequisite to successful talc pleurodesis. Talc can be administered thoracoscopically or *via* slurry. MARES and MATHUR

[31], in their small case series, reported a 100% success rate of thoracoscopically administered talc pleurodesis in lymphoma-related chylothorax. The dose of talc used in this case series was 4–8 g. Apart from talc, various other pleurodesis agents, including tetracycline, bleomycin, povidone and elemene, have also been successfully used [3, 4, 32, 33].

Pleuroperitoneal shunt

Pleuroperitoneal shunt (PPS) may be used as an option for palliation of dyspnoea in selected cases of chylothorax. A PPS, placed subcutaneously or externally and connected to a pump which is activated by gentle pressure, allows unidirectional drainage of chyle from the pleural cavity to the peritoneum where it may be quickly absorbed, maintaining its nutritional and possibly its immunological value [4, 34]. PPS, despite being an effective modality in draining chylothorax to alleviate symptoms, carries considerable risks such as shunt displacement, blockage, infection, skin erosions and pneumoperitoneum [34].

Thoracic duct embolisation

Thoracic duct embolisation (TDE), a percutaneous minimally invasive procedure performed usually by interventional radiology, can help address the chyle leak. Fundamentally, TDE can be performed *via* two lymphangiographic techniques [35].

- 1) Bilateral pedal lymphangiography is a traditional technique where pedal lymphatic vessels are cannulated followed by transabdominal catheterisation of the cisterna chyli or TD. After successfully accessing the TD, N-butyl cyanoacrylate glue and/or embolisation coils are deployed to repair the leak. This is a complicated, often technically challenging procedure, which takes a considerable time to complete.
- 2) Ultrasound-guided inguinal intranodal lymphangiography is a relatively new technique which has made the procedure significantly shorter with promising results.

In non-traumatic chylothorax, TDE can be successful in 73.8% of cases on the first attempt [35], but overall success rates are lower than for traumatic chylothorax [9]. Failed cases are mostly related to technical difficulty in accessing the TD, and suboptimal opacification of the retroperitoneal lymphatic system. Use of an intranodal approach can potentially improve technical success rates [35].

Acute complications associated with TDE are minor and generally self-limited and are estimated at 2–6%. Long-term complications may be seen in up to 14% of patients and may include leg swelling, abdominal swelling or chronic diarrhoea [7].

Surgery

In non-traumatic chylothorax, due to the majority of cases being related to cancer with associated disease burden, surgery may be a less suitable option than TDE. There is also no universal agreement which patients should undergo fixation of the TD defect surgically. In selected cases, where surgical TD ligation is deemed suitable, it can either be performed *via* open thoracotomy or video-assisted thoracic surgery (VATS) [8]. Generally, VATS is preferred over open thoracotomy owing to its short post-operative recovery period and being minimally invasive.

Overall, surgical TD ligation can be successful in about 90% of cases of chylothorax, but one in nine patients might have to undergo multiple procedures [8, 36]. The data on surgical TD ligation, however, are mostly related to traumatic causes and there is a paucity of specific data in non-traumatic chylothorax.

Earlier literature reported complication rates of up to 38.3% and mortality in a quarter of patients undergoing surgery for chylothorax [8, 37], but they have since improved with time owing to early intervention, better case selection and advancement in supportive measures [8].

A proposed treatment algorithm for non-traumatic chylothorax is summarised in figure 5.

Prognosis

Prognosis of non-traumatic chylothorax is variable, mostly dependent on the underlying cause. Chylothorax secondary to benign causes may have a better outcome, especially if the site of chyle leak is obvious and amenable to definitive intervention. Poor prognostic indicators include bilateral chylothoraces, malignant chylothorax and chronic chylothorax with on-going nutrient loss [38]. The mortality due to chylothorax, which in the 1940s was more than 50% [39], has gradually improved due to a gradual shift towards more aggressive management strategies [3] and overall improvement in healthcare facilities, but currently specific mortality data in the setting of non-traumatic chylothorax are limited.

