TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Pediatria

Neonatal Chylothorax: a retrospective study in a level III Neonatal Intensive Care Unit

Cláudia Nicole Ornelas Rocha

Orientado por:

Dr. Alberto Berenguer

Julho'2023

Resumo

Introdução: O quilotórax neonatal é uma condição rara, potencialmente fatal, multifatorial, que se caracteriza pela acumulação de linfa no espaço pleural. Pode ser responsável por complicações nutricionais, metabólicas e imunológicas. O objetivo deste estudo é descrever a experiência da abordagem de recém-nascidos (RN), com o diagnóstico de quilotórax, internados numa Unidade de Cuidados Intensivos Neonatais (UCIN) terciária.

Métodos: Estudo observacional, descritivo, retrospetivo, com base na análise dos processos clínicos de RN com o diagnóstico de quilotórax, internados na UCIN do Hospital de Santa Maria, CHULN, EPE, de janeiro de 2012 a fevereiro de 2023.

Resultados: Foram incluídos oito doentes. A mediana da idade gestacional foi de 34 semanas e a mediana do peso foi 2350g. Metade dos casos foram congénitos, com diagnóstico pré-natal, 3 dos quais submetidos a intervenção pré-natal com colocação de shunt pleuro-amniótico. Metade foram iatrogénicos, secundários a trauma durante cirurgia torácica ou cervical. A maioria dos derrames pleurais eram unilaterais (n=5) e localizados à direita (n=3). Dois recém-nascidos apresentavam doença genética. Todos necessitaram de ventilação invasiva e sete de drenagem torácica. Todos fizeram nutrição parentérica e nutrição entérica com fórmula hipolipídica. Sete fizeram MCT oil. Nenhum respondeu totalmente à terapêutica conservadora pelo que todos foram tratados com octreótido, 6 dos quais com sucesso. Dois RN foram submetidos a pleurodese. Três necessitaram de terapêutica com imunoglobulina. Todos apresentaram complicações: 6 tiveram sépsis tardia, 2 tiveram pneumonia. A mediana do tempo de internamento foi de 35 dias. Registaram-se dois óbitos, um no contexto de sépsis com pneumonia e outro por hipoplasia pulmonar.

Conclusão: Nesta série de casos, metade dos doentes tinham diagnóstico pré-natal e metade foram iatrogénicos, refletindo a estreita colaboração da nossa unidade com o centro de diagnóstico pré-natal do Departamento de Obstetrícia e Ginecologia e com o Serviço de Cirurgia Pediátrica do CHULN, EPE. No que diz respeita à abordagem, não há diretrizes, nacionais ou internacionais, universalmente aceites ou baseadas na evidência, gerando controvérsia nalgumas das terapêuticas utilizadas. São imprescindíveis mais estudos, sobretudo multicêntricos, para avaliar a eficácia e os resultados a curto e longo prazo das várias estratégias utilizadas na prática clínica.

PALAVRAS-CHAVE: quilotórax; recém-nascido; Unidades de Cuidados Intensivos Neonatais

Abstract

Introduction: Neonatal chylothorax is a rare, potentially fatal, multifactorial condition characterized by the accumulation of lymph in the pleural space. It can be responsible for nutritional, metabolic, and immunological complications. The aim of this study is to describe the management´s experience of newborns (NB) admitted with chylothorax to a tertiary Neonatal Intensive Care Unit (NICU).

Methods: This is an observational, descriptive, retrospective study based on the analysis of clinical records of NB diagnosed with chylothorax, from January 2012 to February 2023, at the NICU of Hospital de Santa Maria, CHULN, EPE.

Results: Eight patients were included. The median gestational age was 34 weeks, and the median weight was 2350g. Half of the cases were congenital, with pre-natal diagnosis, three of which underwent prenatal intervention with pleuro-amniotic shunt placement. The other half were iatrogenic, secondary to trauma during cervical or thoracic surgery. Most were unilateral effusions (n=5), and right-sided (n=3). Two newborns had genetic diseases. All required invasive ventilation, and seven underwent thoracic drainage. All received parenteral nutrition and enteral nutrition with a low-fat formula. Seven received MCT oil treatment. None responded completely to conservative therapy, so all were treated with octreotide, six successfully. Two NB were submitted to pleurodesis. Three required immunoglobulin therapy. All patients experienced complications: six had late-onset sepsis, and two had pneumonia. The median length of hospital stay was 35 days. Two deaths were recorded, one due to sepsis with pneumonia and the other due to pulmonary hypoplasia.

Conclusion: In our case series, half of the patients had a prenatal diagnosis, and the other half were iatrogenic, reflecting the close collaboration of our unit with the prenatal diagnostic center of the Department of Obstetrics and Gynecology and the Pediatric Surgery Service of CHULN, EPE. Regarding its approach, there is a knowledge gap, without national or international evidence-based guidelines, causing controversy regarding some of the therapeutic interventions recurrently used. Further studies, especially multicenter studies, are essential to evaluate the effectiveness and short- and long-term outcomes of the various strategies used in clinical practice.

Keywords: chylothorax; newborn; neonatal intensive care unit

Index

1. Introduction 9
2. Literature review 10
   - 2.1. Anatomy 10
   - 2.2. Pathophysiology 11
   - 2.3. Etiology 12
   - 2.4. Clinical Presentation 13
   - 2.5. Diagnosis 15
   - 2.6. Management 16
   - 2.7. Complications 22
3. Methodology 25
   - 3.1. Aim of the study 25
   - 3.2. Study design 25
   - 3.3. Study Framework 25
   - 3.4. Population 25
   - 3.5. Data analysis 27
   - 3.6. Ethical considerations 27
4. Results 28
5. Discussion 34
6. Conclusion 37
7. Appendices 38
8. References 39

Acknowledgments

To my advisor, Dr. Alberto Berenguer for all the availability and assistance in the development of this work.

To Dra. Carolina Gonçalves, Dra. Filipa Carmo, and Dra. Alexandra Andrade, for their readiness in collaborating on data collection.

To my parents, for their unconditional support and everything they do for me.

To my friends, who have always been by my side and have made this journey easier and more enjoyable.

Abbreviations and acronyms

AGA - Appropriate for gestational age

b-FGF - Basic fibroblast growth factor

CHULN, EPE - Centro Hospitalar Universitário Lisboa Norte, EPE

HSM - Hospital Santa Maria

IgA - Immunoglobulin A

IgG - Immunoglobulin G

IVIG- Intravenous immunoglobulin

IgM - Immunoglobulin M

LCT - Long-chain triglycerides

LGA - large for gestational age

MCT - Medium-chain triglycerides

MMP-2 - Matrix metalloproteinase-2

NB - Newborn

NICU- Neonatal Intensive Care Unit

RN - Recém-nascido

SGA - Small for gestational age

SVC - Superior vena cava

TPN - Total parental nutrition

UCIN - Unidade de Cuidados Intensivos Neonatais

VEGF - Vascular endothelial growth factor

Index of tables and figures

1. **Figure 1.** Thoracic duct and its anatomic relations 10
2. **Table 1.** Demographic variables 28
3. **Table 2.** Characterization of chylothorax 30
4. **Table 3.** Treatment of chylothorax 31
5. **Table 4.** Complications of chylothorax 33
6. **Table 5.** Outcome of chylothorax 33
7. **Table 6.** Characterization of the cases admitted at NICU with chylothorax 38

1. Introduction

Chylothorax is a rare and potentially life-threatening condition characterized by the presence of chyle, a milky fluid composed mainly of fat, in the pleural cavity. It can either be congenital or acquired (Soto-Martinez & Massie, 2009). It is the most common cause of pleural effusion in the neonate (Van Straaten et al., n.d.). Significant long-term morbidity and mortality due to metabolic, immunologic, and nutritional issues in newborns have been described (Soto-Martinez & Massie, 2009).

The management of neonatal chylothorax is not standardized across neonatal units, with differences in current approaches and treatment options, resulting from the absence of specific guidelines. The limited studies on this subject hinder our understanding of both its short- and long-term results.

This study consists of a retrospective review of the course and management of all patients with neonatal chylothorax, admitted to the Neonatal Intensive Care Unit of Hospital de Santa Maria, in the last 11 years. Additionally, the current understanding of chylothorax will be explored including its main etiologies, clinical presentation, and diagnostic evaluation. Finally, current management approaches and potential new strategies will be discussed along with complications.

2. Literature review

2.1.Anatomy

Chylothorax occurs due to leakage from the thoracic duct which can happen due to compression, obstruction or rupture (Beghetti et al., 2000). Therefore, it becomes crucial to know the anatomy of the thoracic lymphatic system to understand the etiology and management of the patient.

The thoracic duct extends from the upper end of the cisterna chyli, a confluence of the intestinal and lumbar lymphatic vessels, to the junction of the left internal jugular and left subclavian veins (Hillerdal, 1997). The duct enters the thorax through the aortic hiatus of the diaphragm and then ascends in the posterior mediastinum to the right of the midline on the front of vertebral bodies. When reaching the fourth to sixth thoracic vertebrae, crosses the midline from right to left side and enters the superior mediastinum, ascending between the aortic arch and the subclavian artery. At the level of C7, it arches laterally, behind the left common carotid artery and descends anterior to the subclavian artery, finally opening into the junction of the left subclavian and left internal jugular veins (Maira Ilahi et al., n.d.).

During its embryological development, the thoracic duct may evolve to numerous anatomic variations in all its portions having been described in approximately 35% of the population. (Van Straaten et al., n.d.).

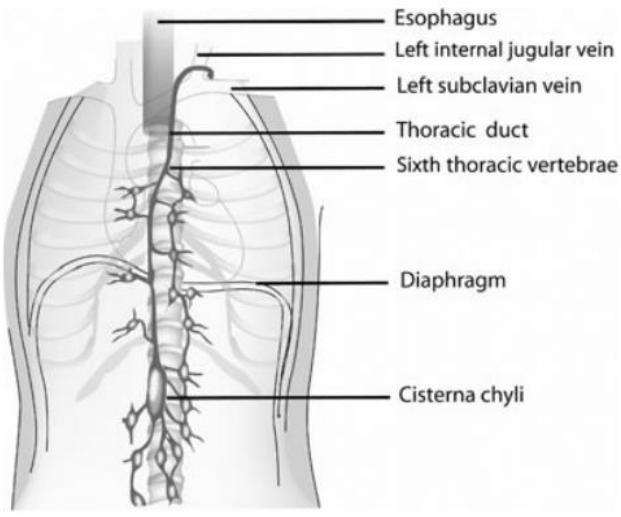

Fig. 1 Thoracic duct and its anatomic relations (Panthongviriyakul & Bines, 2008)

2.2. Pathophysiology

The lymphatic system has ***three major roles*** in the human body.

