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Chylothorax in the neonate—A stepwise approach algorithm

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Abstract

Background: Chylothorax in neonates results from leakage of lymph from thoracic lymphatic ducts and is mainly congenital or posttraumatic. The clinical course of the effusion is heterogeneous, and consensus on treatment, timing, and modalities of measures has not yet been established. This review aims to present, along with levels of evidence and recommendation grades, all current therapeutic possibilities for the treatment of chylothorax in neonates.

Methods: An extensive search of publications between 1970 and 2020 was performed in the PubMed, Cochrane Database of Systematic Reviews, and UpToDate databases. A stepwise approach algorithm was proposed for both congenital and traumatic conditions to guide the clinician in a rational and systematic way for approaching the treatment of neonates with chylothorax.

Discussion and Conclusion: The treatment strategy for neonatal chylothorax generally involves supportive care and includes drainage and procedures to reduce chyle flow. A stepwise approach starting with the least invasive method is advocated. Progression in the invasiveness of treatment options is determined by the response to previous treatments. A practical stepwise approach algorithm is proposed for both, congenital and traumatic chylothoraces.

1 | INTRODUCTION

Chylothorax refers to the accumulation of lymph in one or both pleural cavities and is the most frequent pleural effusion in neonates. It results from leakage of lymph from thoracic lymphatic ducts and is a cause of respiratory distress in neonates. The diagnosis of chylothorax is confirmed when the analysis of pleural fluid shows a cell count greater than 1000 white blood cells per µl, with more than 70%–80% lymphocytes and, in enterically fed patients, a triglyceride concentration greater than 110 mg/dl (1.1 mmol/L).[1,2] Most authors distinguish between three forms of chylothorax: congenital, traumatic, and nontraumatic.[1]

Congenital chylothorax (CC) is a rare condition affecting approximately 1:10,000–24,000 live births, has a male:female ratio of approximately 2:1, and tends to occur more frequently in the right pleural cavity due to the usual location of the thoracic duct largely in the right mediastinum. It results from lymphatic vessel anomalies or thoracic cavity defects, and may accompany other congenital anomalies or be a part of a genetic syndrome (including Noonan, Turner, Down, Ehlers-Danlos, and Costello syndromes). Most cases of CC resolve with time. Neonates with an occluded

Abbreviations: AT, antithrombin; bFGF, basic fibroblast growth factor; BSI, bloodstream infection; CC, congenital chylothorax; CT, computed tomography; CVC, central venous catheter (CVC); FFP, fresh frozen plasma; GnRH, gonadotropin hormone-releasing hormone; HFV, high-frequency ventilation; Ig, immunoglobulin; ILE, injectable lipid emulsion; IV, intravenous; IVIg, intravenous immunoglobulin; LH, luteinizing hormone; LoE, levels of evidence; MCT, medium-chain triglycerides; MMP-2, matrix metalloproteinase-2; mTOR, mammalian target of rapamycin; NK, natural killer; RG, recommendation grades; SVC, superior vena cava; VEGF, vascular endothelial growth factor.

thoracic duct need weeks to months to develop alternative lymphatic routes, explaining why some cases are bulky, prolonged, and difficult to treat. In the foetus, chylothorax can compromise lung growth and vascular flow, causing pulmonary hypoplasia, pulmonary hypertension, reduced venous return, heart failure, hydrops, and foetal death in the most severe cases. Most patients with CC are prenatally detected, while others become symptomatic after starting enteral feeding.[3–8]

Traumatic chylothorax is an iatrogenic complication that often follows thoracic trauma or surgery with thoracic duct injury. The estimated incidence of traumatic chylothorax is 0.25%–0.5% after cardiovascular surgery. It has also been reported to occur after oesophageal, mediastinal, diaphragmatic, and pleuropulmonary surgeries. It usually develops after an enteric diet is started following thoracic surgery and can be bilateral. Variations in lymphatic pathways and the presence of accessory lymphatic channels can lead to chylous effusions resulting from operative approaches that do not expose the main thoracic duct.[3,9–11]

Nontraumatic chylothorax is rare in neonates and results from lymphatic drainage obstruction secondary to a mediastinal tumour, venous thrombosis, inflammatory disease, or lymphangiomatosis.[12] There is increasing evidence supporting the association between central venous thrombosis and chylothorax in infants who underwent cardiothoracic surgery for congenital heart disease. This makes the interpretation of the cause challenging, as chylothorax may occur after surgery even in the absence of trauma to the thoracic duct. For this reason, some authors advocate routine investigations for venous thrombi after cardiac surgery.[13–16]

Lymph contains cellular components with a predominance of lymphocytes, proteins including albumin, antibodies, complement, coagulation factors, enzymes, and peptide hormones, as well as nutrients, chylomicra (fat globules of emulsified long-chain fatty acids), electrolytes, bicarbonate, and fluid. The significant loss or drainage of these elements puts the patient at risk for hypovolemia, hypotension, malnutrition, hypoproteinemia, electrolyte imbalance, metabolic acidosis, lymphocyte depletion, hypogammaglobulinemia, immune deficiency, and increased risk of infections.[6,17]

Lymph does not contain short- and medium-chain fatty acids since they are absorbed directly into the portal venous circulation.[8]

Expertise in performing lymphatic imaging studies in neonates (lymphangiography, magnetic resonance lymphangiography, lymphoscintigraphy, and nonionizing lymphography) is limited.[5] Open lung biopsy may be important in selected cases such as congenital pulmonary lymphangiectasia.[18]

Lymphatic vascular anatomy and physiology, lymphatic vascular anomalies, and intestinal and hepatic mechanisms of lymph formation and drainage are described elsewhere[6,18,19] and will not be addressed in this review.

