The changing management of chylothorax in the modern era

Bradley Bender, Vijayashree Murthy and Ronald S. Chamberlain

INTRODUCTION

Chylothorax (CTx) results from the accumulation of lymphatic fluid in the pleural space due to an obstruction or leakage of the thoracic duct or one of its contributors [1]. Although rare, CTx is a serious, even life-threatening event if not properly treated. The aetiology of a chyloous effusion can be classified into two categories, spontaneous and traumatic (injury or surgery) (Table 1). A spontaneous, or non-traumatic, CTx may be congenital, infectious, neoplastic or due to many other conditions that can cause obstruction of the thoracic duct or aberrant lymphatic flow, such as lymphangiomegaly, lymphangiectasia, mediastinal tumour resection, thoracic aneurysm repair and ascending lymphangitis. A variety of neoplasms include lymphoma, lung cancers, oesophageal cancer or metastatic carcinoma may also cause CTx.

Traumatic CTx results from either blunt or penetrating trauma such as a gunshot wound, knife wound or a fracture or a dislocation of the spine. However, the most common cause of a traumatic CTx is a surgical complication following a thoracic operation or procedure. An increased incidence in postoperative CTx has recently occurred, most notably following increasingly radical procedures that occur after neoadjuvant chemoradiation. Kunitoh et al. [5] found that 2 of 76 patients developed a CTx after receiving chemoradiation before surgical resection of the superior sulcus for non-small-cell lung cancers, while Hagry et al. [4] reported 2 of 90 patients who developed a CTx following chemoradiotherapy before oesophagectomy for oesophageal carcinoma. Among all thoracic procedures, oesophagectomy has the highest incidence of postoperative CTx (1–9%). Additional procedures associated with a relatively high rate of chylous effusions include mediastinal and cervical lymph node dissection, subclavian vein catheterization, lobectomy or pneumonectomy, mediastinal tumour resection, thoracic aneurysm repair and sympathectomy.

Patients with a CTx typically present with symptoms of respiratory compromise or distress such as dyspnoea, chest pain, cough and fatigue, similar to a pleural effusion, as a result of mechanical compression of the heart and lungs [6]. Long-term CTx complications include lymphopenia (absolute circulating peripheral lymphocyte count of <1500/µl), which directly correlates with a longer duration of chyloous leak [7]. Decrease in
cellular and humoral immunity (hypogammaglobulinemia) ultimately leaves the patient immunosuppressed and susceptible to infection and sepsis. Haematological CTx complications have also been reported in children. Bernet-Buettker et al. [8] reported an increased loss of antithrombin in children with a CTx, which potentially predisposes to an increased risk of developing thrombosis. Conversely, these children have haemorrhagic complications due to the loss of fibrinogen and prothrombin [2].

Electrolyte imbalance following a CTx can also result in metabolic acidosis, hyponatraemia or hypocalcaemia. Hypovolaemia may also be present due to the intravascular volume depletion. The loss of proteins, fat-soluble vitamins, lipids and electrolytes raises great concern for nutritional deficiency [6]. Patients may enter a catabolic state from chyle drainage and develop malnutrition [2]. The greater the duration of chylous leak, the greater are the detrimental effects, and the need for urgent treatment.

To date, consensus guidelines on the management of CTx are unavailable, and institution- or surgeon-specific approaches are the current norm. This paper critically examines the current evidence-based therapeutic approaches to the treatment of CTx and attempt to provide clear clinical guidelines as to which one approach is preferred in various clinical situations.