The first one is to collect excess fluid from the interstitial space and extravasated proteins and return it to the bloodstream, allowing for the maintenance of fluid balance and avoiding edema (Bagur Krishnamurthy & Malhotra, 2017).

The second is the role in immune surveillance since it is responsible for transporting lymphocytes between the bone marrow and the lymph nodes, where they are stored, and producing an immune response by transporting antigen-presenting cells to the lymph nodes. Antigen presentation leads to the differentiation and proliferation of B lymphocytes and activation of T lymphocytes, initiating adaptive immunity (Bagur Krishnamurthy & Malhotra, 2017).

The third function is to carry lipids and lipid-soluble vitamins also known as vitamins A, D, E, and K from the lymphatic capillaries in the small intestine, where they are absorbed, into the systemic circulation (Soto-Martinez & Massie, 2009).

Chyle is mostly formed in the gastrointestinal tract during the digestion of lipid-rich foods and is absorbed by the lymphatic capillaries called lacteals. Most of all dietary triglycerides are long-chain triglycerides (LCT), which are water-insoluble. For this reason, in order to be carried through circulation, they must be transformed into lipoproteins, specifically chylomicrons (Bell et al., 1997). Chyle has a milky appearance since it contains primarily great amounts of chylomicrons, that combine the LCTs, cholesterol and phospholipids. It is abundant in lymphocytes, ranging from 400 to 6800/mm3, with the majority being T lymphocytes (Soto-Martinez & Massie, 2009). Apart from that, chyle also contains glucose, a comparable electrolyte content to the serum, and proteins, with levels usually >3 g/L, including albumin, immunoglobulins and prothrombin (Bagur K, et al 2017).

The ***thoracic duct flow*** of the chyle is approximately 1,38 ml/kg per hour, fluctuating significantly with diet (Bessone et al., 1971a). Evidence shows that chyle flow can increase up to ten times, following ingestion of fat. Specifically, in neonates, the chyle output can be greater than 250 ml a day (Van Straaten et al., n.d.). Since it is mainly composed of fat, in a fasting state, the chyle is usually clear, instead of having the typical milky appearance (Bagur Krishnamurthy & Malhotra, 2017).

2.3. Etiology

Most authors consider ***three types of chylothorax***: congenital (primary), traumatic (post-surgical and nonsurgical) and non-traumatic (Bessone et al., 1971b).

2.3.1 Congenital Chylothorax

Despite being a rare occurrence, congenital chylothorax is the most common type of pleural effusion in newborns, occurring in approximately 1:10,000–24,000 live births, with a male: female ratio of 2 (Rocha et al., 2021) with mortality rates ranging between 30% and 50% (Dorsi et al., 2018) (Caserío et al., 2010).

The etiology of congenital chylothorax is not yet well established. It is, however, associated with malformations of the lymphatic system, found in congenital lymphangiectasia and pulmonary lymphangiomatosis (Kirkland, 1965). Likewise, these malformations can also occur in some genetic syndromes such as Down, Turner, and Noonan's syndromes (Bagur Krishnamurthy & Malhotra, 2017).

It may also be caused by defects in the thoracic duct, particularly, atresia (Kargl & Maier-Hiebl, 2019).

In the absence of a lymphatic anomaly, the etiology of congenital chylothorax is believed to be a consequence of trauma due to hyperextension of the thoracic spine or stretching of the chest wall, or even as a result of higher venous pressure during a strenuous birth (Van Straaten et al., n.d.).

Congenital heart disease, particularly in correlation to blockage of pulmonary venous blood flow, superior vena cava thrombosis, and lobar sequestration are additional disorders in the neonate connected to congenital chylothorax (Resch et al., 2022).

The majority of newborn chylothorax cases, however, lack a clear cause, known as idiopathic congenital chylothorax (Büttiker et al., 1999).

2.3.2 Traumatic Chylothorax

In traumatic chylothorax, the thoracic duct is injured due to surgical or nonsurgical causes. It has been demonstrated that practically any surgical treatment in the mediastinum can result in traumatic postoperative chylothorax (Resch et al., 2022). The most typical

scenario for this condition in children is after cardiothoracic surgery, due to congenital heart disease, for instance, with an estimated incidence between 0.85% and 6.6% (Chan et al., 2006) (Panthongviriyakul & Bines, 2008). Similarly, any other surgery that involves the thorax such as esophageal or diaphragmatic surgery may also cause chylothorax, having been described in infants with esophageal atresia and congenital diaphragmatic hernia (Rocha et al., 2006). Moreover, it may even happen in head and neck surgery (Hillerdal, 1997).

Other therapeutic procedures, particularly, central venous catheter insertions have also been reported as one of the explanations, since they can lead to venous hypertension from intravascular blood clots or direct disruption of the thoracic duct during catheterization (Premuzic et al., 2018). When a venous thrombus is suspected as the cause of chylothorax, a screening for thrombosis, through Doppler ultrasound or angio-CT, should be considered (Rocha et al., 2021).

Regarding nonsurgical causes, any physical trauma that damages or stretches the thoracic spine or chest wall, including childbirth, as well as episodes of intense emesis or coughing, have been documented (Soto-Martinez & Massie, 2009).

2.3.3 Non-traumatic chylothorax

Non-traumatic chylothorax typically occurs in adults and less often in children due to an obstruction of the thoracic duct. The most frequent non-traumatic cause is malignant lymphoma (Soto-Martinez & Massie, 2009). Nonetheless, other intra-thoracic tumors, for instance, sarcoma, teratoma or neuroblastoma have been linked to it (Easa et al., 1991).

In children, benign tumors and a few diseases have been associated, including sarcoidosis, tuberculosis and histoplasmosis since lymphadenopathies can restrain the lymphatic flow (Soto-Martinez & Massie, 2009).

2.4. Clinical Presentation

Most of the clinical manifestations are a result of the accumulation of fluid in the pleural cavity. Therefore, the neonate develops respiratory distress, this being one of the main reasons to be admitted to the neonatal intensive care unit (Edwards et al., 2013).

Respiratory distress is often recognized in the newborn through some common signs of increased difficulty to breath such as tachypnea (respiratory rate greater than 60 breaths per minute in the newborn), tachycardia (heart rate greater than 160 beats per minute in the newborn), flaring of the nostrils, grunting, and chest wall retractions (suprasternal, subcostal and intercostal) (Edwards et al., 2013). If the infant finds it difficult to meet his respiratory needs, it can lead to respiratory failure manifesting in cyanosis or respiratory acidosis (Edwards et al., 2013).

Other physical signs include unilateral or bilateral decreased range of respiratory movements, dullness to percussion and there can also be a shift of the apex beat to the contralateral side. In addition to mediastinal shift, a quick buildup of a significant amount of fluid can cause compression of the heart and vascular structures and impair circulation (Bagur Krishnamurthy & Malhotra, 2017).

Specifically, in the case of congenital chylothorax, 50% of newborns present with respiratory distress within the first 24h of life, although it can also appear within the first week of life (W. Samuel et al., n.d.). When presented antenatally, congenital chylothorax may impair blood flow and the normal development of the lungs as a result of pressure effects, leading to conditions such as pulmonary hypoplasia, pulmonary hypertension, decreased venous return, heart failure, hydrops, and, in most extreme instances, fetal mortality (Rocha et al., 2021) (Philips & Atkinson, 2022).

Although rare, congenital chylothorax is a known cause of nonimmune *hydrops fetalis* (Bagur Krishnamurthy & Malhotra, 2017). This fetal disorder is defined by the abnormal accumulation of interstitial fluid in two or more body compartments (peritoneal cavity, pleura, and pericardium) or body tissue (subcutaneous edema) (Bellini & Hennekam, 2012). The pathogenesis of *hydrops fetalis* is explained by two mechanisms: decreased capillary osmotic pressure as a result of loss of albumin through chyle and/or increased capillary hydrostatic pressure as a result of the decreased venous return due to mass effect on the heart and vena cava (De Haan et al., 2005).

According to the location of the leak, the pleural effusion can be either unilateral or bilateral. A left-sided effusion arises from injury to the duct above the fourth to sixth thoracic vertebra, whereas a right-sided effusion results from a lesion of the duct below this level (*Successful Use of Octreotide for Chylothorax*, 2012). Due to the thoracic duct's typical position predominantly in the right mediastinum, chylothorax tends to occur more

commonly in the right pleural cavity (Van Straaten et al., n.d.). If the injury occurs where the duct crosses the midline, it can result in bilateral chylothorax (Bessone et al., 1971c).

2.5. Diagnosis

The diagnosis of chylothorax should be considered whenever a significant pleural effusion occurs in a neonate or when there are other risk factors, including cardiothoracic or neck surgery, trauma, dysmorphic features and major lymphatic malformations (Soto-Martinez & Massie, 2009).

2.5.1 Prenatal diagnosis

A prenatal diagnosis of congenital chylothorax is based on ultrasound and hinted when showing the presence of an isolated pleural effusion, in the context of hydrops fetalis, or even when there is a known congenital abnormality of the fetus previously linked to congenital chylothorax (Caserío et al., 2010). Fetal thoracocentesis with analysis of the pleural fluid confirms the diagnosis (Bagur Krishnamurthy & Malhotra, 2017).

2.5.2 Postnatal diagnosis

The most often performed evaluation to determine the presence of pleural effusion is a chest radiograph. Features like the ipsilateral white-out appearance, the blunting of the costophrenic angle and the layering of the pleural fluid can be seen (Weerakkody Y, Vadera S, Bell D, et al. Chylothorax. Reference article, Radiopaedia.org (Accessed on 25 Apr 2023). Nevertheless, the radiographic diagnosis of pleural effusion in a newborn is often challenging since most of them may already have pulmonary disease. Therefore, the classic sign of layering of the pleural fluid might be absent. In those cases, a chest ultrasound is the best approach to check for pleural effusion (Azizkhan et al., n.d.).

