Chylothorax

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KEYWORDS

• Chylothorax • Pleural effusion • Chylous effusion • Thoracic duct

KEY POINTS

- Chylothorax is a rare condition in the general population, with increased incidence in patients with cancer and following specific thoracic and neck surgical interventions.
- Typically described as a milky fluid, it is crucial to differentiate chylothorax from other conditions such as pseudochylothorax, empyema and or complications from misplaced feeding or intravenous catheters with leakage of nutritional formulas into the pleural space.
- Etiologies of chylothorax are broadly categorized into traumatic and non-traumatic, with thoracic surgery being the leading cause of the former and malignancy the most common cause of the latter. Thoracentesis remains the gold standard for diagnosis.
- A multidisciplinary approach is necessary for effective management of chylothorax. Multiple interventions are available, but no randomized controlled trials exist to recommend one over another.
- The resolution of chylothorax and the prognosis of affected patients vary significantly and are heavily influenced by the underlying disease process responsible for the chylous effusion.

INTRODUCTION

Chylothorax, a rare form of pleural effusion, results from disruption of the thoracic duct, leading to the accumulation of chyle in the pleural cavity. Chyle, a milky fluid, comprises mainly lymphocytes, immunoglobulins, water, vitamins, and fat. The earliest documented cases of chylothorax trace back to observations in animals by Eustachius in 1565 and Asellius in 1622. Human cases were subsequently described by Bartolet and Vesilingius in 1633 and 1634, respectively, with Quincke publishing the initial human case report in 1875. Blalock's experimental occlusion of the superior vena cava in 1936 provided insight into its pathophysiology, and Lampson's successful therapeutic duct ligation in 1948 marked a pivotal advancement in treatment.[1–4]

The thoracic duct originates in the cisterna chyli near the first or second lumbar vertebrae, ascending through the posterior mediastinum via the aortic hiatus. By the fifth or sixth thoracic vertebrae, it veers leftward behind the esophagus, ultimately draining into the venous circulation at the left venous angle, also known as Pirigoff's angle.[5,6] The thoracic duct measures 36 to 45 cm in length and has a diameter that ranges from 5 to 8 mm at its origin, tapering to 2 to 3 mm in the midthoracic region before widening again toward its termination. Its diameter varies with the rate of lymphatic flow, estimated at 1500 to 2400 mL/d, and increases with dietary fat intake.[6,7]

This anatomic configuration, however, is not uniformly present, appearing in only 40% to 65% of cases.[5,8] The path of the thoracic duct facilitates the efficient drainage of lymph from all body regions except for the right side of the head and neck, the right upper extremity, and the right side of the thorax. These areas are served by the right lymphatic duct, which empties into the right subclavian vein at the junction with the right internal jugular vein.[9]

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Abbreviations	
CC	cisterna chyli
CXR	chest x-ray
IPC	indwelling pleural catheters
LDH	lactate dehydrogenase
MR	magnetic resonance
TD	thoracic duct
TDD	thoracic duct disruption
TDE	thoracic duct embolization
TPN	total parenteral nutrition

Understanding the anatomy of the thoracic duct is crucial when evaluating and managing patients with chylothorax. Most patients present with unilateral effusions, with 50% occurring on the right side, 33% on the left side, and only 16% exhibiting bilateral effusions.[10] The side of the effusion depends on the location of the chylous leak, presenting specific therapeutic challenges. Despite significant advances in medicine, the treatment of chylothorax remains complex, with no consensus among the various specialties involved in patient care.

This review aims to detail the essential aspects of chylothorax, outline the available treatment modalities, and evaluate supporting evidence for each therapeutic approach.

CLINICAL PRESENTATION

Patients with chylothorax often present with nonspecific symptoms such as shortness of breath, cough, and chest discomfort.[11] Notably, there is no definitive correlation between the volume of pleural fluid and the severity of dyspnea, and the mechanisms underlying dyspnea on patients with pleural effusions remain poorly understood.[12–14] The timeline of symptom onset is crucial in differentiating the etiology of chylothorax. Acute, high-output chylothorax, often seen in posttraumatic cases, presents abruptly within hours to days of the injury, whereas a gradual onset over weeks to months usually indicates nontraumatic chylothorax.[15,16] Establishing the timeline is particularly important in suspected drug-induced cases, as the effusion must appear after the initiation of the medication.