### Table 1: Aetiology of spontaneous and traumatic chylous pleural effusions

<table>
<thead>
<tr>
<th>Spontaneous</th>
<th>Congenital</th>
<th>Idiopathic</th>
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<tbody>
<tr>
<td></td>
<td>Lymphangiectasis</td>
<td>Lymphangiomatosis</td>
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<td></td>
<td>Tuberous sclerosis</td>
<td>Congenital heart disease 5% [2]</td>
</tr>
<tr>
<td></td>
<td>Chromosome abnormalities (Turner’s or Down’s syndrome)</td>
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<tr>
<td>Neoplastic</td>
<td>Lymphoma</td>
<td>Lung cancers</td>
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<td></td>
<td>Oesophageal cancer</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>Infectious</td>
<td>Tuberculous lymphadenosis</td>
<td>Mediastinitis</td>
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<tr>
<td></td>
<td>Ascending lymphangitis</td>
<td></td>
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<tr>
<td>Obstruction</td>
<td>Superior vena cava thrombosis</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Obstructive</td>
<td>Amyloidosis</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Lymphangioleiomyomatosis (Women)</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>Gunshot wound</td>
<td>Knife wound</td>
</tr>
<tr>
<td>Penetrating</td>
<td>Fracture or dislocation of the spine</td>
<td>Fracture or dislocation of the spine</td>
</tr>
<tr>
<td>Thoric surgery</td>
<td>Oesophagectomy 1–9% [3]</td>
<td>Radical lymph node dissection of the chest, neck and mediastinum</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>Lobectomy or pneumonectomy</td>
<td>Mediastinal tumour resection</td>
</tr>
<tr>
<td>Thoracic</td>
<td>Thoracic aneurysm repair</td>
<td>Excessive pleural resection</td>
</tr>
<tr>
<td>surgery</td>
<td>Excision of cervical lymph nodes</td>
<td>Excision of cervical lymph nodes</td>
</tr>
<tr>
<td></td>
<td>Sympathectomy</td>
<td>Sympathectomy</td>
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<tr>
<td></td>
<td>Subclavian vein catheterization with a central line</td>
<td>Subclavian vein catheterization with a central line</td>
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</tbody>
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### MATERIALS AND METHODS

A systematic review of the English language literature from 1948 to 2012 was performed using Medline, Google Scholar, Embase and Cochrane Central Register of Controlled Trials to obtain access to all publications pertaining to the aetiology, pathophysiology, complications and management (conservative and surgical techniques) of CTx. The search strategy used keywords such as CTx, chylous leak, CTx treatment, CTx surgery and CTx postoperative. Articles were retrieved and reviewed, and evidence derived from the literature in combination with consensus reports was applied to derive evidence-based management of CTx in both the traumatic and non-traumatic setting.

### Anatomy of thoracic duct and pathophysiology of chylorhox

The thoracic duct originates as the cisterna chyli on the anterior surface of the bodies of the first and second lumbar vertebrae, lateral to the aorta [1, 3, 9]. Although the thoracic duct can have a variable course, it is most consistently found at the level of the diaphragm where it passes through the aortic hiatus concomitantly with the aorta and azygous vein as it enters the posterior mediastinum. The thoracic duct then continues its course between the aorta and azygous vein and crosses to the left side of the body at either the fifth or sixth thoracic vertebrae. It runs posterior to the aortic arch and next to the oesophagus until it drains into the junction of the left subclavian and internal jugular veins, where lymph enters the systemic circulation [10, 11]. That said, the termination of the thoracic duct in consistently inconsistent, with many having up to three terminal vessels of the thoracic duct, rather than a single-vessel termination [12]. Furthermore, the location in which the thoracic duct vessel(s) terminate can vary as well and ranges from ending at the venous angle, the terminal end of the internal jugular vein and the terminal end of the external jugular vein [13]. Forty percent of individuals have multiple branches of the thoracic duct located in the mid-thoracic region [10].

The thoracic duct functions to transport chyle back to the bloodstream. In a normal adult, the thoracic duct transports between 1.5 and 4 l of chyle per day [14, 15]. Chyle is produced in the small intestine via the capillary filtrate, which consists of fluids, electrolytes, peptides and lipoproteins, and intestinal absorption and secretion by enterocytes that line the intestinal epithelium [12]. Long-chain triglycerides in the diet are converted into chylomicrons and very-low-density lipoproteins. Chyle is mainly composed of chylomicrons (a form of triglycerides that are large spherical proteins that transport large amounts of dietary fat absorbed by the small intestine to the lymph from the enterocytes), lymphocytes (predominately T-lymphocytes), electrolytes, immunoglobulins, albumin, fibrinogen, glucose and fat-soluble vitamins.

### Clinical presentation and diagnosis

Rapid identification of the presence of a CTx is crucial in managing a chylous leak, since early detection has been shown to improve patient outcomes and limit complications. Many times it can be very difficult to identify the location of a chylous leak intraoperatively as most patients have fasted overnight. Several techniques including the administration of butter or
cream, or methylene blue through a nasogastric tube one hour before or during surgery have proved valuable to identify the leak at the CTx location at the time of surgery [16–18].