The diagnosis is confirmed by performing thoracocentesis and analyzing the pleural fluid. Due to high lipid concentration, the typical chylous effusion is usually milky white or turbid. However, it only becomes milky after the introduction of enteral feeding. Before that, it appears serous due to the absence of chylomicrons (Behrman et al., n.d.).

It is important to note that turbid or milky pleural fluids can be found in other conditions, for instance, an empyema or a pseudo chylothorax- a chronic pleural effusion with high cholesterol content but without triglycerides or chylomicrons. For this reason, it's mandatory to do a biochemical analysis of the fluid (Soto-Martinez & Massie, 2009).

A pleural effusion with a triglyceride level > 110 mg/dL and a cell count > 1000/L with > 80% lymphocytes is the criteria to diagnose chylothorax (Büttiker et al., 1999). When triglyceride levels are between 50–110 mg/dL, lipoprotein electrophoresis might help establish the diagnosis. The chylous character of the fluid is shown by a distinct chylomicron band at the origin (Maldonado et al., 2009). In cases of non-enteral feeding patients, the diagnosis consists of a predominance of lymphocytes (> 80 %) in the pleural fluid (Das & Shah, 2010).

2.6. Management

2.6.1. Pre-natal management

The prenatal care strategy is usually determined by fetal lung compromise, the severeness of the pleural effusion and the gestational age at diagnosis (Caserío et al., 2010).

In the case of fetal chylothorax, pulmonary hypoplasia has a higher probability of developing before 24 weeks. Therefore, after the 24-week mark, and when there's a minor effusion the preferred approach is watchful waiting and follow-up ultrasound (Bagur Krishnamurthy & Malhotra, 2017).

When there's a higher risk of fetal compromise or a severe pleural effusion, several measures can be implemented, starting with changing the mother's diet to a low-fat, high medium-chain triglyceride (MCT) diet (Fetal Chylothorax Response to Maternal Dietary Treatment, n.d.). In addition, more invasive treatments such as thoracocentesis and pleuro-amniotic shunting (Caserío et al., 2010)

Pleuro-amniotic shunting is used in severe and reoccurring cases, allowing for progressive fetal lung development, preventing cardiac failure, and, overall improving survival rate with numbers above 48% (Smith et al., 2005) (Mallmann et al., 2017). Sometimes, due to the growth of the chest, fetal movements, or poor placement, the shunt might become detached (Sepulveda et al., 2005).

OK-432 has been successfully used in congenital chylothorax as a sclerosing treatment, through increased cytokine levels that enhance vascular permeability and, as a result, cause the migration of inflammatory cells to the pleura. Moreover, it's thought that the increased permeability hastens the drainage of collected lymph (M. Samuel et al., 2000).

2.6.2. Postnatal management

When there is a prenatal diagnosis of a pleural effusion, the delivery should be scheduled at a tertiary neonatal unit, in order to provide resuscitation measures and appropriate care for the neonate. In addition to pleural drainage, respiratory support might be offered through endotracheal intubation, positive pressure ventilation and oxygen supplementation (Philips, 2022).

The management of neonatal chylothorax aims to reduce chyle leakage in order to prevent sequelae such as malnutrition, infection and immunodeficiency (Bagur Krishnamurthy & Malhotra, 2017). The initial approach to chylothorax in the neonate is based on supportive measures: drainage of pleural fluid, respiratory support, replacement of fluid losses, nutritional modifications and pharmacological treatment (Rocha et al., 2021).

First, it is important to *improve respiratory* symptoms through drainage of the pleural fluid, allowing for lung decompression, therefore the initial thoracocentesis is both diagnostic and therapeutic. Because recurrences are often seen, it may be encouraged to place a chest tube for continuous suction drainage (Soto-Martinez & Massie, 2009).

Additionally, supportive mechanical ventilation is required in most neonates to relieve respiratory distress and restrain chylothorax from reaccumulating through lung expansion (Bagur Krishnamurthy & Malhotra, 2017).

Management of chylothorax also involves a decrease in chyle production by *nutritional measures*.

An MCT diet is usually the initially chosen intervention since MCTs are absorbed from the gastrointestinal tract directly into the portal veins without going via the lymphatic system, causing reduced drainage (Bagur Krishnamurthy & Malhotra, 2017). Therefore, formulas with high MCT content or converted low-fat breast milk supplemented with MCT can be used, since statistically there was no difference between the two in the volume or duration of chyle drainage (Rocha et al., 2021). Reports describe that most neonates

respond well to this initial approach, showing a chyle drainage lower than 10 mL/kg/day (Bagur Krishnamurthy & Malhotra, 2017).

Alternatively, total parenteral nutrition, with enteric rest, should be considered in more severe cases that fail to respond to an MCT-enriched diet, especially when the drainage persists for more than a week (Beghetti et al., 2000). This approach has been linked to serious complications like cholestasis, sepsis and vein thrombosis, hence it's usually considered a second-line approach (Philips & Atkinson, 2022). Chest drains can be withdrawn whenever the total drainage volume falls to 2 ml/kg/day, maintaining this diet for six more weeks, until drainage has subsided (Rocha et al., 2021).

To prevent deficits there should also be administered weekly perfusions of a 20% lipid solution and fat-soluble vitamins that lack in the exclusive MCT diet (Rocha et al., 2021). After cessation of the drainage, transition to breast milk or standard formula can be initiated in one or two weeks (Philips & Atkinson, 2022).

For newborns who don't respond to dietary measures presented within 2 weeks, ***pharmacological treatment*** is offered as an attempt to decrease chyle flow. Regarding pharmacological agents, somatostatin and octreotide have been successfully used in the treatment of chylothorax (Rocha et al., 2021). However, in the past few years, medication-based approaches have mostly focused on octreotide which has the advantage of having a longer-acting duration, superior efficacy and the option of subcutaneous administration (Roehr et al., 2006) (Helin et al., 2006).

Octreotide, a synthetic somatostatin analogue has been used as a treatment in neonates since 2001 (Cheung et al., 2001). Although it has been demonstrated its effectiveness, clinical trials and observational studies are still limited in neonates and some reported no additional benefit, this being the reason why it's mostly used as a second-line approach (Rocha et al., 2021).

As a somatostatin analogue, octreotide suppresses insulin and glucagon release which may lead to hyperglycemia or hypoglycemia, respectively. As a result, blood glucose levels should be closely monitored (Panthongviriyakul & Bines, 2008). Its mechanism of action consists of vasoconstriction of splanchnic vessels resulting in a decrease in intestinal blood flow and less fat absorption which reduces lymphatic fluid production (Rocha et al., 2021).

Other pharmacological agents may be used as ***adjunctive therapy***. For instance, in the case of chylothorax linked to lymphatic abnormalities propranolol and sildenafil should be considered.

Propranolol suppresses lymphangiogenic factors (VEGF1, bFGF, and MMP-2), leading to the apoptosis of endothelial cells while sildenafil also inhibits the proliferation of lymphatic endothelial cells as well as the development of new lymphatic vessels (Rocha et al., 2021).

Sirolimus, an antiangiogenic agent, has been described as helpful in cases associated with lymphangiomatosis however, there is a severe lack of knowledge, particularly for newborns in terms of dosage (Rocha et al., 2021) (Mizuno et al., 2017).

In the case of postoperative chylothorax, the use of etilefrine, a sympathomimetic, has been described in newborns as causing smooth muscle contraction of the thoracic duct, although its efficacy and safety are yet to be proven (Muniz et al., 2018). In order to constrict lymphatic vessels, midodrine, a selective alpha-1adrenoreceptor agonist may also be useful as an additional treatment. Nonetheless, there's still insufficient evidence of its use since it has only been reported once in the literature (Rocha et al., 2021).

Additionally, there are reports that postoperative chylothorax may benefit from glucocorticoid therapy, although its action is not fully comprehended yet. It has been proposed that glucocorticoids can minimize the effusion by causing the fluids to move from the interstitial tissue to the blood. This is due to its ability to increase protein breakdown, leading to hepatic protein synthesis and, consequently increasing osmotic pressure in the blood (Costa & Saxena, 2018).

In neonates unresponsive to conservative measures after 1 week, with drainage > 10 ml/kg/day or that experience significant nutritional and metabolic complications, or with constant and large pleural drainage (> 100 ml per day) for five straight days, a more ***invasive approach*** should be considered as the next step (Soto-Martinez & Massie, 2009) (Rocha et al., 2021). However, the exact timing to resort to invasive therapy is still not uniformly defined. Other authors advise delaying surgery until after a four-week period of conservative care (Le Coultre et al., 1991) (Resch et al., 2022). Invasive treatments include pleurodesis, thoracic duct ligation, thoracic duct embolization, pleuroperitoneal shunts, diaphragmatic fenestration, superior vena cava (SVC) thrombectomy or bypass and lymphovenous anastomosis (Bagur Krishnamurthy & Malhotra, 2017) (Rocha et al., 2021).

Pleurodesis seeks to obliterate the pleural space through the adhesion of the parietal and the visceral pleura, and it can be done chemically or mechanically (Philips & Atkinson, 2022) (Bagur Krishnamurthy & Malhotra, 2017). Povidone-iodine (betadine), talc, tetracycline derivatives, fibrin glue, and OK-432 are a few of the chemical agents utilized in newborns (Rocha et al., 2021) (Philips & Atkinson, 2022).

Intrapleural injection of povidone-iodine has been demonstrated to be effective, apparently well tolerated and less invasive when compared to surgical abrasion of the pleura (Rocha et al., 2021). Due to its cytotoxic and oxidative qualities, it creates an inflammatory response leading to sclerosis. Additionally, this substance seems to be linked to the chelation of proteins, therefore, being anti-exudative (Cohan et al., 1988). However, adverse effects have been reported: allergic responses, nephrotoxicity, cardiopulmonary failure and thyroid function impairment (Rocha et al., 2021).

Talc has been shown to be the most effective treatment in adults with malignant pleural effusions and its use has been reported in a single case of persistent congenital chylothorax associated with a lymphatic malformation (Hodges et al., 2016). However, its repercussion in neonatal chylothorax has yet to be documented (Hodges et al., 2016).

Although still uncertain, the mechanism of action of tetracycline derivatives is thought to be the induction of fibrosis due to the increased recruitment of inflammatory cells like macrophages and lymphocytes in the pleura (Antony et al., 1992). Oxytetracycline has been successfully documented as a treatment for pleural effusions in adults with malignant chylothorax and it has been used in bilateral congenital chylothorax unresponsive to octreotide, but just like other agents is still uncertain in newborns (Walker-Renard et al., 1994) (Utture et al., 2016).