Patients with high-output chylothorax may experience immunologic and nutritional deficiencies due to the continuous loss of fat, vitamins, electrolytes, and immunoglobulins, leading to impaired absorption of fat-soluble vitamins (A, D, E, and K). Although immunodeficiency may occur, Infection of the pleural space is rare due to the bacteriostatic effect of immunoglobulins within the fluid.[17] An exceedingly rare manifestation is chyloptysis (Fig. 1), which requires a communication between the lymphatic vessels and the tracheobronchial tree or a bronchopleural fistula with a chylous effusion, allowing for the expectoration of chylous fluid.

EVALUATION

The usual next step in evaluating chylothorax is to obtain chest imaging: chest x-ray (CXR), thoracic ultrasound, or computed tomography. On CXR and ultrasound, the findings are nonspecific and common to other causes of pleural effusion, such as opacification of the hemithorax (Fig. 2) with a meniscus sign. Ultrasound examination typically shows an anechoic effusion that is freely flowing in most cases.[18] Computed tomography of the chest, abdomen, and pelvis can identify the cisterna chyli and the thoracic duct nearly 100% of the time and is useful for narrowing the differential diagnosis of chylothorax.[19] Magnetic resonance (MR) lymphangiography has emerged as a superior alternative, offering detailed anatomic imaging of the lymphatic system and identifying specific pathologies such as masses, diffuse lymphatic diseases, and lymphatic leaks without exposure to radiation and minimal or no contrast media.[20,21] Furthermore, MR has been incorporated into diagnostic and treatment algorithms, contributing to the successful management of patients with nontraumatic chylothorax.[22] Despite continuous improvements in diagnostic techniques, thoracentesis remains the gold standard for the diagnosis of chylothorax.

Thoracentesis is crucial for the diagnosis of chylothorax. Classically, the fluid has been described as milky in appearance (see Fig. 2) with a triglyceride level above 110 mg/dL considered the cutoff value for the diagnosis.[23] Conversely, a triglyceride level below 50 mg/dL classically typically rules out chylothorax; however, retrospective research indicates that 2% of the patients had triglyceride levels below 50 mg/dL.[24] If the index of suspicion remains high despite normal or low triglycerides levels, chylomicrons (lipoprotein electrophoresis) must be ordered in the pleural fluid to confirm the diagnosis. Recent evidence suggests that chylothorax can be a diagnostic dilemma due to the heterogeneity and variables affecting the fluid analysis. A retrospective analysis reported that only 44% of the cases had milky fluid, with appearance directly correlated with triglycerides levels and inversely correlated with the nutritional status of the patient; subjects with poor nutritional status often present with serous or serosanguinous fluid on gross examination.[24] Typically, the fluid will be an exudate by Light's criteria, but 14% of the cases will be labeled as transudate effusions, often associated with liver cirrhosis.[25] Furthermore, the

