Review Article

Chylothorax: pathophysiology, diagnosis, and management—a comprehensive review

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Abstract: Chylothorax is a rare condition characterized by the accumulation of chyle in the pleural space. While it accounts for a small percentage of pleural effusions, chylothorax can lead to significant morbidity and mortality. This article provides a comprehensive overview of chylothorax, covering its relevant anatomy, aetiology, pathophysiology, clinical features, diagnosis, and management. Injury or disruption to the thoracic duct (which is responsible for chyle transport) leads to the development of chylothorax. This may result from trauma, such as iatrogenic injury during surgery, or non-traumatic causes, including malignancy, lymphatic disorders, and heart failure. Recognition of the underlying cause is essential to tailor management. Clinical presentation varies, with symptoms linked to rate of chyle accumulation and the causative condition. Diagnosis relies on pleural fluid analysis, with demonstration of elevated triglyceride levels (>110 mg/dL) and reduced cholesterol levels (<200 mg/dL) being the key diagnostic criteria employed in clinical practice. Various imaging modalities, including computed tomography (CT) scans and lymphatic-specific investigations, may be utilised to aid identification of the site of chyle leak, as well as determine the likely underlying cause. Chylothorax management is multifaceted, with conservative approaches such as dietary modification and pharmacological interventions often initiated as first-line treatment. Drainage of chylous effusion may be necessary for symptom relief. When conservative methods fail, interventional procedures like thoracic duct ligation or embolization can be considered. Due to the diverse aetiological factors and patient characteristics associated with chylothorax, individualized management strategies are recommended. Nonetheless, management of chylothorax is an evolving field with a paucity of high-quality evidence or standardized guidelines, highlighting the importance of ongoing research and a multidisciplinary approach to optimize individual patient care.

Keywords: Chylothorax; pleural disease; effusion

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Introduction

Chylothorax is defined as the accumulation of chyle within the pleural space (1). Chyle is a milky fluid that is produced during fat digestion and has a high content of triglycerides, fat-soluble vitamins, lymphocytes, and immunoglobulins (1). Although chylothorax is relatively uncommon, accounting for around 3% cases of all pleural effusions (2), the 90-day mortality rates associated with this condition may be as high as 82% (3), stemming largely from nutritional losses (owing to the high fat content of chyle), immunosuppression (due to its high lymphocyte and immunoglobulin content) and fluctuating intravascular volumes (4). As such, chylothorax represents a challenging condition for healthcare teams. Management typically involves addressing the underlying cause, careful attention to nutritional support, and selection of appropriate interventions (including judicial drainage of pleural fluid) to achieve the best possible outcome for patients.

This review aims to provide an overview of the relevant anatomy, pathophysiology, diagnosis, and management of chylothorax, highlighting the importance of adopting a multi-disciplinary approach to treatment decisions. An initial PubMed search was conducted using the keywords "chylothorax", "chylous effusion" and "chyle", and relevant articles were selected based on abstract screening and review of bibliographies of the selected articles.

Relevant anatomy

A chylothorax results from rupture of, or disruption to, the thoracic duct (5), which is a 35–46 cm long structure that arises at the cisterna chyli in the abdomen (6). The thoracic duct is formed by the coalescence of intestinal lymphatic vessels known as lacteals (6), and enters the thorax though the aortic hiatus of the diaphragm, running to the right side of the midline between the aorta and azygous vein posterior to the oesophagus (2,7-9). At the level of the thoracic plane (T4-T6) it crosses to the left of the midline and continues superiorly before arching and terminating at the junction between the left jugular and subclavian veins (7-9) (see *Figure 1*). The most common site of termination of the thoracic duct is the internal jugular vein (46% of cases), followed by the jugulosubclavian angle (32% of cases) (10).

The course of the thoracic duct underpins whether injury to this structure results in a left- or right-sided chylothorax: injury above the thoracic plane usually results in a left-sided chylothorax, whereas injury below the thoracic plane typically gives rise to a right-sided chylothorax (11); bilateral chylothoraces may occur when injury occurs at the level of the thoracic plane.

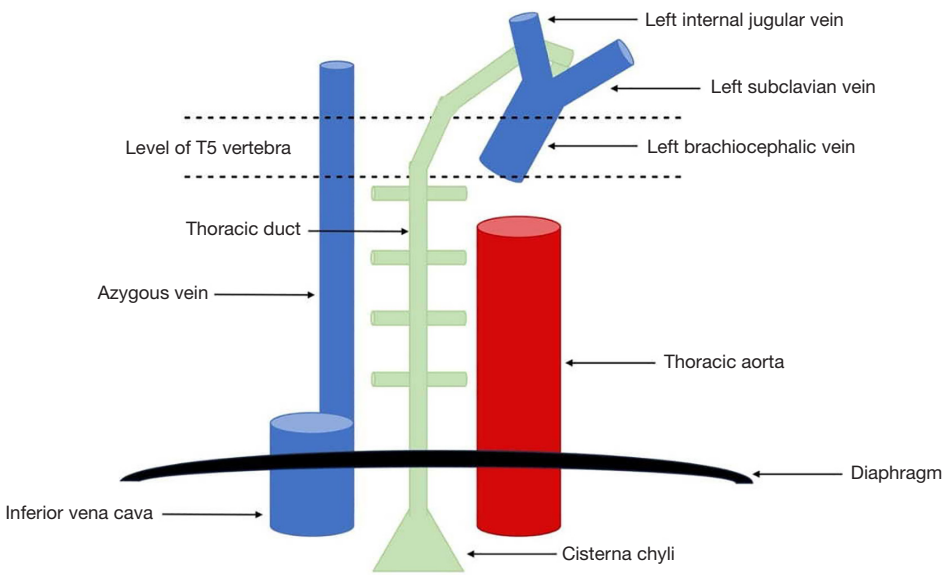

Figure 1 Diagrammatic representation of the course of the thoracic duct (pale green) in relation to its surrounding structures. The thoracic duct arises at the cisterna crista in the abdomen and enters the thorax through the diaphragm (shown as a black curvilinear band) at the aortic hiatus. The thoracic duct ascends superiorly and crosses to the left of the midline at the level of the thoracic plane (between T4 and T6 vertebrae) before terminating at the junction of the left internal jugular and subclavian veins.