Fibrin glue is a combination of fibrinogen and thrombin. It works by converting fibrinogen to fibrin and creating a mesh network. Fibrin glue has also been described as a pleurodesis agent, specifically in congenital and postsurgical chylothorax but it's mostly used in chronic pneumothorax (Mathur et al., 2009) (Drovandi et al., 2018).

OK-432 (picibanil), an inactivated preparation of Streptococcus pyogenes A3, induces an inflammatory response when injected into the pleura, having been used in fetal and chronic congenital chylothorax with a favorable outcome (Bagur Krishnamurthy & Malhotra, 2017).

Mechanical pleurodesis is performed surgically via thoracoscopy or thoracotomy following the same principle of generating an inflammatory response through the pleural surfaces' abrasion, without chemical agents (Rocha et al., 2021).

Thoracic duct ligation is a very effective way to control chyle leakage due to thoracic duct injury when the location of the injury is clear (Kumar et al., 2017). Lymphangiography is useful in identifying the leaking location that needs to be clamped. The non-identification of the site of injury or anatomic variations are two of the reasons why this procedure might fail (Kumar et al., 2017).

An alternative to thoracic duct ligation is thoracic duct embolization, a less invasive percutaneous treatment (Rocha et al., 2021). In neonates, the technique involves intranodal lymphangiography to identify the site of the leak and explore the possibility of anatomical variations. Transabdominal catheterization of the cisterna chyli or its tributaries is then performed, followed by embolization to block the thoracic duct proximal to the leak (Itkin et al., 2011a). A previous case report of a 1-month-old infant suggested that even when the procedure is done successfully, it can recur due to the growth of lymphatic vessels that continue to leak (Itkin et al., 2011b).

Since 1983, pleuroperitoneal shunts have been performed in newborns, having been described as safe and effective with complete chylothorax resolution and improved pulmonary function (Rocha et al., 2021). It consists of a one-way valve structure that allows the transportation of lymph from the pleural cavity to the abdominal cavity. The shunt is in place for a potentially long time up to several months (Rocha et al., 2021). It's an option to consider in patients whose chylous leak location is uncertain (Kumar et al., 2017).

Diaphragmatic fenestration consists of excising a circular portion of the diaphragm followed by the suture of a fenestrated patch in that place. It has been proven to be an efficient and safe strategy with a fast resolution for infants with resistant chylothorax who have undergone cardiac surgery (Kumar et al., 2017).

SVC thrombectomy or bypass is fitting for patients with reported occlusion of this vessel. In this case, the pleural effusion occurs due to the rupture of the thoracic duct or its collaterals secondary to a venous thrombus which can happen as a complication of central venous catheterization (Rocha et al., 2021). The high venous pressure causes significant chyle leakage with high volume output (Beghetti et al., 2000). This leads to a loss of antithrombin III, reducing the effect of heparin (Anderson & Weitz, 2011). As a result, chylothorax secondary to SVC thrombosis doesn't often respond to anticoagulation therapy.

On the one hand, a previous study suggested that endovascular thrombectomy might be too risky in young infants (Wang et al., 2002). On the other hand, it has been reported that open thrombectomy and reconstruction of the SVC was an efficient method for minimizing chyle output in four infants ages between 5 weeks and 4 months (Kumar et al., 2015).

An innovative microsurgical procedure called lymphovenous anastomosis is another option for the management of neonatal chylothorax. Through a less invasive procedure like transabdominal or percutaneous access, an anastomosis between the thoracic duct and the venous system is done and the lymphatic drainage is restored (Rocha et al., 2021). A case series report has proposed that it can be successfully used in young infants when resistant to conventional medical, radiologic or surgical therapies (Weissler et al., 2018).

2.7. Complications

Significant losses of lymphatic fluid prompt fluid and electrolyte imbalance, as well as loss of other essential components including proteins such as albumin and anticoagulants, clotting factors, immunoglobulins and lymphocytes. Consequently, these patients might present with hypovolemia, hypoalbuminemia, malnutrition, coagulation disorders and secondary immunodeficiency (Bagur Krishnamurthy & Malhotra, 2017).

Continuous chest tube drainage might result in substantial ***volume and electrolyte loss*** that might lead to hypotension and hypovolemia. For this reason, it is required to do daily evaluations of weight and electrolytes as well as monitoring blood pressure. Depending on the size of the losses and changes in serum electrolytes, replacement may be needed. Guidelines suggest that if the volume loss is greater than 6 mL/kg per hour, there should be a replacement with normal saline solution, which should be administered intravenously, every six to twelve hours (Philips & Atkinson, 2022). It could be essential to replace fluid losses with bicarbonate-containing solutions, since the continuous drainage can lead to bicarbonate loss, resulting in metabolic acidosis (Rocha et al., 2021).

Moreover, ***protein loss*** may also be significant, so the analysis of protein concentration in the pleural fluid and monitoring of serum albumin levels indicate if replacement therapy is needed. It consists of fresh frozen plasma or IV 5% albumin in order to keep serum albumin >2.5 g/dl (Philips & Atkinson, 2022) (Rocha et al., 2021).

As we know, long-chain triglycerides are the main source of ***fat*** in a healthy non-restricted infant's diet, whether it comes from breast milk or formulas. In the management of chylothorax, the ingestion of LCT is restricted and substituted for a diet rich in MCT through defatted, fortified breast milk or formulas with predominantly MCT, in order to reduce the chylous drainage, and in more severe cases, total parental nutrition (TPN) can also be initiated (Bagur Krishnamurthy & Malhotra, 2017).

To minimize the risk of malnutrition and its impact on growth and development, it is important to assure adequate nutritional support. An MCT-enriched diet may lead to a deficiency in essential fatty acids**,** specifically, linoleic acid and alpha-linolenic acid which are unable to be synthesized by the body, so they must be obtained from the diet (Marino et al., 2019). This deficiency can be prevented through supplementation with intravenous lipid emulsions with an average infusion of 2.5-5 mL/kg/day (0.5-1 g/kg/day) (Fogg et al., 2022).

Regarding ***coagulation disorders***, on the one hand, the loss of antithrombin and other anti-coagulant proteins such as protein C and protein S that occurs in chylous drainage in patients with chylothorax leads to a hypercoagulable state and, consequently a higher risk of vascular thrombosis (Healy et al., 2017) (Bernet-Buettiker et al., 2006). On the other hand, the loss of clotting factors including fibrinogen (factor I) and prothrombin (factor II) causes an increased risk of hemorrhagic events (Bernet-Buettiker et al., 2006). Some authors defend that the replacement of these clotting factors is made by administering fresh frozen plasma, however, specifically for children, evidence is still lacking. Some authors suggest that it should be considered when there are abnormal coagulation parameters or when active bleeding is present (Rocha et al., 2021). In addition to the assessment of coagulation parameters, antithrombin should also be monitored to minimize thrombotic complications with the replacement of antithrombin. Additionally, anticoagulation therapy is suggested if needed (Bernet-Buettiker et al., 2006).

Hypogammaglobulinemia, mainly immunoglobulin G (IgG), as well as immunoglobulin M (IgM) and immunoglobulin A (IgA), has been reported in patients with chylothorax (Hoskote et al., 2012a).

Although previous studies advocated that the administration of intravenous immunoglobulin (IGIV) hasn't shown any additional benefits, the truth is that it's still provided when there are lower levels of immunoglobulins (Hoskote et al., 2012b). This happens since children with hypogammaglobulinemia, have a higher incidence of infections, including sepsis (Hoskote et al., 2012b). Considering that the average level of IgG in a one-

month infant is 500 mg/dL, serum concentrations should be monitored and the administration of IGIV should be adjusted in order to reach this target level (Philips & Atkinson, 2022). Some authors also defend prophylactic antibiotic therapy along with IVIG particularly due to the chest drain (Healy et al., 2017) (Resch et al., 2022). Nonetheless, further studies are still needed in the pediatric population.

Since most of the lymphocytes presented in chyle are T-cells, it is expected to have a selective depletion of these cells, especially of naive T-cells as a result of pleural drainage (Soto-Martinez & Massie, 2009) (Orange et al., 2003). However, studies have reported that there is no correlation between the loss of T lymphocytes and a higher incidence of *infections* which means that it may not be a reliable predictor of immunologic proficiency. They suggest that the low quantity of circulatory lymphocytes does not adequately represent total body lymphocytes, since it only represents 2% of the total (Orange et al., 2003) (Hoskote et al., 2012c). Apart from that, it has been demonstrated that some subpopulations of lymphocytes such as natural killer cells and T memory cells are retained since they tend to adhere to vessel walls persisting in the blood vessels instead of being lost in chyle drainage (Orange et al., 2003).

3. Methodology

3.1. Aim of the study

This study aims to characterize a population of neonates admitted with chylothorax to a tertiary neonatal intensive care unit while exploring the management and therapeutic approaches used, along with the complications and outcomes.

3.2. Study design

An observational, descriptive and retrospective study was based on the analysis of institutional records of newborns diagnosed with chylothorax between January 2012 to February 2023, at the Neonatal Intensive Care Unit of Hospital de Santa Maria, CHULN, EPE.

3.3. Study Framework

Chylothorax, although rare, is the most common cause of pleural effusion in the neonate and has been described as a life-threatening condition with consequential long-term morbidity and mortality. However, the existing studies in this field are limited and there are no standard guidelines for the approach of chylothorax in this period. Thus, is relevant and essential to analyze the cases of infants diagnosed with chylothorax at the NICU of Hospital de Santa Maria, after reviewing the major aspects of its pathophysiology, etiology, clinical presentation, diagnosis, management and complications.

3.4. Population

Newborns with the diagnosis of chylothorax were selected using the clinical coding system, according to ICD-9-CM (International Classification of Diseases 9th edition – Clinical Modification) and ICD-10-CM/PCS (International Classification of Diseases 10th edition – Clinical Modification / Procedural Classification 37 System), and by consulting the NICU discharge notes, stored in files on the unit itself.