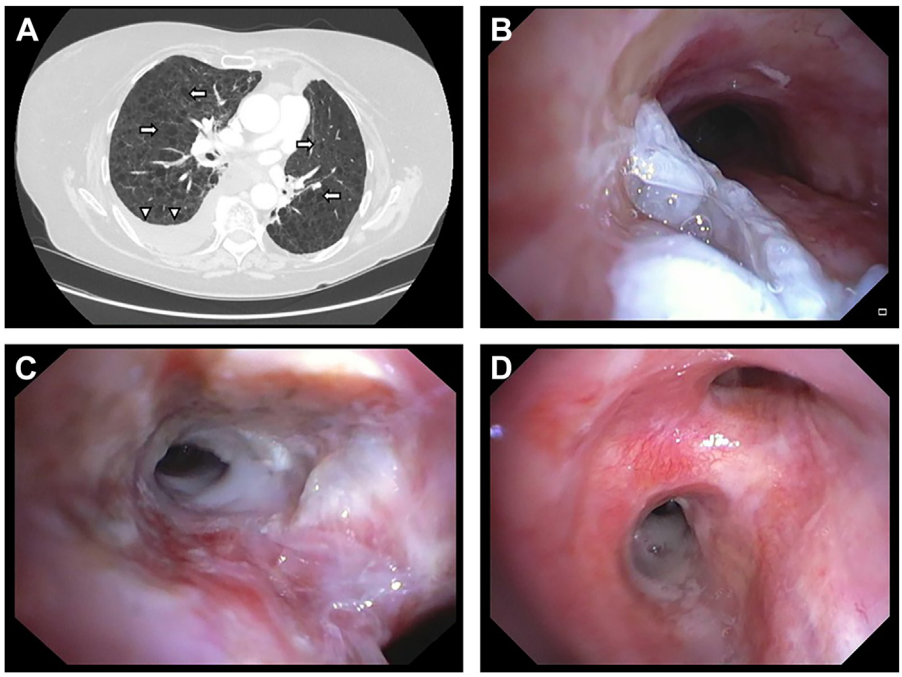

Fig. 1. Patient with lymphangioleiomyomatosis and stage IIIA adenocarcinoma, likely pulmonary lymphatic perfusion syndrome leading to chyloptysis. (*A*) Computed tomography of the chest demonstrating diffuse thin-walled cysts of different sizes (*arrows*) and a right-sided chylous effusion (*arrowhead*). (*B*) Bronchial casts formed of chyle in the trachea. (*C*) Chyle freely flowing in the left mainstem in the background of airway changes related to radiation therapy received. (*D*) Chyle pooling in the distal bronchus intermedius.

lactate dehydrogenase (LDH) is usually low, and the protein level in the fluid is around 2 to 3 g/dL.[24,26]

A thorough evaluation of pleural fluid is essential, as not all "milky" effusions indicate chylothorax. Misidentification can lead to improper management. The primary differential diagnosis for a white pleural effusion includes chylothorax, pseudochylothorax, empyema, and extravasation of parenteral nutrition or tube feeds due to catheter or tube feeding migration into the pleural space. Pseudochylothorax involves effusions rich in cholesterol (as opposed to chylomicrons) or lecithin–globulin complexes, and it is usually related to pleural

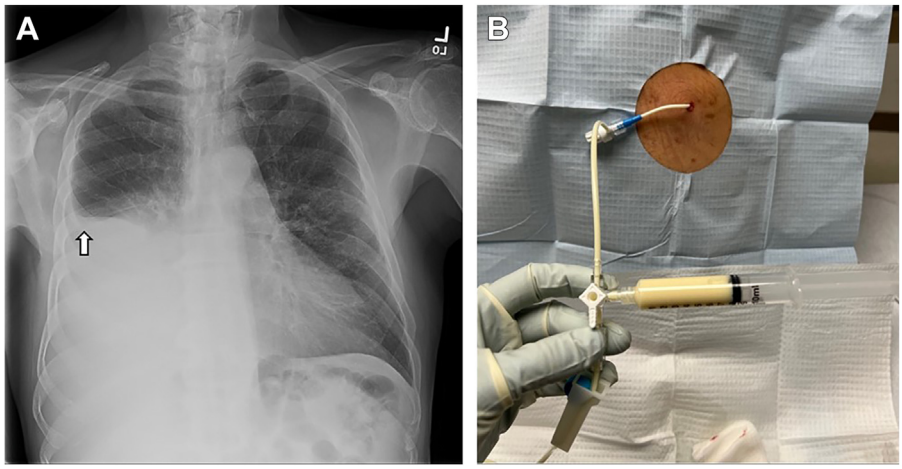

Fig. 2. Patient with medication-induced chylothorax (selpercatinib). (*A*) Chest radiograph (PA projection) demonstrating increased density in the right hemithorax with a meniscus sign laterally (*arrow*). (*B*) Milky appearance of pleural fluid.