The gross appearance of the pleural fluid from a chest tube or thoracocentesis is often used to raise suspicion of a CTx. The fluid of a chylous effusion although mainly milky, can also appear serous, sanguineous or bloody. Maldonado et al. [19] observed that less than half of chylothoraces (44%) had the characteristic milky appearance. Absence of a milky pleural effusion does not exclude the diagnosis of a CTx. A clear appearance of the pleural fluid may be most common in the immediate postoperative patient since they are typically kept in a fasting state and thus are not consuming triglycerides or proteins. The differential diagnosis of a milky pleural fluid also includes a cholesterol pleural effusion or an empyema.

Early indications of a CTx include a daily chest tube output of ≥400 ml. High outputs from the chest tube should prompt the clinician to order a pleural fluid analysis to confirm suspicions [9]. Staats et al. have suggested that a pleural fluid analysis revealing a pleural fluid with a triglyceride level of >110 mg/dl (1.24 mmol/l) is associated with a >1% chance of being non-chylous, thus supporting the diagnosis and giving this test a high specificity. Similarly, a triglyceride level <50 mg/dl is associated with less than 5% chance of being chylous, and allows physicians to confidently exclude a CTx, with a high degree of sensitivity. In this study, a chylous pleural effusion was defined as the presence of a distinctive band of chylomicrons on the lipoprotein electrophoregram [20]. Using the cut-off values from the study, ambiguity exists only when pleural triglyceride levels fall between 50 and 110 mg/dl. A lipoprotein electrophoresis, the gold standard for diagnosis of a CTx, should be performed in this setting to confirm the diagnosis. Although these cut-off values are widely accepted, the nutritional status of the patient must be considered. Maldonado et al. [20] has recently reported that 14% of chylothoraces may be diagnosed with triglyceride levels <110 mg/dl and two patients in their study had triglyceride levels <50 mg/dl.

Additional methods of pleural fluid analyses include cell count, pH, cholesterol, glucose, amylose, lactic dehydrogenase (LDH) and total protein. Agrawal et al. [21] have highlighted the importance of using these variables mentioned above to differentiate between a CTx caused solely by extravasation of chyle from the thoracic duct or its tributaries, versus the presence of coexisting conditions. Although chyle has a protein concentration of 2–3 g/dl (which would cause chyle to be a transudate), most chylothoraces are exudative (86%) [20]. These authors describe typical chyle as a lymphocyte-predominant (>50% lymphocytes), protein-discordant exudate (fluid/serum total protein ratio of >0.50 and an LDH concentration of <160 IU/l) with elevated triglyceride or chylomicron levels. Transudative effusions have also been observed secondary to congestive heart failure, lymphoma, pancreatic cancer, radiation therapy, amyloidosis and obstruction of the superior vena cava, nephrotic syndrome and cirrhosis [19, 21, 22]. Increased LDH levels have also been seen in the diagnosis of infected biliopleural fistula and pneumonia, and cirrhosis. Patients with chylous pleural effusions who do not fit the criteria of lymphocyte-predominant, protein-discordant exudate should be further evaluated for secondary causes of a CTx.

Traditionally, imaging for CTx is not novel and includes chest radiography to identify a pleural effusion, but offers little diagnostic value. Computed tomography (CT) of the thorax and abdomen may be useful in identifying the location and secondary causes of the chylous leak such as retroperitoneal lymphadenopathy or a cystic lesion due to mediastinal lymphangioma [23], pulmonary causes such as lymphangioleiomyomatosis, thoracic lymphangiectasia, lymphangiomatosis or giant lymph node hyperplasia [24].

Lymphangiography and lymphoscintigraphy are typically used to locate the leak and assess the thoracic duct patency as well as differentiate partial from complete thoracic duct transection. Notohamipodjo et al. [25] have recently reported the sensitivity and specificity of lymphangiography and lymphoscintigraphy for abnormal lymph vessels and an abnormal pattern of lymphatic drainage (Table 2). In a retrospective study, Itkin et al. [26] found that 108 of 109 patients underwent successful lymphangiograms. However, Chen et al. [27] found that a lymphangiogram was able to only identify the cause in 63% of patients with a non-traumatic CTx. The anatomical localization data obtained from these studies is key to the determination of the treatment method, particularly in cases of aberrant thoracic duct anatomy [28]. In some instances, lymphangiography has been therapeutic as well as diagnostic. Alejandre-Lafont et al. [29] reported that lymphangiography successfully occluded the lymphatic leak in 70% of patients when the lymphatic drainage was less than 500 ml/day. That said, lymphangiography may potentially cause significant adverse side-effects such as local tissue necrosis, fat embolism to the lungs, hypersensitivity reaction or worsening of lymphoedema from the contrast material. In contrast, lymphoscintigraphy is quick, minimally invasive and has a low side-effect profile; though it does not share the potential therapeutic qualities of lymphangiography [30].