Table 1 Potential causes and aetiology of chylothorax

Traumatic
1. Iatrogenic lymphatic injury
1.1 Surgery (especially cardiothoracic, oesophageal)
1.2 Central venous access (neck lines, pacemaker insertion)
2. Non-iatrogenic lymphatic injury
2.1 High-energy trauma (e.g., road traffic collision)
2.2 Penetrating chest trauma
2.3 Vertebral fracture
2.4 Raised intrabdominal pressure (e.g., coughing, childbirth, sneezing)
Non-traumatic
1. Direct tumour invasion into lymphatic wall
1.1 Lymphoma
1.2 Carcinoma
2. Increased hydrostatic pressure within lymphatics
2.1 Obstruction by tumour/lymphoma/thromboembolism
2.2 Increased central venous pressure (heart failure, congenital cardiac abnormality)
3. Hyperpermeability of lymphatics
3.1 Conditions causing primary lymphatic dysfunction
3.1.1 Lymphangioleiomyomatosis
3.1.2 Generalised lymphatic anomalies
3.1.3 Lymphatic aplasia
3.1.4 Yellow nail syndrome
3.1.5 Congenital chylothorax
3.2 Conditions causing secondary lymphatic dysfunction
3.2.1 Rarely
3.2.1.1 Previous mediastinal radiotherapy
3.2.2 Very rarely
3.2.2.1 Tuberculosis/non-tuberculous mycobacterium
3.2.2.2 Sarcoidosis
3.2.2.3 Filariasis
3.2.2.4 Histoplasmosis
4. Passage of chylous ascites into the pleural space via transdiaphragmatic lymphatic anastomoses
4.1 Liver cirrhosis
4.2 Pancreatitis
4.3 Nephrotic syndrome
5. Idiopathic

Approximately 83% of chylothoraces are unilateral (50% right-sided, 33% left-sided), while 17% are bilateral (12,13). There is, however, substantial anatomical variation between individuals (2,10), with the thoracic duct running the course described in around 60% of cases. This accounts for the high incidence of iatrogenic chyle leak following surgery despite careful planning and approach (14).

Overview of chyle

Chyle is a milky substance formed in the small intestine. Its primary function is to transport fat and fat-soluble vitamins into the venous circulation following digestion (14). Long-chain triglycerides (LCTs), obtained from dietary sources, coalesce with cholesterol and phospholipids to form chylomicrons in the cells lining the jejunal wall. Lacteals (small lymphatic channels within the villi of the small intestine) take up chylomicrons and transport them as chyle in the thoracic duct. By contrast, small and medium-chain triglycerides (MCTs) are absorbed directly into the portal circulation (15). This underpins the use of MCTs as the primary source of nutrition in the conservative management of chylothorax, as outlined later in this review. Other constituents of chyle include lymphocytes and immunoglobulins, which are derived from the liver and gastrointestinal tract (16).

Pathophysiology

A chylothorax may be broadly classified as either traumatic or non-traumatic in nature (12). Traumatic chylothoraces are most commonly encountered, with iatrogenic injury during surgery the leading cause within this category (17). This may include, for example, lung cancer resection, coronary artery bypass surgery, thoracic aneurysm repair, or cardio-pulmonary transplantation (18-21). The incidence is particularly high (up to 4%) in oesophageal surgeries (22) owing to the close proximity and inconsistent course of the thoracic duct in relation to the oesophagus (10). Other iatrogenic causes include duct blockage due to central venous catheter-related thrombosis, and damage following subclavian vein catheterization (23). Non-iatrogenic traumatic chylothorax, although less common, has been reported in the literature in up to 20% of cases (14), usually in the context of raised intra-abdominal pressure, such as occurs during severe vomiting or childbirth (24,25).

Non-traumatic chylothoraces are less commonly encountered but encompass a wide range of differential diagnoses (see *Table 1*). Four pathophysiological

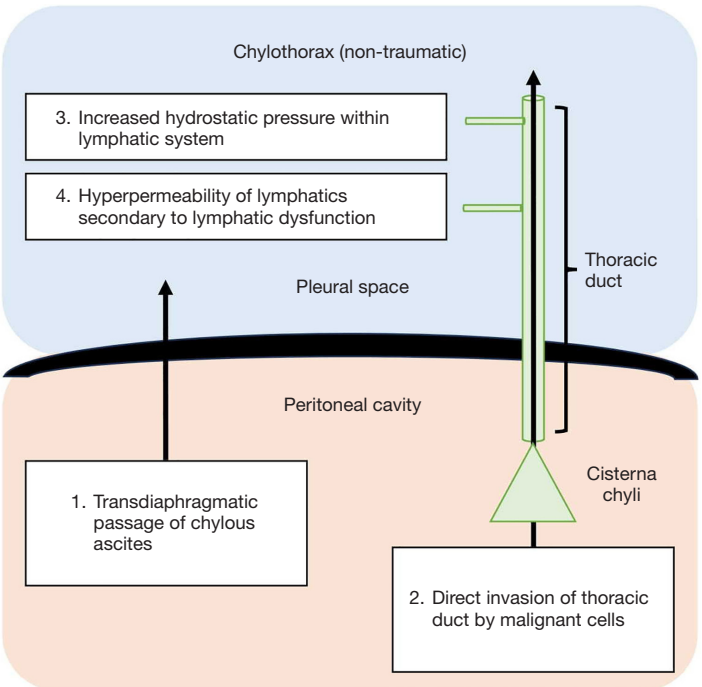

Figure 2 Proposed mechanisms (boxes 1 to 4) underpinning the development of non-traumatic chylothorax. The pleural cavity is depicted in blue, while the peritoneal cavity is depicted in orange, separated by the diaphragm (represented as a black curvilinear band). The thoracic duct and associated lymphatic structures are shown in green. Increased hydrostatic pressure, lymphatic dysfunction, and direct invasion by malignant cells may occur at any level of the thoracic duct. Examples relating to each of these pathophysiological mechanisms are summarised in *Table 1*.