Data collection, particularly the demographic and clinical characteristics of the patients, was carried out by consulting the clinical files of the newborns. The collected data included:

- Demographic data: gender, gestational age, mode of delivery, birth anthropometry and respective classification small for gestational age (SGA), appropriate for gestational age (AGA) or large for gestational age (LGA) AND Apgar score.
- Clinical data: associated malformations, prenatal diagnosis, age at diagnosis, etiology, side, duration of chylothorax, length of stay in NICU, mortality and cause of death.
- Laboratory data:
    - Characterization of pleural fluid: cells, lymphocytes, triglycerides, proteins
    - Immunoglobulins (IgM, IgA and IgG)
    - Thyroid function: TSH, FT4
- Management data:
    - Prenatal interventions and respective gestational age
    - Pleural drainage duration
    - Ventilation mode and duration
    - Nutritional: use of low lipid formula (basic F®), MCT oil, regular milk formula, total parenteral nutrition (TPN) and its duration
    - Pharmacologic agents: octreotide, immunoglobulin, pleurodesis agents
    - Complications: infectious, nutritional and mechanical

The inclusion criteria were the presence in a newborn of a pleural effusion characterized by > 1000 cells/µL with > 80% of lymphocytes and triglycerides greater than 110 mg/d if they were on enteral feeding. In non-fed infants, we used only the identification of a high number of lymphocytes (> 80%).

3.5. Data analysis

The information was inserted into a database built in Microsoft Excel® and a descriptive analysis of the results was carried out. Regarding quantitative variables, the median was used as a measure of central location and the range as a measure of dispersion. Categorical variables were described as absolute numbers and percentages.

3.6. Ethical considerations

The data collected and analyzed in this study are anonymized, and the identity of any of the patients is not disclosed at any time during the study.

4. Results

4.1. Demographic, clinical and laboratory data

Eight patients were included. As shown in table 1, most of the neonates were female (n=5) and preterm (n=6). The **median gestational age** was 34 weeks [32- 39 weeks]. Regarding **mode of delivery**, the majority were born through a cesarean section (n=5), two were vaginal delivery and one was assisted vaginal delivery (vacuum).

Table 1. Demographic variables

	Total (n=8)
Female	5 (62,5%)
Male	3 (37,5%)
Gestational age (weeks)	34 [32-39]
Preterm	6 (75%)
Term	2 (25%)
Mode of delivery	
• Vaginal	2 (25%)
• Assisted vaginal (vacuum)	1 (12,5%)
• Cesarean section	5 (62,5%)
Birth weight (g)	2350 [1700-3470]
• AGA	7 (87,5%)
• LGA	1 (12,5%)
Length at birth (cm)	48 [39,5-50]*
Head circumference at birth (cm)	32 [30,5-35,5]*
Apgar score	
• 1st min	7 [5-8]
• 5th min	8 [7-10]
• 10th min	9 [8-10]

The data in this table are presented through the median, range or through the absolute number with percentages in parentheses.
*n=7 because it was not possible to access these data in 1 of the 8 patients included in the study.

The **median birth weight** was 2350 g [1700-3470 g], with only one newborn classified as LGA, while the remaining seven were considered AGA.

The median APGAR score at the 1st, 5th and 10th minutes was 7 [5-8], 8 [7-10] and 9 [8-10], respectively.

Genetic disorders were diagnosed in two infants: one with spinal muscular atrophy and one with Down Syndrome.

The **prenatal diagnosis** of pleural effusion was made in four patients: *hydrops fetalis* (n=3) and right pleural effusion (n=1), with a median gestational age of 29 weeks [21-33 weeks].

The **median age at diagnosis** was 1,5 days of life [1-44 days of life]: seven were in the neonatal period, while one had the diagnosis at 44 days of life.

There were four cases of **congenital chylothorax** and four cases of **iatrogenic chylothorax** whose surgical causes were: esophageal atresia (n=1), congenital heart disease (n=1), diaphragmatic hernia (n=1) and cervical lymphangioma (n=1).

Effusions were **unilateral** on five patients: two on the left side and three on the right side. Three patients had a **bilateral** effusion.

Cytochemical analysis of pleural fluid revealed that six patients had cell count > 1000/L and > 80% lymphocytes. In one infant, the cell count, lymphocytes and triglyceride levels were not determined. Triglyceride levels were > 110 mg/dL in three patients and were not evaluated in four cases. The median levels of proteins in the pleural fluid were 2,55 g/dL [0,6-3,5 g/dL].

The **median duration of chylothorax** was 35 days [2-56 days].

The **immunoglobulin levels** were performed in five infants: IgM levels were < 5 mg/dL in only one patient, IgA levels were < 5 mg/dL in three of the infants and IgG levels were lower than 100 mg/dL in three patients.

Thyroid function was assessed in three patients and was in the reference range.

Table 2. Characterization of chylothorax

	Total (n=8)
Prenatal diagnosis	4 (50%)
• *hydrops fetalis*	3 (37,5%)
• right pleural effusion	1 (12,5%)
Gestational age at prenatal diagnosis (weeks)	29 [21-33]
Age at diagnosis (days of life)	1,5 [1-44]
Neonatal	7 (87,5%)
Etiology	
• Congenital	4 (50%)
• Iatrogenic	4 (50%)
○ esophageal atresia	1 (12,5%)
○ surgery for congenital heart disease	1 (12,5%)
○ diaphragmatic hernia	1 (12,5%)
○ cervical lymphangioma	1 (12,5%)
Unilateral	5 (62,5%)
• left	2 (25%)
• right	3 (37,5%)
Bilateral	3 (37,5%)
Characterization of pleural fluid	
• cell count > 1000/L	6(75%)*
• lymphocytes > 80%	6 (75%)*
• triglycerides > 110 mg/dL	3 (37,5%)*[1]
• proteins (g/dL)	2,55 [0,6-3,5]
Duration of chylothorax (days)	35 [2-56]

The data in this table are presented through the median, range or through the absolute number with percentages in parentheses.

*n=7 because it was not possible to access these data in 1 of the 8 patients included in the study.
*[1]n=4 because it was not possible to access these data in 4 of the 8 patients included in the study.

4.2. Management data

As shown in table 3, three of the four infants who had a prenatal diagnosis went through **prenatal intervention** – pleuro-amniotic shunt, at the median age of 31 weeks.

Table 3. Treatment of chylothorax

	Total (n=8)
Prenatal interventions	3 (37,5%)
• Pleuroamniotic shunt	3 (37,5%)
Age at prenatal intervention (weeks)	31 [31-32]
Pleural drainage	7 (87%)
• Duration (days)	7 [1-49]*[1]
Ventilation mode	8 (100%)
• invasive ventilation	8 (100%)
○ median duration (days)	33 [1-65]
• non-invasive ventilation	5 (62,5%)*
○ median duration (days)	8 [3-181]*
Nutritional management	
• Low lipid formula (basic F®)	8 (100%)
○ Initiation of a low lipid formula (basic F) (day of life)	13 [3-34]*[1]
• MCT oil	6 (75%)
○ Initiation of MCT oil (day of life)	7 [6-48]*[2]
• Regular milk formula	8 (100%)
○ Initiation of regular milk formula (day of life)	27 [4-98]*
• Exclusive regular milk formula	7 (87,5%)
○ Initiation of exclusive regular milk formula (day of life)	66,5 [35-98]*[3]
• TPN	8 (100%)
○ Duration of TPN (days)	31 [1-61]
Pharmacological treatment	
• Octreotide	8 (100%)
○ Duration of octreotide (days)	34,5 [7-60]*[1]
○ Median dose of octreotide (mcg/kg/h)	4,5 [1,5-10]*[1]

Immunoglobulins	3 (37,5%)
Pleurodesis	2 (25%)
• Chemical	2 (25%)
• Mechanical	1 (12,5%)

The data in this table are presented through the median, range or through the absolute number with percentages in parentheses.
*n=7 because it was not possible to access these data in 1 of the 8 patients included in the study.
*[1] n=6 because it was not possible to access these data in 2 of the 8 patients included in the study.
*[2] n=3 because it was not possible to access these data in 5 of the 8 patients included in the study.
*[3] n=4 because it was not possible to access these data in 4 of the 8 patients included in the study.

Pleural drainage was performed in seven patients, with a median duration of 7 days [1-49 days].

Invasive ventilation was required in all eight cases, with a median duration of 33 days [1-65 days]. Five of those patients also required non-invasive ventilation, with a median duration of 8 days [3-181 days].

A low-fat formula (basic F®) was initiated in all patients at the median age of 13 days of life [3-34 days]. MCT oil was initiated in six patients at the median of 7 days of life [6-48 days]. Regular milk formula was also initiated in all cases at the median age of 27 days of life [4-98 days]. Most of them (n=7) had total regular milk formula at the median age of 66,5 days of life [35-98 days of life]. Total parenteral nutrition was administered in all eight cases with a median duration of 31 days [1-61 days].

Octreotide was administered in all patients with a median duration of 34,5 days [7-60 days] and a median dose of 4,5 mcg/kg/h [1,5-10 mcg/kg/h]. No side effects were registered.

Immunoglobulins were administered in three patients.

In two of the infants, conservative treatment was considered not effective. In these patients a pleurodesis was performed, one chemical and one both chemical and mechanical.

Complications, as presented in table 4, were reported in seven patients. Six had infectious complications: six had late sepsis, two of them with pneumonia. Nutritional complications occurred in five cases: failure to thrive. A mechanical complication occurred in one case: drain obstruction.

Table 4. Complications of chylothorax

	Total (n=8)
Complications	7 (87%)
• Infectious	
○ Late sepsis	6 (75%)
○ Pneumonia	2 (25%)
• Nutritional	
○ Failure to thrive	5 (62,5%)
• Mechanical	
○ Drain obstruction	1 (12,5%)

The data in this table are presented through the absolute number with percentages in parentheses.

As displayed in table 5, The median length of stay in the Neonatal Intensive Care Unit was 35 days [2-134 days]. Until the date of data collection, one of these infants was still hospitalized.

Regarding the short outcome, table 5 indicates that six of the infants survived, while the remaining two died: one in the context of pneumonia at 39 days of life and the other one due to pulmonary hypoplasia at 2 days of life.

Table 5. Outcome of chylothorax

	Total (n=8)
Length of stay in the Neonatal Intensive Care Unit (days)	35 [2-134]
Mortality	2 (25%)
• Cause of death	
○ Pneumonia	1 (12,5%)
○ Pulmonary hypoplasia	1 (12,5%)
Time at death (days of life)	20,5 [2-39]

The data in this table are presented through the median, range or through the absolute number with percentages in parentheses.