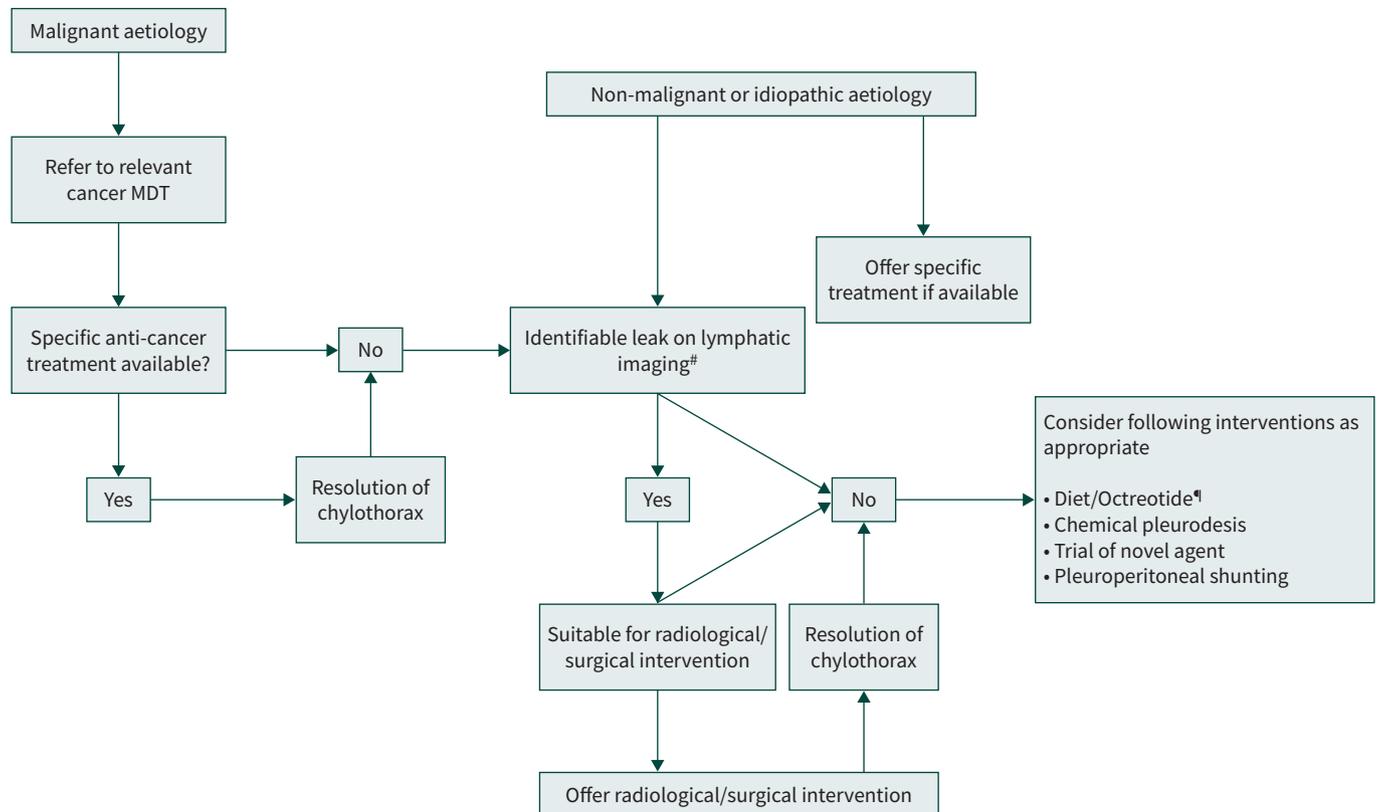


FIGURE 5 Proposed treatment algorithm for non-traumatic chylothorax. MDT: multidisciplinary team. #: CT/MR lymphangiography, SPECT/CT or lymphoscintigraphy, etc., as appropriate; ¶: these can also be used in conjunction whilst treating the underlying cause or awaiting imaging work-up or definitive treatment.