mechanisms have been proposed for the development of non-traumatic chylothorax, including: direct invasion of the thoracic duct by malignant cells; increased hydrostatic pressure within the lymphatic vessels; hyper-permeability of the lymphatic vessels secondary to lymphatic dysfunction; and transdiaphragmatic passage of chylous ascites into the pleural space (2). These are diagrammatically represented in *Figure 2*.

Malignancy represents the most common cause of non-traumatic chylothorax (14,17,26), with lymphoma (most prominently non-Hodgkin lymphoma) accounting for approximately 70% of cases (12,14,22,27). Other haematological malignancies such as multiple myeloma, solid organ tumours, and metastatic epithelial tumours have also been described (17,27-29). The pathophysiology is somewhat controversial but is thought to relate to chyle leak following direct invasion of the thoracic duct, and/or extrinsic compression of lymphatics by enlarged lymph nodes (30). Additionally, it has been proposed that the upstream movement of chyle into the thoracic space through transdiaphragmatic defects secondary to a negative intrathoracic pressure gradient may also contribute to development of malignant chylothorax (31).

Primary lymphatic disorders, such as lymphangioleiomyomatosis (LAM) and lymphangiectasia syndromes, are rare. LAM affects women of childbearing age and is characterized by the abnormal proliferation of smooth muscle cells in the lymphatics of the peribronchial, perivascular and perilymphatic spaces of the lungs (32-34). Perilymphatic proliferation leads to lymphatic dysfunction which, in-turn, leads to hyperpermeability of lymphatic vessels and lymph leakage (2,35,36). Akin to malignant obstruction, a chyle leak in the retroperitoneum stemming from lymphatic dysfunction can migrate preferentially into the chest through transdiaphragmatic connections (31). This is also the mechanism observed in chylothoraces that develop in the setting of chylous ascites. Moreover, it is possible that raised intra-abdominal pressure in the presence of ascites contributes to thoracic duct obstruction and subsequently, chyle leak (2,12,26).

Yellow nail syndrome is a clinical entity characterized by brittle yellow nails, lower limb lymphoedema, and

respiratory manifestations, most commonly bronchiectasis and bilateral pleural effusions (37,38). Although only 12.1–30% of effusions in this syndrome are chylous, the underlying mechanism is considered to be that of lymphatic dysfunction secondary to lymphatic transport failure (37-39). Lymphatic dysfunction may also arise in the context of tuberculosis (40), atypical mycobacterial infections (41), Kaposi's sarcoma (42), and following radiation therapy (22,43,44), all of which may rarely lead to chylothorax formation. It is estimated that the incidence of congenital chylothorax is between 1:10,000 and 1:24,000 (45,46).

Occasionally, a chylothorax may develop in the setting of a transudative pleural effusion. Examples include decompensated liver cirrhosis with chylous ascites, and chronic heart failure (47,48). The proposed mechanism for chyle leak in heart failure is that of increased central venous pressure, raising flow through the thoracic duct. However, owing to the stiffness of the veno-lymphatic junction in the neck, maximal lymphatic flow is limited, leading to increased hydrostatic pressure and lymph extravasation (48). Additionally, increased pressure in the left subclavian vein results in restricted lymphatic drainage and development of lymphatic venous collaterals, ultimately causing a chyle leak (2,48). In up to 9% of cases, the cause of non-traumatic chylothorax remains unknown and is termed idiopathic (49).

Clinical features

The clinical symptomatology in chylothorax is similar to that of any pleural effusion and is influenced by the aetiology and rate of accumulation of chyle in the pleural space (12,14,15). Most patients are asymptomatic in the initial stages when the volume of chyle is low, which is classically observed in non-traumatic aetiologies (15,27). As chyle insidiously accumulates in the pleural cavity in these cases, patients may develop breathlessness progressively over time. By contrast, in traumatic cases, sudden damage to the thoracic duct causes rapid fluid accumulation in the pleural space, which may lead to respiratory and haemodynamic compromise (14,50). Occasionally, for instance following pneumonectomy, patients can present with a tension chylothorax and mediastinal shift secondary to large volumes of chyle accumulating over several weeks (51,52). However, in the post-surgery setting, chylothorax most commonly presents incidentally as a pleural effusion on chest radiography, or by persistent drainage of chylous fluid in pre-existing drains (12).

While cough is a frequently reported symptom, patients may rarely also experience chyloptysis (the expectoration of chylous fluid in sputum), secondary to reflux of chyle into the bronchial tree (53). As chyle is not an irritant to the pleural surface, chest pain and fever are uncommon (54,55). Other symptoms, such as weight loss, asthenia and night sweats may occur in the context of malignancy-associated chylothorax (15). In chronic cases, chyle leak may lead to marked nutritional deficits, weight loss and muscle wasting, as well as electrolyte imbalances (14,50). Loss of immunoglobulins and T lymphocytes can also lead to secondary immunosuppression, thereby predisposing the individual to opportunistic infections (56-58). Notably, however, as chyle is bacteriostatic, infection of the pleural space is rare (14).