tuberculosis, chronic pneumothorax, and chronic rheumatoid pleuritis (Table 1).[27]

ETIOLOGY

The etiology of chylothorax can be categorized into traumatic and nontraumatic causes. Traumatic causes encompass chest trauma, neck or chest surgeries, central venous catheter or pacemaker insertion, and even forceful emesis or coughing. Nontraumatic etiologies include malignant and nonmalignant conditions, as well as idiopathic, drug-induced, and congenital chylothoraces (Table 2).

Nontraumatic chylothorax can arise from one or more theoretic mechanisms.[20] These include the transdiaphragmatic migration of chylous ascites into the pleural space, often seen in patients with liver cirrhosis, abdominal malignancies, pancreatitis, and nephrotic syndrome. Another mechanism involves the invasion of the thoracic duct by malignant conditions, resulting in duct obstruction and impaired flow. Elevated hydrostatic pressure within the thoracic duct or lymphatic vessels, which occurs in conditions such as thoracic malignancies causing extrinsic compression of the lymphatic system, heart failure, or, rarely, thoracic aortic aneurysm, also contributes to chylothorax.[28] Finally, dysfunction of the lymphatic vessels leads to hyperpermeability and chyle leakage into the pleural space, as seen in lymphangioleiomyomatosis, yellow nail syndrome, infections, and medication-induced cases (Fig. 3).

The incidence of chylothorax varies based on the population studied. A review of over 5500 thoracenteses performed at a cancer hospital over 9 years revealed that 10% were chylothoraces.[29] Among adults undergoing thoracic surgery, the incidence is approximately 0.42%, increasing to 2% to 4% following esophagectomy.[30–32] For patients undergoing lung surgery and mediastinal dissection for lung cancer, the incidence ranges from 0.6% to 2.58%.[33,34] After total thyroidectomy with neck dissection, the incidence is 1.85%, rising to 7.3% when a thoracic approach is utilized and to 4.7% for chyle fistula, including chylothorax, following neck dissection involving level IV lymph nodes.[35,36]

Lymphoma accounts for 75% of chylothoraces associated with malignancy.[37] Tyrosine kinase inhibitors are the medications most frequently linked to chylothorax, with selpercatinib associated with a 7% incidence, followed by agerafenib (4%), cabozantinib (0.3%), and lenvatinib (0.02%).[38] Although the estimated incidence of pleural effusions associated with dasatinib is 20% to 30%, chylothorax remains extremely rare (see Fig. 3).[39–41]

MANAGEMENT

Managing chylothorax presents significant challenges due to the absence of standardized guidelines. A multidisciplinary approach is essential to achieve optimal patient outcomes. Whenever feasible, addressing the underlying cause is paramount. Conservative measures are universally recommended, regardless of etiology. In refractory cases characterized by high chyle output, more invasive interventions are considered, albeit with heightened patient risk. Treatment objectives include relief of dyspnea, preventing dehydration, maintenance of nutrition, reduction, or resolution of the chylothorax and, in nontraumatic cases, establishing the cause of the chylothorax and initiating of specific treatment.[37] The cornerstone of treatment entails therapeutic thoracentesis, nutritional management, medications to reduce thoracic duct flow, interventional radiology procedures, surgeries, and pleural interventions.

Thoracentesis

The initial thoracentesis should be performed for diagnostic and therapeutic purposes, achieving maximal drainage of pleural fluid guided by symptoms.[42] In many cases, only a few therapeutic thoracenteses are needed to relieve dyspnea,

Table 1
Pleural fluid characteristics of chylothorax, pseudochylothorax, and empyema

Pleural Fluid	Chylothorax	Pseudochylothorax	Empyema
Cellularity	Lymphocytic	Neutrophilic	Neutrophilic
Light's criteria	Exudate	Exudate	Exudate
Triglycerides (mg/dL)	>110	<50	<110
LDH	Low	Low	High
Glucose	Normal	Normal	Low
Cholesterol (mg/dL)	<200	>200	>45
Protein (g/dL)	2–3	>3	>3