The most significant factor affecting the rapidity of treatment of a CTx is the volume of output of chyle. Chyle flow rates <500 ml/day are associated with a favourable spontaneous closure rate and are typically managed medically, while outputs of >1 l/day should be treated surgically to reduce both morbidity and mortality [18, 31]. Low flow rates are not emergent since most patients are not at risk of severe metabolic or nutritional deficiencies as most occur with high flow rates. If a CTx persists beyond 7–14 days or a patient with a low-volume CTX begins to deteriorate, surgery is indicated [32–35]. In patients not considered for surgical therapy, chemical pleurodesis can be attempted in efforts to cure the CTx [36].

### Table 2: Sensitivity and specificity of lymphangiography and lymphoscintigraphy for identifying the site of chylous leak [25]

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<tr>
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<th>Lymphangiography</th>
<th>Lymphoscintigraphy</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Specificity</td>
<td>79%</td>
<td>100%</td>
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### Chylothorax treatment

Management of chylothoraces may be either conservative or surgical. Conservative management aims to reduce chyle production through nutritional measures and control symptoms by draining the chylous effusion from the chest cavity. The end point for conservative management is spontaneous closure of the lymphatic
Octreotide is a synthetic somatostatin analogue that inhibits the release of octreotide and somatostatin in the management of CTx. Itkin et al. (2010) [26] 45 Non-traumatic Chylous drainage, dietary restrictions, drainage and TPN 87%

Several investigators have also shown the reported efficacy of octreotide and somatostatin in the management of CTx. Octreotide is a synthetic somatostatin analogue that inhibits the secretion of growth hormone, glucagon, insulin and lymph fluid excretion [47, 48]. Somatostatin also reduces splanchnic blood flow and secretion of water and electrolytes [48]. Foo et al. studied the effectiveness of octreotide treatment in a pre-term infant with a CTx that was refractory to all other modes of non-surgical, medical management. Octreotide was initially administered at a dose of 16 µg/kg/d subcutaneously and subsequently titrated up to 48 µg/kg/d over a 6-day period. The chylous drainage subsided after 4 days of treatment [47].

In symptomatic patients, the initial step in management is aimed at relieving intrathoracic pressures followed by respiratory distress which results from lung compression and this is achieved by placement of a thoracostomy tube. Merely draining chyle from the pleural space and allowing re-expansion of the lung decreases the size of the potential pleural space and seals the leak [38].

If the chyle flow rate is <500 ml, conservative measures can be employed and may seal the leak in 27–100% of cases (Table 3). Conservative management after a chest tube placement involves dietary management, namely avoidance of oral and enteral fat intake in order to reduce chyle production [45]. The absence of long-chain triglycerides results in decreased production of chyle. Maldonado et al. [33] showed that the decreased flow of chyle through its tributaries in a non-traumatic CTx allows for the possibility of spontaneous closure in up to 50% of cases. Nil per oral regimen is secondary, but should only be used in conjunction with a total parental nutrition regimen in order to replenish caloric, electrolyte and protein deficits [46].

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Pleurodesis is an additional non-surgical method for the treatment of CTx, which may be used alone or conjunction with thoracic duct ligation for intractable CTx and has been another appealing method for resolving chylous effusions [1, 36, 41]. Agents that have been shown effective in pleurodesis include tetracycline, minocycline, bleomycin, OK-432, povidone iodine and talc, which is the most utilized method [50–52]. Multiple case studies have documented the efficacy of using chemical pleurodesis without thoracic duct ligation with success rates ranging from 80 to 100 percent (Table 3) [33, 36, 44].