Chyle leak may also affect the bioavailability of certain medications, such as amiodarone (59), digoxin (60) and ciclosporin (61), since these agents are sequestered in chyle and can be lost during its drainage. This can cause a subsequent reduction in therapeutic levels and may lead to symptoms relating to poor control of the conditions they are used to treat.

Diagnosis

Pleural fluid analysis remains central to the diagnosis of chylothorax, supported by various thoracic imaging modalities to help establish the underlying cause. Of note, the classic description of milky or opalescent fluid in the pleural space is thought to occur in only 22–44% of patients meeting the diagnostic criteria for chylothorax (26,62), highlighting the importance of performing pleural fluid analysis and maintaining a high index of suspicion even in the absence of classical macroscopic features.

Pleural fluid analysis

The macroscopic appearance of chylothorax is typically described as milky, though may occasionally appear serous in nature (particularly if patients are fasting, secondary to reduced lipid ingestion, e.g., in the post-operative setting), or blood-stained (especially after trauma) (12). Other reported descriptions include serosanguineous, yellow, and green coloured fluid (12,63). Important differentials, based on gross appearance, are pseudochylothorax and pleural infection, both of which may cause an opalescent appearance of pleural fluid similar to chylothorax (27). Pseudochylothoraces usually occur in the context of longstanding exudative effusions that have become enriched

Table 2 Comparison of diagnostic criteria for chylothorax and pseudochylothorax

Condition	Chylothorax	Pseudochylothorax
Diagnostic criteria		
Pleural fluid triglyceride level	>110 mg/dL (>1.24 mmol/L)	<50 mg/dL (<0.56 mmol/L)
Pleural fluid cholesterol level	<200 mg/dL (<5.18 mmol/L)	>200 mg/dL (>5.18 mmol/L)
Pleural fluid to serum triglyceride level	>1	<1
Pleural fluid to serum cholesterol level	<1	>1
Additional confirmatory diagnostic criteria		
Presence of chylomicrons in pleural fluid	Yes	No
Presence of cholesterol crystals in pleural fluid	No	Yes
Classic appearance of pleural fluid	Milky white or opalescent (Note: the absence of this appearance does not exclude chylothorax)	Milky white or opalescent

with cholesterol; common causes include tuberculosis, rheumatoid-related effusions, chronic pneumothorax or haemothorax, and poorly drained empyema (12). Pleural fluid centrifugation can help to distinguish chylothorax and infected pleural fluid with a milky appearance, with separation of the constituent components (cell debris and clear supernatant) characteristic of pleural space infection/empyema (64). Nonetheless, it is not possible to diagnose chylothorax based on appearances alone.

A definitive diagnosis of chylothorax is based on demonstrating the presence of chylomicrons within the pleural fluid (27,62,65). Ideally, detection of chylomicrons is achieved via lipoprotein electrophoresis, yet this remains an expensive and often inaccessible technique. Therefore, in clinical practice, measurement of pleural fluid triglyceride and cholesterol levels is the most widely adopted method for diagnosis of chylothorax (14). Specifically, a pleural fluid triglyceride level greater than 110 mg/dL (1.24 mmol/L), and a cholesterol level less than 200 mg/dL (5.18 mmol/L) are diagnostic for chylothorax (65). Conversely, a pseudochylothorax may be diagnosed when pleural fluid triglyceride levels are less than 50 mg/dL (0.56 mmol/L) and cholesterol levels greater than 200 mg/dL (5.18 mmol/L), particularly in the presence of cholesterol crystals (14). *Table 2* provides a summary of these diagnostic criteria.

It is important to note that nutritional status has a direct impact on pleural fluid triglyceride levels; as demonstrated by Maldonado *et al.* (26), poor nutritional status can cause low triglyceride levels, making the diagnosis of chylothorax challenging. In these circumstances, lipoprotein electrophoresis may be a useful clarifying investigation. Where pleural fluid triglyceride levels are greater than 110 mg/dL, there is a small (1%) chance that the effusion is non-chylous. In contrast, the chance of a chylous effusion occurring with triglyceride levels less than 50 mg/dL is roughly 5% (64,65), though this could be impacted by secondary pathology (e.g., when chylothorax is complicated by an additional transudative cause of pleural effusion) (66). Therefore, in situations where pleural fluid triglyceride values are between 55 and 110 mg/dL, or when there is suspicion of dual pathology (such as cirrhosis, or heart failure), lipoprotein electrophoresis may help to clarify the diagnosis by direct detection of chylomicrons within the pleural fluid (67). Other reported diagnostic criteria include a pleural fluid to serum triglyceride ratio of greater than 1, and a pleural fluid to serum cholesterol ratio of less than 1, respectively (14); such criteria may be particularly relevant in patients who have high baseline serum triglyceride levels or, rarely, in patients with pseudochylothorax who have both high fluid triglyceride and cholesterol levels.

The majority of chylous effusions can be termed 'protein-discordant exudates'—characterised by high protein content but not elevated lactate dehydrogenase (LDH) (57)—despite the relatively low protein content of chyle (2–3 g/dL) (68). The paradoxically high protein content of chylothoraces has been attributed to high rates of fluid and solute reabsorption from the pleural cavity into the intravascular space, leading to high protein concentration within the pleural space (26,27,62,67). By comparison, the low levels of LDH observed in chylothoraces may be

explained by its large molecular size, limiting filtration from capillaries into the pleural space (62). Consequently, an elevated LDH in a chylous effusion indicates the presence of alternative pathology that should be further investigated. As outlined above, in around 14% of cases, a chylous effusion may be transudative in nature, particularly in the setting of decompensated liver disease (47) or heart failure (26).