Table 2
Etiology of chylothorax

Traumatic	Nontraumatic
Chest trauma	Malignancy
Neck or chest surgery	Liver cirrhosis and chylous ascites
Pacemaker or central venous catheter insertion	Nephrotic syndrome
Forceful emesis or coughing	Heart failure
Spinal surgeries (thoracic and lumbar)	Medications
—	Idiopathic stenosis of the thoracic duct
—	Sarcoidosis and other causes for enlarged mediastinal adenopathies
—	Parasitosis (Paragonimus and filariasis)
—	Lymphangioleiomyomatosis
—	Yellow nail syndrome
—	Congenital chylothorax
—	Radiation therapy to chest
—	Goiter
—	Idiopathic chylothorax

either because the cause of the chylothorax is successfully addressed or due to the patient's poor overall condition, necessitating different noninvasive palliative measures. A recent retrospective review reported that 34% of patients with chylothorax were managed with repeated therapeutic thoracenteses as the exclusive invasive intervention.[43]

Nutritional Management

Nutritional management plays a fundamental role in chylothorax treatment by reducing chyle production and supporting ongoing nutritional losses. A low-fat, high-protein diet emphasizing medium-chain triglycerides is typically recommended to facilitate absorption via portal circulation (as opposed to lymphatics), thereby minimizing chylomicrons processing.[44] Concerns regarding potential fat-soluble vitamin deficiencies necessitate careful supplementation alongside dietary fat restriction. As the patient improves, dietary fat intake can be gradually increased. However, if there is no improvement, some patients may need to switch to total parenteral nutrition (TPN) instead. Further robust research is warranted to better understand the direct impact of dietary interventions on managing chylothorax.[45]

Pharmacologic Interventions

Pharmacologic interventions such as somatostatin and its analogs like octreotide, aim to reduce thoracic duct flow by enhancing splanchnic blood flow and intestinal absorption.[46] Evidence supporting their efficacy primarily derives from small retrospective studies.[47] One of the largest reports included 7 patients with malignant etiology who were successfully treated with octreotide alongside dietary modifications.[48] Additional medications, including etilefrine and midodrine, lack substantial supporting evidence.[49–51] Sirolimus, an mechanistic target of rapamycin (mTOR) inhibitor, holds conditional recommendation for refractory chylous effusions in lymphangioleiomyomatosis, based on limited observational data.[52,53]

Conversely, certain medications can induce chylothorax, most commonly tyrosine kinase inhibitors used for the treatment of malignancies. Due to the rarity of these adverse effects, there is no clear strategy for managing this select group of patients. A multicenter retrospective study found that selpercatinib had the highest association with chylothorax (7%) and noted no improvement in the rate of chylothorax recurrence after the medication dose was reduced.[38] Ideally, the oncologist should lead a discussion about switching therapeutic regimens, but not all patients are candidates for such changes based on the molecular profiling of their underlying malignancy.

Interventional Radiology Procedures

Interventional radiology plays an essential role in treating chylothorax, utilizing lymphangiography (**Fig. 4**) to map anatomy and identify leaks. Procedures such as thoracic duct embolization (TDE) and thoracic duct disruption (TDD) are reserved for patients with high-output chylothorax or those with prolonged drainage or poor nutritional status.[54] TDE involves performing lymphangiography followed by cannulating the thoracic duct and using platinum coils and/or n-butyl cyanoacrylate glue (N-BCA) glue to occlude it below the leak site.[55] TDD is reserved for cases where cannulation of the thoracic duct is not feasible due to anatomic complexities such as small size, extensive collateral vessels, or failure of lymphatics to opacify.[56] This technique involves multiple needle passes to isolate and disrupt feeder vessels supplying the thoracic duct,