Table 3 lists all reports on the efficacy of surgical management of chylothoraces. Overall, surgical therapy is successful in 67–100% of the cases. Direct thoracic duct ligation via VATS or open surgery results in popular and successful means to resolve a CTx resulting from post-surgical complication [44]. The thoracic duct is ligated just proximal to the aortic hiatus, in cases where the leak site cannot be directly identified [54]. Lai et al. [14] have described ligation of the thoracic duct at the level between the inferior pulmonary vein and the diaphragmatic hiatus using direct suture ligation to encircle all the lympho-fatty tissue located among the pleura, aorta and spine, including theazygos vein [55]. However, a leak at more than one site may occur, particularly from one of the tributaries, which favours ligation proximal to the aortic hiatus when the site cannot be visualized. Although lymphoedema may occur following thoracic duct ligation, it typically resolves rapidly or new venous–lymphatic collateral circulation develops [1].

VATS has become the gold standard surgical approach for CTx management and is associated with less postoperative pain, quicker recovery and shorter hospital stay [53, 56]. VATS may also be useful in precisely determining the site of the chyle leak, if it is not detected by other methods (Fig. 1). Administration of any of the aforementioned substances, such as butter, cream or...
methylene blue, prior to local anaesthesia and camera insertion may facilitate direct visualization of the leak site. Although clip ligation is the most common procedure performed, application of fibrin glue to the leak site is also effective when the exact leak site cannot be identified [57, 58].

If conservative or VATS ligation of the thoracic duct fails, and the CTx becomes intractable, a pleuroperitoneal or pleurovenous shunt may be the last resort. The two different types of shunts that are available include an active Denver pleuroperitoneal shunt and the passive LeVeen pleuroperitoneal shunt (preferred), with the

| Table 4: All published reports on CTx outcomes following operative management (1981–2009) |
|---------------|------------------|-----------------|--------------------------|
| Study (year) | Number of patients (n) | Cause of CTx | Surgical management | Success ratea |
| Strausser et al. (1981) [39] | 4 | Non-traumatic | Thoracic duct ligation ± pleurodesis | 75% |
| Orringer et al. (1988) [16] | 11 | Traumatic | Thoracic duct ligation | 100% |
| Bolger et al. (1991) [40] | 3 | Traumatic | Thoracic duct ligation | 67% |
| Marts et al. (1992) [32] | 6 | Traumatic | Conservative therapy failed → Thoracic duct ligation | 67% |
| Cerfolio et al. (1996) [42] | 47 | Traumatic | Dietary restrictions, drainage and TPN/thoracic duct ligation ± pleurodesis | 91.2% |
| Dugue et al. (1998) [34] | 9 | Traumatic | Thoracic duct ligation | 77.8% |
| Merigliano et al. (1999) [17] | 15 | Traumatic | Thoracic duct ligation | 93.3% |
| Christodoulou et al. (2006) [53] | 6 | Non-traumatic | VATS thoracic duct ligation | 83% |
| Paul et al. (2009) [44] | 22 | Traumatic | Thoracic duct ligation | 95% |

VATS: video-assisted thoracic surgery.

aSuccess rate was defined by the absence of chylous effusion and without recurrence in the follow-up period.

Figure 1: Proposed algorithm for stepwise conservative and surgical management of CTx in the spontaneous and traumatic setting.
latter being the shunt of choice [59]. The shunt is implanted in the chest and the catheter is used to transport chyle into the peritoneal cavity, where its components can be absorbed [60]. Numerous reports detailing the successful use of a pleuroperitoneal shunt to prevent and cure the recurrence of idiopathic chylous effusion in both children and adults while maintaining TPN and medium-chain triglyceride diet have been described [44, 61, 62]. That said, pleuroperitoneal shunts should not be overused, as complications are significant and include shunt occlusion by fibrin clots, infection, skin erosions, shunt relocation and pneumoperitoneum [59, 63]. Figure 1 provides an algorithmic approach based on best available data for selecting the 'ideal' approach for a specific patient with spontaneous or postoperative CTx.

New directions: surgical approach to high output or intractable chylothorax

Surgical therapy typically requires identification of the leak, which can be accomplished by lymphangiography or lymphoscintigraphy. Once the site of extravasation is visualized, a minimally invasive technique can be performed. In the case of traumatic chylothorax, a minimally invasive approach has been developed, using VATS to identify thoracic duct and either provide occlusion of the leak site, or accomplish a complete thoracic duct ligation. Pleurodesis in conjunction with thoracic duct ligation can also be effective in some patients, and offer relief prior to thoracic duct ligation, though with limited supporting data [36, 39, 41, 42]. If all methods are ineffective, or there is a persistent high-output CTx, pleuroperitoneal shunts can be curative to control chylous effusions [59, 62].

Conflict of interest: none declared.

REFERENCES