In addition to measurement of pleural fluid triglyceride and cholesterol levels, it is important that pleural fluid cytology is performed, particularly given the possibility of underlying malignant aetiology. Notably, chylothorax is characterized by a lymphocyte predominant exudate (typically >70% of the differential cell count), reflecting the cellular composition of chyle (27); however, the normally mature lymphocytes may demonstrate atypical features in the context of haematological disease (69,70). While pseudochylothorax also demonstrates a lymphocyte-predominant cell differential, in 39% of cases there may be a polymorphonuclear cell predominance, which would not be typical of chylothorax (71).

Imaging

Chest radiography has limited value in the specific diagnosis of chylothorax, though can confirm the presence of a pleural effusion more broadly (49). It may serve as a screening tool for underlying aetiologies, such as the identification of a lung mass or hilar lymphadenopathy relating to malignancy, or chest wall injury in traumatic chylothorax.

Thoracic ultrasound has become a widely adopted tool in pleural medicine (72). However, much like chest radiography, this modality alone is unable to distinguish chylothorax from other causes of pleural effusion, and its primary role is to facilitate ultrasound-guided pleural intervention.

Computed tomography (CT) (with or without contrast) remains central to thoracic imaging and is useful in identifying non-traumatic causes of chylothorax (such as malignancy, ascites, or lymphadenopathy) as well as detecting traumatic injuries to the lymphatic system (2,49). In cases where no obvious cause for chylothorax is identified, imaging the lymphatics may be warranted to aid both diagnosis and management options. In particular, CT lymphangiography involves administration of water-soluble contrast directly into the cisterna chyli under CT-guidance, allowing demonstration of thoracic duct anatomy and identification of chyle leak (2). Thoracic images constructed from CT lymphangiography may also help detect underlying parenchymal disease, such as LAM (73).

Where CT imaging fails to identify the site of chyle leak, nuclear medicine imaging techniques—such as lymphoscintigraphy and single photon emission computed tomography (SPECT)—may be utilized (2). Through these methods, a water-soluble radiotracer is injected subcutaneously and subsequently absorbed by the lymphatics to be distributed throughout the lymphatic circulation (74), visible by CT/SPECT. This not only allows identification of the potential site of chyle leak, but also offers functional assessment of lymphatic flow, which may indicate presence of a primary lymphatic disorder (74-77).

Magnetic resonance lymphangiography can also help to identify chyle leaks related to primary lymphatic disorders such as LAM and lymphangiomas, non-Hodgkin's lymphoma, and trauma. This can be performed either with or without contrast or using the more novel technique of dynamic contrast-enhancement (78-80). Whilst this modality has the advantages of high spatial resolution and no exposure to ionizing radiation, its availability may be more limited (79).

Conventional lymphangiography remains the gold standard investigation for evaluating the lymphatic circulation (81). This is performed by injection of a poppyseed-based oil into a lymphatic vessel of the foot or ankle and following the flow of contrast under fluoroscopic guidance (81). The technique can successfully identify lymphatic defects and anomalous anatomy and may additionally have a role in treating the chyle leak once established (82). Nonetheless, lymphangiography is not without risk, and has been associated with various complications including oil embolization, lipoid pneumonia, infection, pulmonary oedema, and urticaria at the site of contrast injection (83-85). These risks, alongside its invasive nature and limited availability, make conventional lymphangiography a less attractive initial diagnostic option (2,49). It is therefore largely reserved for a select group of patients who are likely to gain diagnostic and therapeutic benefit from the procedure.

Management

There are currently no established guidelines regarding the management of chylothorax. High quality evidence, including randomised controlled trials, is lacking, and so management approaches are based largely on clinical consensus, case series data and observational studies. A multi-disciplinary approach is crucial, involving respiratory