5. Discussion

Between January 2012 and February 2023, 8 infants were diagnosed with chylothorax. It represents less than one case per year of study, which confirms the rarity of this pathology. This certainly may influence the internal and external validity of the study.

Chylothorax was more frequent in premature infants with a preponderance of the male gender, as reported in the literature (Ibrahim et al., 2013). Most of the cases (n=7) were neonatal, with only 1 being diagnosed later at 44 days of life.

There were two main etiologies: half of the cases were congenital while the other half were iatrogenic. The four congenital cases were premature infants. The high percentage of iatrogenic etiology might be a selection bias as the convenience sample was taken from a tertiary hospital, reference for prenatal diagnosis and neonatal surgery in Lisbon metropolitan region.

Regarding congenital chylothorax, 50% of these cases were associated with genetic disorders, one of them being trisomy 21. Contrary to what has been described in previous studies, about the association between congenital chylothorax and Down Syndrome, in this study, the only infant with Down Syndrome did not present with congenital chylothorax (Kallanagowdar & Craver, 2006) (Rocha et al., 2006). This infant, however, presented with iatrogenic chylothorax due to surgery for congenital heart disease, which is well-documented in patients with Down Syndrome, with a prevalence of 50% (Irving & Chaudhari, 2012) (Weijerman et al., 2008). Apart from Down Syndrome, the other genetic disorder identified in this study was spinal muscular atrophy. However, there are no reports of association between this disease and chylothorax.

Besides surgery, for congenital heart disease, the other iatrogenic causes included surgery for esophageal atresia and surgery for diaphragmatic hernia, which have also been described in previous studies as causes of chylothorax (Shirota et al., 2019) (Kamiyama et al., 2010). The remaining iatrogenic cause was surgical resection for cervical lymphangioma. Although lymphatic anomalies have been linked to congenital chylothorax or non-traumatic chylothorax when presented later in life, in the of cervical lymphangioma, it must have occurred due to injury of a lymphatic duct during neck surgery as reposted by several authors (Soto-Martinez & Massie, 2009) (Nandy et al., 2022).

In unilateral pleural effusions, the right-sided collection was more frequent, which is consistent with the predominant position of the thoracic duct in the right mediastinum, as reported previously (Van Straaten et al., n.d.).

Half of the infants (n=4) had a prenatal diagnosis, mostly *hydrops fetalis* (n=3) which corroborates the association of chylothorax with *hydrops fetalis* previously described in the literature (Brock & Bradshaw, 2016) (Bagur Krishnamurthy & Malhotra, 2017). Only one of the prenatally diagnosed cases was an isolated right pleural effusion.

Prenatal intervention, with insertion of a pleuro-amniotic shunt (n=3), was done in two of the three hydroptic fetuses and in the one with isolated right pleural effusion, at the third trimester of gestation. The shunt placements might have improved the survival of the fetuses (Resch et al., 2022) (Bagur Krishnamurthy & Malhotra, 2017). However, despite the shunt placement, one of the infants had pulmonary hypoplasia. According to the literature, there's a higher risk of developing pulmonary hypoplasia, when the pleural effusion occurs before 24 weeks of gestation and when the effusion persists for more than 2 weeks (Dendale et al., 1999). In our patient, the prenatal diagnosis occurred at 28 weeks of gestation, when the risk is supposed to be lower, but it persisted for more than 2 weeks.

Invasive ventilation was required in 100% of the cases, while non-invasive ventilation was required in 62,5%. The relief of respiratory symptoms with the use of positive end-expiratory pressure ventilation is advised as it may tamponade the injured duct, helping to decrease chyle flow (Kurtz & Hsu, 1980) (Ragosta & Alfieris, 2000).

Nutritional management included total parenteral nutrition (n=8), a low lipid formula (basic F®) plus MCT oil. Progression to exclusively regular milk formula was possible in all the cases.

In our study, all of the infants started parenteral nutrition with enteric rest, according to chylothorax drainage and response to implemented measures. The current recommendations are that dietary measures are a mainstay in the treatment of chylothorax. Using a low-fat diet without long-chain fatty acids but supplemented with medium-chain triglycerides (MCTs), reduces lymphatic drainage because MCTs are absorbed directly into the portal venous system, bypassing the lymphatic system. Cases that don´t respond to a low-fat diet, as described above, need parenteral nutrition with total enteric rest. The small sample size and the population of premature and surgical infants might be the explanation for this approach.

Pharmacological treatment, such as octreotide, was used in all of the cases in order to reduce chyle production. As discussed previously, observational studies suggest that octreotide should be considered in the conservative treatment of chylothorax when other conservative measures were not successful. There is a recent systematic review that concludes that octreotide is a relatively effective and safe treatment option in neonates with chylothorax (Bellini et al., 2018). However, there are no firm recommendations concerning the timing, dose and duration of this therapy. (Das & Shah, 2010) (Panthongviriyakul & Bines, 2008).

The three infants who presented with low levels of IgG required the administration of intravenous immunoglobulins in order to prevent infectious complications (Hoskote et al., 2012b). Unfortunately, all of them still developed sepsis, one of them with pneumonia.

As discussed previously, concerning surgical management of chylothorax, most studies recommend it if the effusion persists for more than three or four weeks, despite conservative management. Surgery may be anticipated if the effusion volume is persistently high, despite drainage or if there are severe metabolic or nutritional complications. A thoracoscopic approach should be considered. In our case, pleurodesis, either chemical or both chemical and mechanical was performed successfully in 2 of the 8 cases.

Complications were very prevalent (n=7), most of them with late sepsis. The causes might be multifactorial mainly related with features of our sample (preterm and surgical patients), diagnosis (chylothorax) or treatment (the use of total parenteral nutritional). The second main complication was poor weight gain (62,5%) as described previously.

In this study, 2 patients died (25%, as reported in the literature), one with pneumonia and the other with pulmonary hypoplasia. These two infants were preterm, had a prenatal diagnosis of hydrops fetalis, and had a bilateral chylothorax, which are all poor prognostic factors (Longaker et al., n.d.). Additionally, the infant that died from pneumonia had a genetic disorder (spinal muscular atrophy) and other non-specified concomitant anomalies that might also have a negative impact on prognosis (Resch et al., 2022). The survival rate was 75%.

Limitations of this study include the retrospective design, single center-based and small size sample related with the rarity of the disease. Because it is based on previously recorded information, it is susceptible to registry bias when retrieving data (memory bias) besides the selection bias (convenience sample). Moreover, there might have been different approaches of the patients over the last 11 years, due to the scientific knowledge advances.

6. Conclusion

Neonatal chylothorax is a complex and challenging condition that requires a prompt diagnosis and multidisciplinary approach to optimize outcomes. It remains a challenging pathology with significant morbidity and mortality.

Despite advancements in neonatal care, there is still a limited understanding of the etiology, risk factors, clinical presentation, and optimal treatment strategies for neonatal chylothorax.

In our small series, half of the patients had prenatal diagnosis and half were iatrogenic, reflecting the close collaboration of our unit with the prenatal diagnostic center of the Department of Obstetrics and Gynecology and the Pediatric Surgery Service of CHULN, EPE.

This is a small study that reflects the rarity of this entity. The absence of national or international evidence-based guidelines originates controversy regarding some of the therapeutic interventions of the clinical practice. Further studies, especially multicenter studies, are essential to evaluate the effectiveness and short and long-term outcomes of the various strategies used in clinical practice.

7. Appendices

Table 6: Characterization of the cases admitted at NICU with chylothorax

Case	1	2	3	4	5	6	7	8
Gestational age	32	34	33	34	39	33	35	38
Birth weight (g)	2080	1860	1700	2620	3470	2180	2521	3470
Age at diagnosis (days)	1	1	1	6	1	2	6	44
Etiology	Cong.	PS	Cong.	Cong.	PS	Cong	PS	PS
Duration of chylothorax (days)	4	50	35	34	ND	2	42	56
Prenatal intervention (PA shunt)	Yes	No	Yes	No	No	Yes	No	No
Invasive Ventilation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pleural drainage	Yes	Yes	ND	Yes	Yes	Yes	Yes	Yes
TPN	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Octreotide	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
IVIG	No	Yes	Yes	Yes	No	No	No	No
Pleurodesis	No	Yes	Yes	No	No	No	No	No
Complications	Yes Low IG	Yes Failure to thrive Sepsis Pneumonia Mechanical	Yes Failure to thrive Sepsis	Yes Failure to thrive Sepsis	Yes Failure to thrive Sepsis Pneumonia	Yes Lung hypoplasia	Yes Failure to thrive Sepsis	Yes sepsis
Mortality	No	No	No	Yes	No	Yes	No	No

Cong. – congenital; PS – Post-surgery; IG – Immunoglobulin; ND – information unavailable

8. References

Anderson, J. A. M., & Weitz, J. I. (2011). Hypercoagulable states. *Critical Care Clinics*, *27*(4), 933–952, vii. https://doi.org/10.1016/j.ccc.2011.09.007

Antony, V. B., Rothfuss, K. J., Godbey, S. W., Sparks, J. A., & Hott, J. W. (1992). Mechanism of tetracycline-hydrochloride-induced pleurodesis. Tetracycline-hydrochloride-stimulated mesothelial cells produce a growth-factor-like activity for fibroblasts. *The American Review of Respiratory Disease*, *146*(4), 1009–1013. https://doi.org/10.1164/ajrccm/146.4.1009

Azizkhan, R. G., Canfield, J., Alford, B. A., & Rodgers, B. M. (n.d.). *Pleuroperitoneal Shunts in the Management of Neonatal Chylothorax*.

Bagur Krishnamurthy, M., & Malhotra, A. (2017). Congenital chylothorax: current perspectives and trends. *Research and Reports in Neonatology*, *Volume 7*, 53–63. https://doi.org/10.2147/rrn.s128703

Beghetti, M., La Scala, G., Belli, D., Bugmann, P., Kalangos, A., & Le Coultre, C. (2000). Etiology and management of pediatric chylothorax. *Journal of Pediatrics*, *136*(5), 653–658. https://doi.org/10.1067/mpd.2000.104287

Behrman, R. E., Chernick, V., & Reed, M. H. (n.d.). *FETAL AND NEONATAL M E D I C I N E Pneumothorax and chylothorax neonatal period in the*.