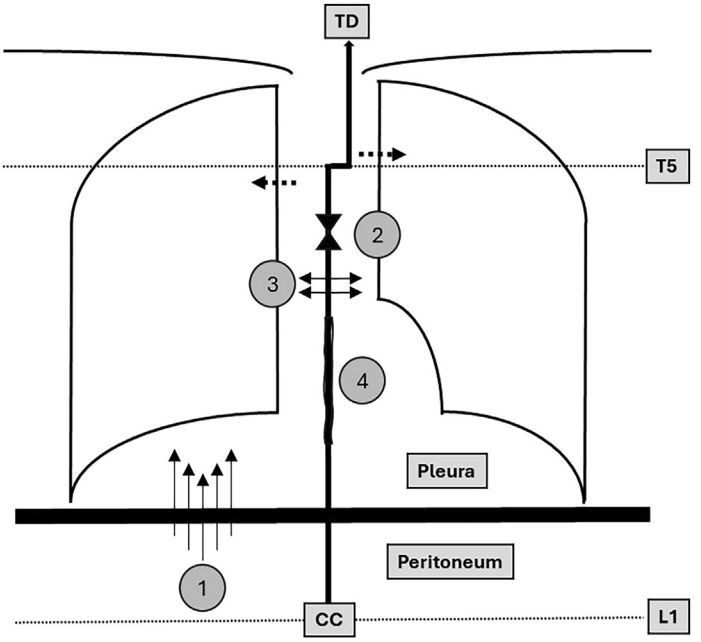

Fig. 3. Theoretic mechanisms responsible for the development of nontraumatic chylothorax. The mechanisms include (1) transdiaphragmatic migration of chyle, (2) thoracic duct (TD) obstruction, (3) elevated lymphatic hydrostatic pressure, and (4) lymphatic dysfunction. The thoracic duct shifts to the left side at the level of T5 (*dotted line*). Dashed arrows indicate the direction of chyle leakage depending on whether the injury occurs above or below T5. The cisterna chyli (CC) is at the level of L1.