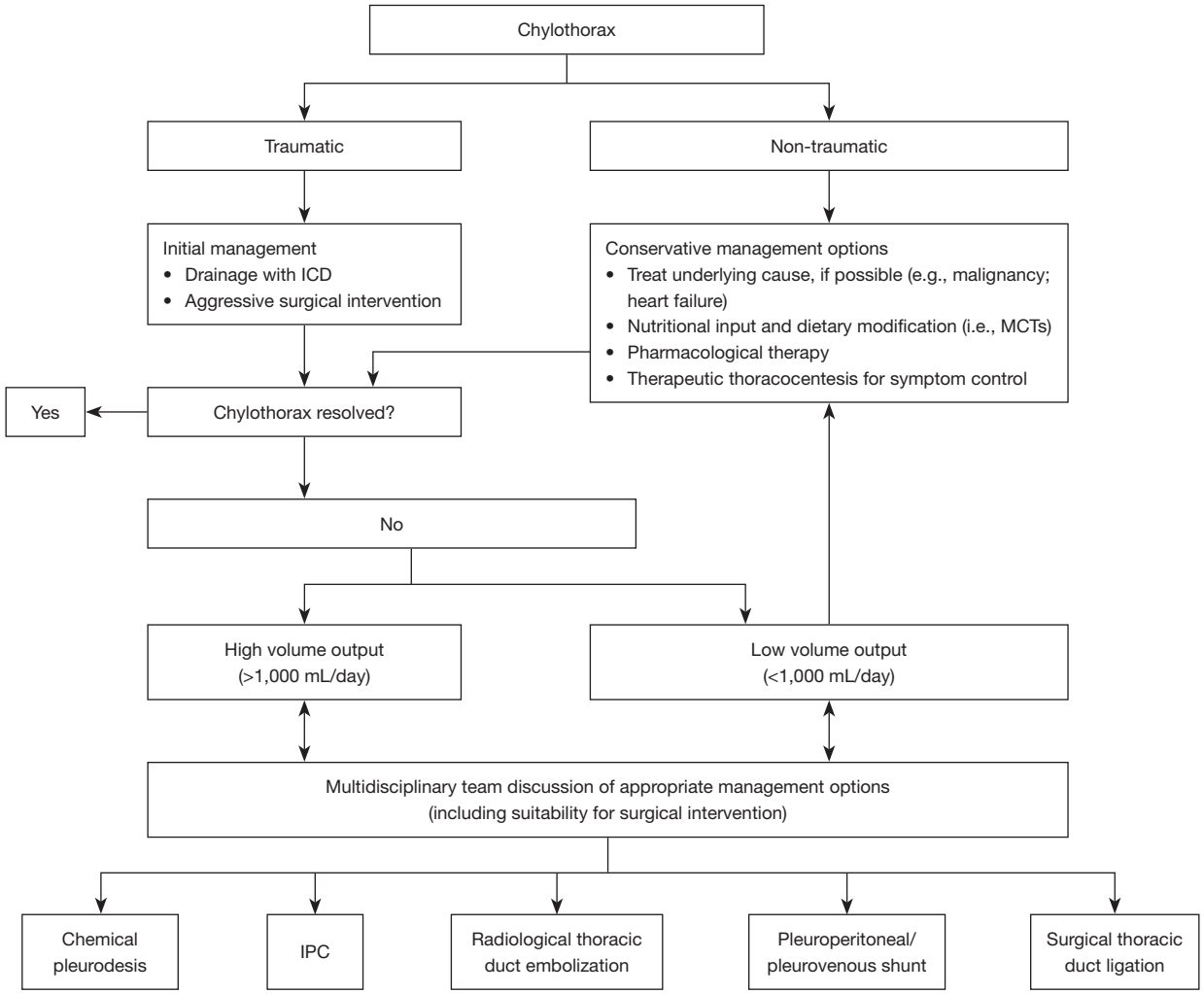

Figure 3 Proposed approach to the management of chylothorax, highlighting the various invasive and non-invasive treatment options available. Initial management is usually focused on conservative therapies, particularly in the case of non-traumatic chylothorax, where early surgical/invasive procedures are less critical compared to traumatic chylothorax. In cases of persistent chyle leak, a multi-disciplinary approach is advocated to ensure individualized patient care is optimized. This may involve radiologically-guided interventions (e.g., thoracic duct embolization) or surgical intervention (e.g., thoracic duct ligation) depending on patient suitability and local resources. ICD, intercostal drain; MCTs, medium-chain triglycerides; IPC, indwelling pleural catheter.

physicians, thoracic surgeons, oncologists, dieticians, and pharmacists (15). It is also important to consider the underlying cause of the chylothorax (including the rate of chyle leak), as well as the patients' performance status and nutritional state, to develop an individualised management plan. *Figure 3* depicts a proposed algorithm for the management of chylothorax.

In general, a conservative approach, including drainage of the effusion, nutritional modifications, and pharmacological adjuncts, is adopted first line for a limited period of time, before more invasive interventional measures are considered (15). The primary aim of these conservative measures is to reduce the flow of chyle through the thoracic duct to allow the leak to heal itself (86,87).

Some authors have advocated for the stratification of cases—including subsequent management approaches—into high and low output chylothorax, where high output chylothorax represents an estimated or known volume loss of greater than 1,000 mL chyle per day, and low output

chylothorax represents an estimated or known volume loss of less than 1,000 mL per day (88,89). Notably, low output chylothorax is more commonly observed in patients with non-traumatic causes, whereas high output chylothorax is most commonly encountered in post-surgical patients and those with liver cirrhosis. It is suggested that patients with high output chylothorax are more likely to fail with initial conservative management approaches, and early intervention should be considered in these cases (90).

Conservative approaches

Treatment should be directed towards the underlying cause of the chylothorax, if known. For instance, corticosteroids may be utilised in sarcoidosis; guideline-directed medical therapy (in particular, diuretic medication) can be used in both chylous ascites and chylothorax secondary to heart failure; and mTOR inhibitors (such as sirolimus) can be used in chylothorax associated with LAM (2,11,48,91). In malignant chylothorax, treatments targeted at the underlying malignancy, such as radiotherapy or chemotherapy, can be effective in managing the chylothorax (12,14,87,92).

Oral or enteral dietary modifications are often adopted first line in low output chylothorax (11,15,93). Patients should be assessed by dieticians and instructed to stay on a low or no-fat, high protein diet, ensuring that any fats ingested are MCTs (12,87,94). This serves to decrease fat absorption from the gut, thereby reducing the volume of chyle flow through the thoracic duct. In addition, MCTs, which may be taken as dietary supplements, are directly absorbed into the portal circulation, bypassing the lymphatic system altogether (in contrast to LCTs) (15,64,87,95). Additional nutritional support is often required, as deficiencies of fat-soluble vitamins and essential fatty acids may occur rapidly (e.g., within the first 5 days) of a low or no-fat dietary regimen. In addition, these regimens may not be suitable in malignant chylothorax since these patients are often malnourished or frail at presentation (15).

Total parenteral nutrition (TPN) may be adopted preferentially in high output chylothorax, as a major reduction in chyle flow can encourage healing of the leak and avert acute nutritional deficiencies (90). TPN is also considered when oral or enteral dietary modifications have failed to reduce chyle flow sufficiently (12,64,94). Although there is no specified duration of oral or enteral low-fat regimens, some authors have suggested that a lack of response at 2 weeks indicates the need to transition to TPN (96). TPN should, however, be used with caution: there are significant associated risks, such as line infection and cholestasis, and current evidence does not suggest a significant difference between oral or enteral dietary regimens and TPN in the rate of chylothorax resolution (97). Of note, no fat restrictions are required for TPN since this is administered intravenously and fat is therefore not absorbed as chyle in the gut.