Bell, S. J., Bradley, D., Forse, R. A., & Bistrian, B. R. (1997). The new dietary fats in health and disease. *Journal of the American Dietetic Association*, *97*(3), 280–286; quiz 287–288. https://doi.org/10.1016/S0002-8223(97)00072-2

Bellini, C., Cabano, R., De Angelis, L. C., Bellini, T., Calevo, M. G., Gandullia, P., & Ramenghi, L. A. (2018). Octreotide for congenital and acquired chylothorax in newborns: A systematic review. *Journal of Paediatrics and Child Health*, *54*(8), 840–847. https://doi.org/10.1111/jpc.13889

Bellini, C., & Hennekam, R. C. (2012). Non-immune hydrops fetalis: A short review of etiology and pathophysiology. In *American Journal of Medical Genetics, Part A: Vol. 158 A* (Issue 3, pp. 597–605). https://doi.org/10.1002/ajmg.a.34438

Bernet-Buettiker, V., Waldvogel, K., Cannizzaro, V., & Albisetti, M. (2006). Antithrombin activity in children with chylothorax. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery*, *29*(3), 406–409. https://doi.org/10.1016/j.ejcts.2005.12.015

Bessone, L. N., Ferguson, T. B., & Burford, T. H. (1971a). Chylothorax. *The Annals of Thoracic Surgery*, *12*(5), 527–550. https://doi.org/10.1016/s0003-4975(10)65800-6

Bessone, L. N., Ferguson, T. B., & Burford, T. H. (1971b). Chylothorax. *The Annals of Thoracic Surgery*, *12*(5), 527–550. https://doi.org/10.1016/s0003-4975(10)65800-6

Bessone, L. N., Ferguson, T. B., & Burford, T. H. (1971c). Chylothorax. *The Annals of Thoracic Surgery*, *12*(5), 527–550. https://doi.org/10.1016/s0003-4975(10)65800-6

Brock, W. W., & Bradshaw, W. T. (2016). Congenital Chylothorax: A Unique Presentation of Nonimmune Hydrops Fetalis in a Preterm Infant. *Advances in Neonatal Care : Official Journal of the National Association of Neonatal Nurses*, *16*(2), 114–123. https://doi.org/10.1097/ANC.0000000000000257

Büttiker, V., Fanconi, S., & Burger, R. (1999). Chylothorax in children: Guidelines for diagnosis and management. *Chest*, *116*(3), 682–687. https://doi.org/10.1378/chest.116.3.682

Caserío, S., Gallego, C., Martin, P., Moral, M. T., Pallás, C. R., & Galindo, A. (2010). Congenital chylothorax: From foetal life to adolescence. *Acta Paediatrica, International Journal of Paediatrics*, *99*(10), 1571–1577. https://doi.org/10.1111/j.1651-2227.2010.01884.x

Chan, S. yan, Lau, W., Wong, W. H. S., Cheng, L. cheung, Chau, A. K. T., & Cheung, Y. fai. (2006). Chylothorax in Children After Congenital Heart Surgery. *Annals of Thoracic Surgery*, *82*(5), 1650–1656. https://doi.org/10.1016/j.athoracsur.2006.05.116

Cheung, Y. F., Leung, M. P., & Yip, M. M. (2001). Octreotide for treatment of postoperative chylothorax. *Journal of Pediatrics*, *139*(1), 157–159. https://doi.org/10.1067/mpd.2001.115572

Cohan, R. H., Saeed, M., Schwab, S. J., Perlmutt, L. M., & Dunnick, N. R. (1988). Povidone-iodine sclerosis of pelvic lymphoceles: a prospective study. *Urologic Radiology*, *10*(4), 203–206. https://doi.org/10.1007/BF02926570

Costa, K. M., & Saxena, A. K. (2018). Surgical chylothorax in neonates: management and outcomes. *World Journal of Pediatrics : WJP*, *14*(2), 110–115. https://doi.org/10.1007/s12519-018-0134-x

Das, A., & Shah, P. S. (2010). Octreotide for the treatment of chylothorax in neonates. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd006388.pub2

De Haan, T. R., Oepkes, D., Beersma, M. F. C., & Walther, F. J. (2005). Aetiology, Diagnosis and Treatment of Hydrops Foetalis. In *Current Pediatric Reviews* (Vol. 1).

Dendale, J., Comet, F. ?, Amram, D., & Lesbros, D. (1999). Le chylothorax de dkcouverte antenatale. In *Arch PCdiatr* (Vol. 6).

Dorsi, M., Giuseppi, A., Lesage, F., Stirnemann, J., De Saint Blanquat, L., Nicloux, M., Assaf, Z., Khen Dunlop, N., Kermorvant-Duchemin, E., Magny, J. F., Ville, Y., & Lapillonne, A. (2018). Prenatal factors associated with neonatal survival of infants with congenital chylothorax. *Journal of Perinatology*, *38*(1), 31–34. https://doi.org/10.1038/jp.2017.150

Drovandi, L., Cianchi, I., Pratesi, S., & Dani, C. (2018). Fibrin glue pleurodesis for pneumothorax in extremely preterm infants: a case report and literature review. *Italian Journal of Pediatrics*, *44*(1), 91. https://doi.org/10.1186/s13052-018-0533-6

Easa, D., Balaraman, V., Ash, K., Thompson, B., & Boychuk, R. (1991). Congenital chylothorax and mediastinal neuroblastoma. *Journal of Pediatric Surgery*, *26*(1), 96–98. https://doi.org/10.1016/0022-3468(91)90439-z

Edwards, M. O., Kotecha, S. J., & Kotecha, S. (2013). Respiratory Distress of the Term Newborn Infant. In *Paediatric Respiratory Reviews* (Vol. 14, Issue 1, pp. 29–37). https://doi.org/10.1016/j.prrv.2012.02.002

Fetal chylothorax response to maternal diaetary treatment. (n.d.).

Fogg, K. L., Trauth, A., Horsley, M., Vichayavilas, P., Winder, M., Bailly, D. K., & Gordon, E. E. (2022). Nutritional management of postoperative chylothorax in children with CHD. *Cardiology in the Young*, 1–9. https://doi.org/10.1017/S1047951122003109

Healy, H., Gipson, K., Hay, S., Bates, S., & Kinane, T. B. (2017). Management and outcomes of congenital chylothorax in the neonatal intensive care unit: A case series. *Pediatric Investigation*, *1*(1), 21–25. https://doi.org/10.1002/ped4.12007

Helin, R. D., Angeles, S. T. V, & Bhat, R. (2006). Octreotide therapy for chylothorax in infants and children: A brief review. *Pediatric Critical Care Medicine : A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, *7*(6), 576–579. https://doi.org/10.1097/01.PCC.0000235256.00265.C8

Hillerdal, G. (1997). Chylothorax and pseudochylothorax. In *European Respiratory Journal* (Vol. 10, Issue 5, pp. 1157–1162). European Respiratory Society. https://doi.org/10.1183/09031936.97.10051157

Hodges, M. M., Crombleholme, T. M., Meyers, M., Kulungowski, A., Marwan, A. I., Nakano, T., Behrendt, N., & Liechty, K. W. (2016). Massive fetal chylothorax successfully treated with postnatal talc pleurodesis: A case report and review of the literature. *Journal of Pediatric Surgery Case Reports*, *9*, 1–4. https://doi.org/10.1016/j.epsc.2016.03.014

Hoskote, A. U., Ramaiah, R. N., Cale, C. M., Hartley, J. C., & Brown, K. L. (2012a). Role of immunoglobulin supplementation for secondary immunodeficiency associated with chylothorax after pediatric cardiothoracic surgery. *Pediatric Critical Care Medicine : A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, *13*(5), 535–541. https://doi.org/10.1097/PCC.0b013e318241793d

Hoskote, A. U., Ramaiah, R. N., Cale, C. M., Hartley, J. C., & Brown, K. L. (2012b). Role of immunoglobulin supplementation for secondary immunodeficiency associated with chylothorax after pediatric cardiothoracic surgery. *Pediatric Critical Care Medicine : A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, *13*(5), 535–541. https://doi.org/10.1097/PCC.0b013e318241793d

Hoskote, A. U., Ramaiah, R. N., Cale, C. M., Hartley, J. C., & Brown, K. L. (2012c). Role of immunoglobulin supplementation for secondary immunodeficiency associated with chylothorax after pediatric cardiothoracic surgery. *Pediatric Critical Care Medicine : A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, *13*(5), 535–541. https://doi.org/10.1097/PCC.0b013e318241793d

Irving, C. A., & Chaudhari, M. P. (2012). Cardiovascular abnormalities in Down's syndrome: spectrum, management and survival over 22 years. *Archives of Disease in Childhood*, *97*(4), 326–330. https://doi.org/10.1136/adc.2010.210534

Itkin, M., Krishnamurthy, G., Naim, M. Y., Bird, G. L., & Keller, M. S. (2011a). Percutaneous thoracic duct embolization as a treatment for intrathoracic chyle leaks in infants. *Pediatrics*, *128*(1), e237-41. https://doi.org/10.1542/peds.2010-2016

Itkin, M., Krishnamurthy, G., Naim, M. Y., Bird, G. L., & Keller, M. S. (2011b). Percutaneous thoracic duct embolization as a treatment for intrathoracic chyle leaks in infants. *Pediatrics*, *128*(1), e237-41. https://doi.org/10.1542/peds.2010-2016

Kallanagowdar, C., & Craver, R. D. (2006). Neonatal pleural effusion. Spontaneous chylothorax in a newborn with trisomy 21. *Archives of Pathology & Laboratory Medicine*, *130*(2), e22-3. https://doi.org/10.5858/2006-130-e22-NPE

Kamiyama, M., Usui, N., Tani, G., Soh, H., Kamata, S., Nose, K., Kubota, A., & Fukuzawa, M. (2010). Postoperative chylothorax in congenital diaphragmatic hernia. *European Journal of Pediatric Surgery*, *20*(6), 391–394. https://doi.org/10.1055/s-0030-1261956

Kargl, S., & Maier-Hiebl, B. (2019). Pediatric chylothorax—lymphatic imaging enables targeted surgical treatment. *Indian Journal of Thoracic and Cardiovascular Surgery*, *35*(2), 233–236. https://doi.org/10.1007/s12055-018-00779-7

Kirkland, I. (1965). Chylothorax in infancy and childhood: A method of treatment. In *Archives of Disease in Childhood* (Vol. 40, Issue 210, pp. 186–191). BMJ Publishing Group. https://doi.org/10.1136/adc.40.210.186

Kumar, T. K. S., Balduf, K., Boston, U., & Knott-Craig, C. (2017). Diaphragmatic fenestration for refractory chylothorax after congenital cardiac surgery in infants. *The Journal of Thoracic and Cardiovascular Surgery*, *154*(6), 2062–2068. https://doi.org/10.1016/j.jtcvs.2017.08.002

Kumar, T. K. S., Subramanian, S., Sathanandam, S., Alexander, J., Ali, M., & Knott-Craig, C. J. (2015). Superior Vena Cava Reconstruction for Treatment of Chylothorax Resulting From Thrombosis of Superior Vena Cava in Young Infants. *The Annals of Thoracic Surgery*, *100*(4), 1432–1436. https://doi.org/10.1016/j.athoracsur.2015.06.021

Kurtz, T. W., & Hsu, C. H. (1980). Resolution of chylothorax after positive end-expiratory pressure ventilation. *Archives of Surgery (Chicago, Ill. : 1960)*, *115*(1), 73–74. https://doi.org/10.1001/archsurg.1980.01380010061012

Le Coultre, C., Oberhsnsli, L., Mossaz, A., Bugmann, P., Faidutti, B., & Belli, D. C. (1991). *Postoperative Chylothorax in Children: Differences Between Vascular and Traumatic Origin*.