Conclusion

Non-traumatic chylothorax occurs due to the accumulation of chyle in the pleural space in the absence of traumatic disruption to the TD. The diagnosis of chylothorax requires biochemical analysis of the pleural fluid, with pleural fluid triglyceride levels $>1.24 \text{ mmol}\cdot\text{L}^{-1}$ ($>110 \text{ mg}\cdot\text{dL}^{-1}$) and a cholesterol level $<5.18 \text{ mmol}\cdot\text{L}^{-1}$ ($<200 \text{ mg}\cdot\text{dL}^{-1}$) diagnostic of a chylothorax. Once a diagnosis is confirmed, identification of an underlying cause and the site of chyle leak guides its management. Given there is no clear consensus on the most suitable approach to manage chylothoraces, a multidisciplinary approach is recommended; however, future randomised control trials can help devise the most appropriate management strategy.

Key points

- Non-traumatic chylothorax refers to pathological accumulation of chyle in the pleural space in the absence of trauma or injury to the TD.
- The commonest cause of non-traumatic chylothorax is malignancy. Lymphoma is responsible for up to 75% of cases of malignant chylothorax, with non-Hodgkin lymphoma being the most prevalent cause.
- Pleural fluid triglyceride levels $>1.24 \text{ mmol}\cdot\text{L}^{-1}$ ($>110 \text{ mg}\cdot\text{dL}^{-1}$) with a cholesterol level $<5.18 \text{ mmol}\cdot\text{L}^{-1}$ ($<200 \text{ mg}\cdot\text{dL}^{-1}$) is diagnostic of chylothorax. Demonstration of chylomicrons in pleural fluid by lipoprotein electrophoresis can help confirm the diagnosis in borderline cases.
- Due to the variable and complex course of the TD a crucial challenge is to identify the site of chyle leak, where various lymphatic specific investigations, e.g. CT/MR lymphangiography and nuclear medicine studies, can play an important role. Conventional lymphangiography is the gold standard investigation, but today it is rarely performed only for diagnostic purposes.
- Non-traumatic chylothorax is associated with a wide spectrum of medical conditions and there is no consensus guidance on its treatment; therefore, a multidisciplinary approach is recommended for its effective management.

Self-evaluation questions

1. Chylothorax is suspected in a 75-year-old patient with persistent right-sided pleural effusion. Pleural fluid aspiration is performed and a sample sent for triglycerides and cholesterol levels. Which one of the following makes the diagnosis of chylothorax most likely?
 - a) Pleural triglycerides level $<1.24 \text{ mmol}\cdot\text{L}^{-1}$
 - b) Pleural fluid cholesterol level $>5.18 \text{ mmol}\cdot\text{L}^{-1}$
 - c) Pleural fluid triglycerides $>1.24 \text{ mmol}\cdot\text{L}^{-1}$
 - d) Pleural fluid cholesterol level $<5.18 \text{ mmol}\cdot\text{L}^{-1}$
2. What is the commonest cause of non-traumatic chylothorax?
 - a) Tuberculosis
 - b) Malignancy
 - c) Yellow nail syndrome
 - d) Congestive heart failure
3. What is considered the gold standard in studying lymphatic vessels, lymphatic flow and identifying the site of a lymph leak?
 - a) Conventional lymphangiography
 - b) CT lymphangiography
 - c) Lymphoscintigraphy
 - d) MR lymphangiography
4. What do somatostatin and its analogues do?
 - a) Inhibit gastrointestinal and hepatobiliary secretions
 - b) Increase secretions of other hormones
 - c) Have no effect on TD transport
 - d) Have no role in the management of non-traumatic chylothorax

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Suggested answers

1. c.
2. b.
3. a.
4. a.