Pharmacological therapies

Several case series have demonstrated the use of somatostatin and octretotide (a long-acting synthetic somatostatin analogue) in aiding resolution of chyle leaks from a variety of aetiologies, including congenital chylothorax, malignancy, post-operative chylothorax and yellow-nail syndrome (98-103). These are usually adopted in combination with dietary modifications or TPN, as well as drainage of the effusion if required. The exact mechanism of action of these agents in treating chylothorax remains unclear. Somatostatin and octreotide are known to reduce gastric, biliary, and pancreatic secretions, and to induce smooth muscle constriction in splanchnic and lymphatic vessels, thereby reducing lymph production and flow though the thoracic duct. They also increase faecal fat secretion (4,102,104-106).

The optimal timing, dosing, and route of administration of these agents is not known, and varying regimens have been proposed (101,106). In a case series of adult subjects, somatostatin was administered either by intravenous infusion 6 mg/day for 2 weeks or by subcutaneous injection of 50 micrograms every 8 hours. The authors report complete resolution of the chylothorax with adoption of both regimens (101). Reported side effects include flushing, diarrhoea, nausea, thrombocytopaenia, hepatotoxicity and cardiac arrythmias (99). It is advised that caution should be exercised in patients with underlying vascular disease, since the impact on splanchnic vasoconstriction may induce vascular compromise (98).

Isolated case reports have further described the use of alpha-adrenergic agonists, such as midodrine and etilefrine, in the treatment of refractory, idiopathic and post-operative chylothorax (107-109). The numbers reported are very low, with the largest case series to date including only ten patients (98). Alpha-adrenergic agonists are conventionally used to treat postural hypotension but, through smooth muscle contraction, can lead to splanchnic vasoconstriction and modulation of portal blood flow. This may result in

reduced chyle production and flow, augmenting spontaneous closure of chyle leaks in chylothorax (107,108). The optimal dosing regimens and route of administration for alpha-adrenergic agonists is not clear. One case report described using midodrine 20 mg three times daily, alongside octreotide and TPN (110). Etilefrine is less readily available and administered via continuous intravenous infusion, carrying an added treatment burden (109).

Pleural interventions

Drainage of chylothoraces may be required for symptomatic benefit. This can be achieved through therapeutic thoracocentesis, placement of an intercostal chest drain (ICD), or use of an indwelling pleural catheter (IPC). The choice of pleural intervention is often dictated by the underlying aetiology and rate of accumulation of pleural fluid. In post-operative and traumatic cases, an ICD if often already *in situ*.

Thoracocentesis, IPC insertion or ICD placement may be offered in patients with non-traumatic chylothorax that present with large symptomatic effusions. For patients with slowly accumulating chylous effusions, repeated thoracocentesis is likely to be of some symptomatic benefit (11). In malignant chylothorax, periodic thoracocentesis may be used as a palliative measure to alleviate dyspnoea.

ICD insertion may represent a better option for chylous effusions that accumulate rapidly, since it allows quantification of the rate of chylous fluid production and subsequent stratification of cases into low and high output chylothorax. As indicated previously, this may inform further management strategies, including early surgical intervention where appropriate (90). It has been postulated that draining the effusion may assist in sealing the chyle leak by allowing time for other treatments to work, or for the site of leak to heal (86).

Drainage of chylothoraces is not without risk, however. Prolonged chest tube drainage can result in the loss of immunoglobulins, protein, and lymphocytes through chyle, thereby causing malnutrition and immunosuppression (4). Serial monitoring of electrolytes, lymphocyte counts, total protein and albumin is required, as well as monitoring of the patient's nutritional state. As a general principle, pleural drainage via ICD is limited to less than 2 weeks and may be shortened further in more frail patients (111,112). The most appropriate size of ICD for chylothorax is not known, with case series reporting success using both small and large-bore tubes; there is no evidence to support preferential use of one size over the other (3,113-117).

Chemical pleurodesis through ICD may be considered in patients that fail to improve with conservative management and are not candidates for surgery. Several case reports have successfully used agents such as talc, bleomycin, tetracycline, povidone, elemene, and hypertonic glucose for this purpose (12,14,118-120). Talc, which can be used thoracoscopically or via slurry, has been reported to have a 100% success rate in a small case series of 24 patients (121). However, the success rate of pleurodesis may be lower in chylothorax than malignant effusions particularly in high-output leaks where adequate pleural apposition is not achieved.

There is a growing body of evidence to support the use of IPCs in chylothorax, albeit largely in the form of case series. Notably, DePew *et al.* described the successful removal of IPCs in 9 of 14 chylothoraces following drainage, without significant nutritional or immunological compromise (a primary concern with ongoing drainage of chylous fluid) (122). Similarly, the use of IPCs has been successfully demonstrated in both malignant and recurrent chylothoraces, akin to their use in malignant or refractory pleural effusions (123,124). As with ICDs, IPCs permit monitoring of the rate of chyle production and quantification of chyle leak (86), which may influence future management decisions.

Surgical techniques

As previously indicated, surgical intervention may be considered when conservative management of chylothorax fails. This is largely the case for non-traumatic chylothoraces, where there is no strong indication for immediate surgical intervention. The typical criteria for surgery in patients undergoing initial conservative management include large daily chyle leak of more than 1.5 L in an adult, longer than 2 weeks of chest tube output, and rapidly declining nutritional status (125-127). By contrast, post-traumatic or post-surgical chylothorax requires aggressive early surgical intervention (14).