Longaker, M. T., Laberge, J.-M., Dansereau, J., Langer, J. C., Crombleholme, T. M., Callen, P. W., Golbus, M. S., & Harrison, M. R. (n.d.). *Primary Fetal Hydrothorax: Natural History and Management*.

Maira Ilahi, Kayla St Lucia, & Tahir B. Ilah. (n.d.). *Anatomy, Thorax, Thoracic Duct*.

Maldonado, F., Finn, ;, Hawkins, J., Daniels, C. E., Doerr, C. H., Decker, P. A., And, ;, & Ryu, J. H. (2009). Pleural Fluid Characteristics of Chylothorax. In *Mayo Clin Proc* (Vol. 84, Issue 2). www.mayoclinicproceedings.com

Mallmann, M. R., Graham, V., Rösing, B., Gottschalk, I., Müller, A., Gembruch, U., Geipel, A., & Berg, C. (2017). Thoracoamniotic Shunting for Fetal Hydrothorax: Predictors of Intrauterine Course and Postnatal Outcome. *Fetal Diagnosis and Therapy*, *41*(1), 58–65. https://doi.org/10.1159/000446110

Marino, L. V, Bell, K. L., Woodgate, J., British Dietetic Association Paediatric Cardiology Interest Group, & Doolan, A. (2019). An international survey of the nutrition management of chylothorax: a time for change. *Cardiology in the Young*, *29*(9), 1127–1136. https://doi.org/10.1017/S1047951119001525

Mathur, N. B., Singh, B., Kumar, A., & Aggarwal, S. K. (2009). Successful treatment of congenital chylothorax using fibrin glue. *Indian Journal of Pediatrics*, *76*(7), 758. https://doi.org/10.1007/s12098-009-0118-x

Mizuno, T., Fukuda, T., Emoto, C., Mobberley-Schuman, P. S., Hammill, A. M., Adams, D. M., & Vinks, A. A. (2017). Developmental pharmacokinetics of sirolimus: Implications for precision dosing in neonates and infants with complicated vascular anomalies. *Pediatric Blood & Cancer*, *64*(8). https://doi.org/10.1002/pbc.26470

Muniz, G., Hidalgo-Campos, J., Valdivia-Tapia, M. D. C., Shaikh, N., & Carreazo, N. Y. (2018). Successful Management of Chylothorax With Etilefrine: Case Report in 2 Pediatric Patients. *Pediatrics*, *141*(5). https://doi.org/10.1542/peds.2016-3309

Nandy, K., Jayaprakash, D., Rai, S., Kumar, A., Puj, K., & Tripathi, U. (2022). Management of Chyle Leak After Head and Neck Surgery; Our Meritorious Experience in 52 Cases and Review of Literature. *Indian Journal of Otolaryngology and Head and Neck Surgery*, *74*, 5978–5983. https://doi.org/10.1007/s12070-021-02648-z

Orange, J. S., Geha, R. S., & Bonilla, F. A. (2003). Acute chylothorax in children: selective retention of memory T cells and natural killer cells. *The Journal of Pediatrics*, *143*(2), 243–249. https://doi.org/10.1067/S0022-3476(03)00305-6

Panthongviriyakul, C., & Bines, J. E. (2008). Post-operative chylothorax in children: An evidence-based management algorithm. *Journal of Paediatrics and Child Health*, *44*(12), 716–721. https://doi.org/10.1111/j.1440-1754.2008.01412.x

Philips, J. B. (2022). *Official reprint from UpToDate Approach to the neonate with pleural effusions*. www.uptodate.com

Philips, J. B., & Atkinson, T. P. (2022). *Official reprint from UpToDate Management of chronic pleural effusions in the neonate*. www.uptodate.com

Premuzic, V., Smiljanic, R., & Perkov, D. (2018). A conservative approach to a thoracic duct injury caused by left subclavian vein catheterization. *Egyptian Journal of Anaesthesia*, *34*(1), 41–42. https://doi.org/10.1016/j.egja.2017.09.001

Ragosta, K. G., & Alfieris, G. (2000). Chylothorax: a novel therapy. *Critical Care Medicine*, *28*(4), 1208–1209. https://doi.org/10.1097/00003246-200004000-00050

Resch, B., Sever Yildiz, G., & Reiterer, F. (2022). Congenital Chylothorax of the Newborn: A Systematic Analysis of Published Cases between 1990 and 2018. In *Respiration* (Vol. 101, Issue 1, pp. 84–96). S. Karger AG. https://doi.org/10.1159/000518217

Rocha, G., Arnet, V., Soares, P., Gomes, A. C., Costa, S., Guerra, P., Casanova, J., & Azevedo, I. (2021). Chylothorax in the neonate—A stepwise approach algorithm. In *Pediatric Pulmonology* (Vol. 56, Issue 10, pp. 3093–3105). John Wiley and Sons Inc. https://doi.org/10.1002/ppul.25601

Rocha, G., Fernandes, P., Rocha, P., Quintas, C., Martins, T., & Proença, E. (2006). Pleural effusions in the neonate. *Acta Paediatrica, International Journal of Paediatrics*, *95*(7), 791–798. https://doi.org/10.1080/08035250500477545

Roehr, C. C., Jung, A., Proquitté, H., Blankenstein, O., Hammer, H., Lakhoo, K., & Wauer, R. R. (2006). Somatostatin or octreotide as treatment options for chylothorax in young children: A systematic review. In *Intensive Care Medicine* (Vol. 32, Issue 5, pp. 650–657). https://doi.org/10.1007/s00134-006-0114-9

Samuel, M., Mccarthy, L., Boddy, S.-A., & Samuel, M. (2000). Efficacy and Safety of OK-432 Sclerotherapy for Giant Cystic Hygroma in a Newborn. In *Fetal Diagn Ther* (Vol. 15).

Samuel, W., And, Y., & Spock, A. (n.d.). *Spontaneous Neonatal Pleural Effusion*.

Sepulveda, W., Galindo, A., Sosa, A., Diaz, L., Flores, X., & De La Fuente, P. (2005). Intrathoracic dislodgement of pleuro-amniotic shunt: Three case reports with long-term follow-up. *Fetal Diagnosis and Therapy*, *20*(2), 102–105. https://doi.org/10.1159/000082431

Shirota, C., Tanaka, Y., Tainaka, T., Sumida, W., Yokota, K., Makita, S., Oshima, K., Tanaka, T., Tani, Y., & Uchida, H. (2019). Therapeutic strategy for thoracoscopic repair of esophageal atresia and its outcome. *Pediatric Surgery International*, *35*(10), 1071–1076. https://doi.org/10.1007/s00383-019-04541-x

Smith, R. P., Illanes, S., Denbow, M. L., & Soothill, P. W. (2005). Outcome of fetal pleural effusions treated by thoracoamniotic shunting. *Ultrasound in Obstetrics and Gynecology*, *26*(1), 63–66. https://doi.org/10.1002/uog.1883

Soto-Martinez, M., & Massie, J. (2009). Chylothorax: Diagnosis and management in children. In *Paediatric Respiratory Reviews* (Vol. 10, Issue 4, pp. 199–207). https://doi.org/10.1016/j.prrv.2009.06.008

Successful Use of Octreotide for Chylothorax. (2012). http://emedicine.medscape.com/article/172527-over-

Utture, A., Kodur, V., & Mondkar, J. (2016). Chemical Pleurodesis with Oxytetracycline in Congenital Chylothorax. *Indian Pediatrics*, *53*(12), 1105–1106.

Van Straaten, H. L. M., Gerards, L. J., & Krediet, T. G. (n.d.). *Chylothorax in the neonatal period*.

Walker-Renard, P. B., Vaughan, L. M., & Sahn, S. A. (1994). Chemical pleurodesis for malignant pleural effusions. *Annals of Internal Medicine*, *120*(1), 56–64. https://doi.org/10.7326/0003-4819-120-1-199401010-00010

Wang, I.-J., Lu, F. L., Chang, C.-I., & Wang, J.-K. (2002). Conservative treatment in an infant with superior vena cava syndrome after cardiac surgery. *Journal of the Formosan Medical Association = Taiwan Yi Zhi*, *101*(5), 352–354.

Weijerman, M. E., van Furth, A. M., Vonk Noordegraaf, A., van Wouwe, J. P., Broers, C. J. M., & Gemke, R. J. B. J. (2008). Prevalence, neonatal characteristics, and first-year mortality of Down syndrome: a national study. *The Journal of Pediatrics*, *152*(1), 15–19. https://doi.org/10.1016/j.jpeds.2007.09.045

Weissler, J. M., Cho, E. H., Koltz, P. F., Carney, M. J., Itkin, M., Laje, P., Levin, L. S., Dori, Y., Kanchwala, S. K., & Kovach, S. J. (2018). Lymphovenous Anastomosis for the Treatment of Chylothorax in Infants: A Novel Microsurgical Approach to a Devastating Problem. *Plastic and Reconstructive Surgery*, *141*(6), 1502–1507. https://doi.org/10.1097/PRS.0000000000004424