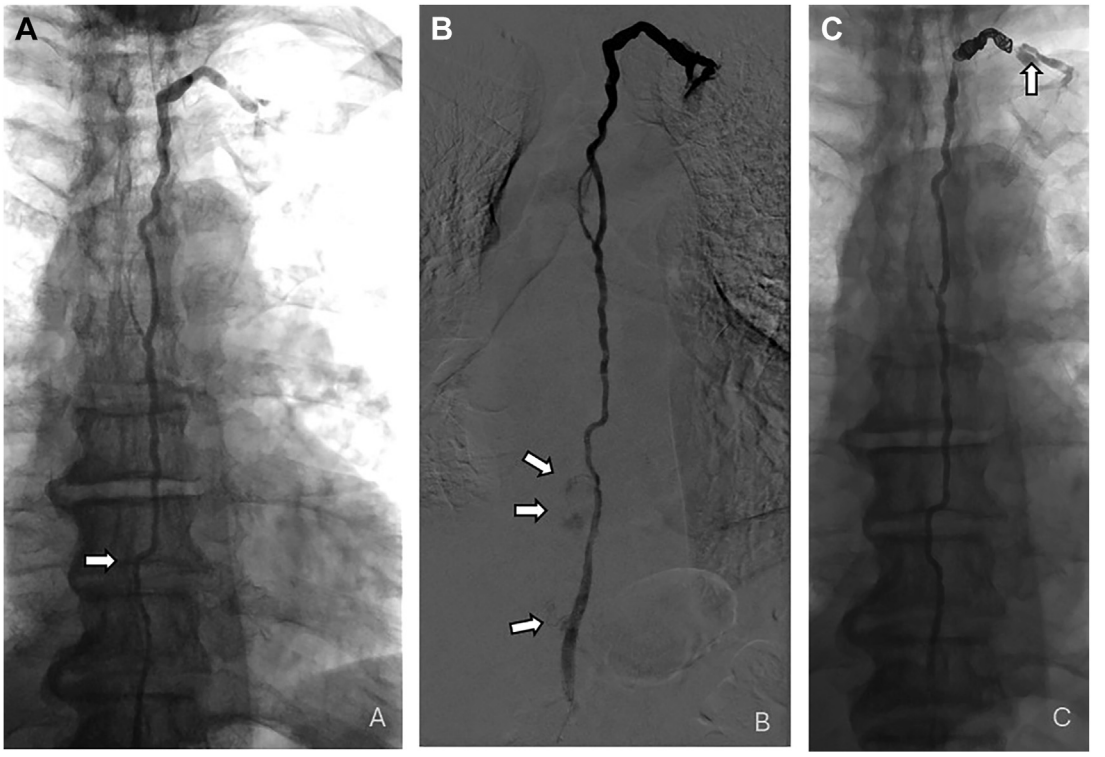

Fig. 4. Lymphangiography and thoracic duct embolization. (*A*) Lymphangiography illustrating the anatomy of the thoracic duct. The arrows indicate the point where the duct crosses the midline and ascends to the left side. (*B*) Digital subtraction lymphangiography identifying the areas (*arrows*) where the chyle is leaking into the right pleural space. (*C*) Postcoil (*arrow*) and glue embolization of the thoracic duct, showing the interruption of contrast flow distal to the coil.

thereby interrupting the drainage into the main duct. Reported outcomes vary in terms of procedural success and clinical efficacy. A recent metanalysis involving 407 patients from 9 studies reported a technical success rate of 63.1% for TDE and a clinical success of 79.4% with a low complication rate of 2.4%.[57] For TDD, the clinical success rate was 60.8%. Interestingly, more recent data suggest that TDE in conjunction with MR using an algorithmic approach has shown promising results with reported clinical success rates reaching up to 93%.[22]

Surgical Interventions

Surgical interventions are typically reserved for patients who are not responding to conservative management or procedures by interventional radiologists and who continue to experience high chyle output or significant nutritional losses. The primary surgical approach is thoracic duct ligation, preferably performed via video-assisted thoracoscopic surgery due to its lower morbidity. This procedure also offers the option of simultaneous surgical pleurodesis.[58] During thoracic duct ligation, identifying the leak site is crucial for ligating the duct proximally. Various techniques have been proposed including increasing fat intake preoperatively, skin dye injection to highlight the duct intraoperatively or employing lymphangiography.[59] Ideally, ligation of the thoracic duct is achieved; however, in cases where intraoperative findings complicate duct dissection, mass ligation of surrounding structures might be necessary, yielding similar outcomes.[58] Clinical success rates for thoracic duct ligation have been reported as high as 85% in a case series involving 97 patients, surpassing those of TDE.[60] Other surgical approaches supported by case reports include laparoscopic ligation of the cisterna chyli (3 cases) in patients unsuitable for or unresponsive to thoracic duct ligation, though with a significantly lower success rate of 67%.[61]

Pleural Interventions

For patients who do not respond to conservative and interventional therapies or who have limited life expectancy, indwelling pleural catheters (IPC) provide a palliative treatment option. Patients with high output chylothorax and IPC are at an increased risk of nutritional and immunologic deficiencies underscoring the rationale for reserving long-term catheter use for palliative care. Limited retrospective data supports IPC efficacy. In a retrospective study spanning 9 years and involving 5594 patients undergoing thoracentesis, 130 met the criteria for chylothorax (triglycerides >110 mg/dL). Among these, 19 experienced recurrent chylothoraces, with 10 undergoing IPC insertion and the remaining 9 managed with other palliative interventions such as repeated thoracentesis, talc pleurodesis, and pleuroperitoneal shunt. The study findings indicated that IPC significantly reduced the need for subsequent procedures compared to the other palliative interventions (only 1 patient in the IPC group required a second procedure whereas 6 patients in the other group underwent a total of 26 additional procedures). However, there were no significant differences in the rates of pleurodesis, associated complication, or symptomatic improvement between the 2 groups. Interestingly, patients in the IPC group experienced a transient decline in albumin levels, which recovered within 6 to 103 days after IPC removal.[29]