The most commonly described surgical technique is that of thoracic duct ligation. The chyle leak may be identified by giving the patient a drink of fat or cream immediately prior to surgery (128), or using a lipophilic dye such as Sudan red or black, methylene blue, or indocyanine green (27,129-131). Once identified, the leak is repaired via video-assisted thoracoscopy or robotic-assisted thoracic surgery (132). This procedure is well-described in the context of traumatic

chylothorax, with a success rate of more than 90% in this cohort (86,127,132,133). The outcomes in non-traumatic cases are less well established (11). Complications associated with thoracic duct ligation include ongoing chyle leak and development of multiloculated chylothorax, in addition to general peri-operative risks of pneumonia, bleeding, and injury to surrounding structures (130). Mortality from the procedure is quoted in the region of 3% (134).

For refractory chylothoraces, pleuroperitoneal shunts (PPS) or pleurovenous shunts (PVS) may be considered (135,136). A PPS diverts the chylous effusion into the peritoneum where it is systemically absorbed but should clearly not be used in patients with concomitant chylous ascites. A PVS, by comparison, redirects chyle into the subclavian or jugular veins. Both PPS and PVS are placed subcutaneously or externally and can be activated manually (Denver shunt) or passively (LeVeen shunt) (86). Despite being less invasive than video-assisted thoracoscopic surgery (VATS) thoracic duct ligation, shunts carry a high risk of complications, including displacement, skin erosion, infection, blockage, and pneumoperitoneum (86).

Interventional radiology

An alternative to the surgical approaches outlined above is thoracic duct embolization (TDE), which aims to seal the chyle leak at its site of origin. This is typically performed percutaneously by interventional radiology colleagues. The technique involves first performing pedal or intra-nodal lymphangiography to opacify the cisterna chyli or other enlarged lymphatic vessels; canulating the thoracic duct with a catheter; performing a thoracic ductography to identify the leak site; and employing embolization coils to repair the defect (137). The overall success rate of TDE is estimated as 60%, with a higher rate of success (approximately 74%) in non-traumatic cases (137,138). The procedure is contraindicated in the presence of untreated coagulopathies, and patients with abdominal lesions such as abdominal aortic aneurysm, where percutaneously traversing the abdomen to the retroperitoneum would be hazardous (139). Reported complications include fat embolism, biliary leak, chronic leg or abdominal swelling, and chronic diarrhoea (138,140). The pooled complication rate of TDE is quoted as 2.4% in a systematic review and meta-analysis performed by Kim *et al.* (138), whilst long-term complication rates were estimated at 14.3% in a retrospective review of cases with successful TDE (140). As such, TDE offers a relatively safe, less-invasive alternative to surgery in the management of chylothorax, with a modest success rate.

In recent years, novel interventional radiology techniques including radiofrequency and microwave ablation of thoracic duct, and needle disruption of retroperitoneal lymph nodes, have been identified as potential therapeutic options in the management of chylothorax (141-143). However, to date these techniques have only been reported in small case series and animal models, and thus require further evaluation before consideration as suitable alternatives to TDE.

Outcomes in chylothorax

The outcome for patients with chylothorax is heavily influenced by the underlying aetiology, and whether this can be successfully reversed. Notably, mortality in post-traumatic chylothorax has greatly improved due to aggressive early therapeutic strategies which counter the ill-effects of chyle loss and, consequently, lead to improved outcomes (134). However, the long-term outcomes for patients with non-traumatic chylothorax remain relatively poor. In a retrospective study of 74 patients, the rate of resolution of chylothorax in non-traumatic cases was worse than traumatic cases (27% versus 50%, P=0.048), even if surgical intervention was utilized as a management strategy for the former (11). Malignancy, chronic chylous effusion, and bilateral chylothorax are all indicative of poor prognosis (144), emphasising the vital role of the multidisciplinary team in formulating appropriate management strategies for these patients.

Conclusions

Chylothorax is an uncommon but important cause of pleural effusion. The clinical presentation can vary between individuals, with symptoms typically related to the rate of chyle accumulation and the underlying cause. Diagnosis depends on appropriate pleural fluid analysis, supported by various imaging studies to help determine the underlying pathology and locate the site of chyle leak. The identification of chylomicrons within pleural fluid is the most definitive diagnostic criterion, although this is not frequently employed in practice, where demonstration of elevated triglyceride and reduced cholesterol levels within the pleural fluid is key (see *Table 3*). Crucially, management of chylothorax must be individualised, considering the anatomical and aetiological factors associated with its development. Conservative approaches, including

Table 3 Key points for clinical practice

Chylothorax is a rare cause of pleural effusion which carries a high risk of mortality
Clinicians should consider the diagnosis in cases of pleural effusion with ongoing output of uncertain cause
The aetiology is wide ranging, but may be categorised broadly as either 'traumatic' or 'non-traumatic' in nature
In practice, diagnosis is based on demonstrating elevated pleural fluid triglyceride levels and reduced cholesterol levels in the presence of a characteristic milky fluid appearance
Occasionally, direct demonstration of chylomicrons within pleural fluid using lipoprotein electrophoresis is necessary to confirm the diagnosis
Various imaging modalities (including CT and MR lymphangiography) may be utilised to support the diagnosis and identify the site of chyle leak
Management is often challenging, involving a combination of conservative methods (e.g., dietary modification, medication, intermittent thoracocentesis) and more invasive radiological or surgical intervention (e.g., thoracic duct embolization or ligation)
In cases of persistent chyle leak, treatment decisions should be guided by adopting a multidisciplinary approach to optimise individual patient care

CT, computed tomography; MR, magnetic resonance.

management of the underlying cause, dietary modification, and pharmacological intervention, are often the first line of treatment. Drainage of the effusion may be required for symptom relief. When conservative methods fail, definitive interventions such as thoracic duct ligation or embolization may be considered. Determining the optimal management of chylothorax represents a nascent field, with a lack of current guidelines. Ongoing research and collaboration among healthcare professionals is essential to improve our understanding and management of this challenging condition.

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