Pleurodesis is a described treatment option for chylothorax; however, existing data originate from retrospective studies with small sample sizes. Successful pleurodesis hinges primarily on 2 factors: the rate of fluid accumulation and adequate lung expansion with good pleural apposition.[50] A retrospective analysis of postoperative lung cancer patients with chylothorax identified a cohort of 67 individuals who initially received conservative measures (nil per os with TPN or low long-chain triglyceride diet). Among those who continued to experience recurrent effusion (27 patients undergoing 32 procedures) chemical pleurodesis using 2 g of talc or 300 mg of minocycline via chest tube, achieved a remarkable 100% success rate.[62] Similarly, a separate retrospective study involving 19 patients (undergoing 24 procedures) with underlying lymphoma use medical thoracoscopy and talc insufflation (4–8 g), reporting a 100% success rate among survivors evaluated at 90 days, without procedure-related mortality.[63] In contrast, data on the use of pleuroperitoneal shunts in adults remain scant and largely confined to case reports.

PROGNOSIS

The prognosis of patients with chylothorax varies significantly and is heavily influenced by the underlying disease process causing the chylous effusion. The available data, primarily derived from retrospective analysis, are limited by short follow-up periods and small sample sizes. A retrospective review conducted across 12 hospitals included 77 patients with a median follow-up of 5 months (range 3–12 months). The overall mortality rate in this in this cohort was 54%, with a mortality rate of 59% among patients with malignancy. Chylothorax resolved in 45% of the overall population and 36% of the patients with underlying malignancy.[43]

SUMMARY

Chylothorax is a rare clinical condition characterized by the accumulation of chyle in the pleural space, with an increased incidence in patients with cancer and following specific thoracic and neck surgical interventions. The etiologies of chylothorax can be broadly classified into traumatic and nontraumatic causes, with thoracic surgery being the leading cause of the former and malignancy the most common cause of the latter. Despite this categorization, some etiologies share similar pathophysiologic mechanisms.

Diagnosing chylothorax involves thoracentesis and pleural fluid analysis as the gold standards. Various imaging modalities, including chest radiography, computed tomography, MR imaging, and lymphangiography, are crucial for evaluation. A thorough anamnesis and a deep understanding of the patient's medical history are also essential.

Effective management of chylothorax requires a multidisciplinary team comprising nutrition specialists, thoracic surgeons, interventional radiologists, pulmonologists, oncologists, radiation oncologists, gastroenterologists, and other relevant specialists. Each specialty offers a range of interventions, yet there is a notable lack of high-quality randomized controlled trials to recommend one approach over another definitively. Conservative measures are universally recommended, but in refractory cases with high chyle output, more invasive interventions may be necessary. The resolution of chylothorax and the prognosis of affected patients vary significantly, heavily influenced by the underlying disease process responsible for the chylous effusion.

CLINICS CARE POINTS

- Chylothorax is a rare condition in the general population, with increased incidence in patients with cancer and following specific thoracic and neck surgical interventions.
- Chylothorax is typically described as a milky fluid, but it is crucial to differentiate it from other conditions such as pseudochylothorax, empyema, and complications from misplaced feeding or intravenous catheters leaking nutritional formulas into the pleural space.
- Pleural fluid analysis remains the cornerstone of chylothorax diagnosis. While it is classically described as a milky, lymphocytic-predominant exudate with high triglycerides, research suggests that results may not always follow this pattern. In such cases, lipoprotein electrophoresis to identify chylomicrons is warranted.
- A complete anamnesis and thorough review of the patient's medical history, along with imaging modalities, are crucial for evaluating chylous effusion and determining the underlying cause.
- High-quality data and randomized controlled trials are needed to improve the care of patients with chylothorax. Although there are no official guidelines for treatment, a multidisciplinary approach is recommended.

DECLARATION OF ARTIFICIAL INTELLIGENCE AND ARTIFICIAL INTELLIGENCE-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this article, the authors used ChatGPT in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

DISCLOSURE

The authors have no disclosures.

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