Evidence-based treatment choices for chylothorax in neonates are lacking. This review aims to present, along with levels of evidence (LoE) and recommendation grades (RG), all current therapeutic possibilities for the treatment of chylothorax in neonates. Finally, a practical, rational and systematic therapeutic algorithm is suggested for both congenital and traumatic conditions.

2 | METHODS

An extensive search of publications between the years 1970 and 2020 was performed in the PubMed, Cochrane Database of Systematic Reviews, and UpToDate databases. The search terms used were: neonate; newborn; intensive care; pleural effusion; chylothorax; CC; chylous effusion; traumatic chylothorax; non-traumatic chylothorax; hydrothorax; iatrogenic; postsurgical chylothorax; hydrops fetalis; lymph; treatment; thoracocentesis; drainage; octreotide; somatostatin; propranolol; sildenafil; etilefrine; sirolimus; lymphopenia; T-cell depletion; hypogammaglobulinemia intravenous immunoglobulin; clotting factors; thrombosis; fresh frozen plasma (FFP); vitamin K1; bicarbonate; low fat breast milk; fat-free human milk; medium-chain triglycerides diet; Monogen®; Portagen®; Enfaport®; pleurodesis; pleural abrasion; thoracic duct embolisation; thoracic duct ligation; pleuro-peritoneal shunt; diaphragmatic fenestration; superior vena cava (SVC) thrombectomy and bypass; and lymphovenous anastomosis. Accessible information was analysed, and the most relevant information was selected and used in this review.

The LoE and RG used are those suggested by the *European Society of Cardiology* (www.escardio.org) (Table 1).

A stepwise approach algorithm was created for both CC and traumatic chylothorax and is represented in flowcharts 1 and 2.

In this review, the volume of the effusion was defined as small if, on a standard chest radiography, it was apparent in not more than a quarter of the lung field, moderate if it was apparent in a quarter to half of the lung field, and large if apparent in more than half of the lung field; or by ultrasound at the posterior pleural costophrenic recess, which may be graded as small (<10 mm), moderate (10–30 mm), or large (>30 mm).[20–22] In addition, a chylothorax with a continuous drainage of >10 ml/kg/day was considered as high volume.[8,21]

2.1 | Goal of treatment

The goal of treatment of a lymphatic pleural effusion is to decrease its volume and to allow time for the injured lymphatic vessels to heal or develop.[2] Treatment begins with supportive management, including respiratory support, pleural drainage, cardiovascular support, nutritional management, pharmacological reduction of intestinal chyle production, and pain therapy.[23]

The initial step in the management of a significant pleural effusion is aimed at relieving respiratory distress that results from lung compression. If evaluation by lung ultrasound finds a moderate or large pleural effusion, an evacuation and diagnostic thoracocentesis may be performed initially, especially in the delivery room. Placement of a chest tube for continuous suction drainage should be considered from the outset because of the commonly observed persistence of lymphatic drainage for an unpredictable period of time, both in

TABLE 1 Levels of evidence and recommendation grades (www.escardio.org)

Level of evidence (LoE)	Description
A	Information collected from several randomised clinical trials or meta-analysis
B	Information collected from a single randomised clinical trial or extended nonrandomised studies
C	Consensus opinion of specialists and/or small studies, retrospective studies and records
Recommendation grades (RG)	
Grade I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. Is recommended/indicated.
Grade II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Grade IIa	Weight of evidence/opinion is in favour of usefulness/efficacy. Should be considered.
Grade IIb	Usefulness/efficacy is less well established by evidence/opinion. May be considered.
Grade III	Evidence or general agreement that the given procedure is not useful/effective, and in some cases may be harmful. Is not recommended.

congenital and posttraumatic chylothoraces (RG I).[1] Intubation and invasive mechanical ventilation should be considered before this procedure, especially in cases of severe pleural effusion or hydrops. The ventilation modality can be conventional or high-frequency ventilation (HFV) with there being no conclusive data regarding the superiority of one over the other. HFV may improve lung opening and volume maintenance.[24]

Cardiovascular support is an important step in the management of chylothorax, especially in critical post-cardiothoracic surgery patients at risk of severe hypotension and hypovolemia. Monitoring blood pressure, central venous pressure, hydric balance and electrolytes, along with 2D-echocardiography, are important measures in the assessment and therapeutic guidance of these patients.[25] The drained fluid is usually partially replaced with a 5% albumin solution (RG IIb).[6]

The heterogeneous clinical presentation of CC, numerous aetiologies, its rarity, difficulties in using diagnostic imaging techniques in small neonates, and the absence of a highly effective treatment render the treatment of CC difficult to standardise. In patients with CC, an initial investigation to exclude congenital anomalies (2D-echocardiography, cranial, lung, abdominal, and kidney ultrasound) and genetic evaluation should be performed because of the frequent association of CC with lymphatic abnormalities and genetic syndromes (RG I).[1,6]

In cases of postcardiothoracic surgery chylothorax, evaluation with Doppler ultrasound and/or angio-computed tomography is recommended for SVC thrombosis (RG IIa). Avoidance of central catheter insertion in the upper body veins may help decrease the incidence of postoperative chylothorax (RG IIa).[15]

Asymptomatic small effusions can be managed conservatively with nutritional measures associated with octreotide, and the volume can be monitored using ultrasound (RG I).[1,23]

Chyle production is reduced through nutritional measures and pharmacological agents.[1]

The management of pain with opioids and paracetamol should always be considered, even in unventilated patients, because of the high prevalence of painful experiences in this population (RG I). Each unit should choose the tools for pain assessment in different populations (full-term or preterm), contexts, and types of pain (procedural or postoperative).[26]

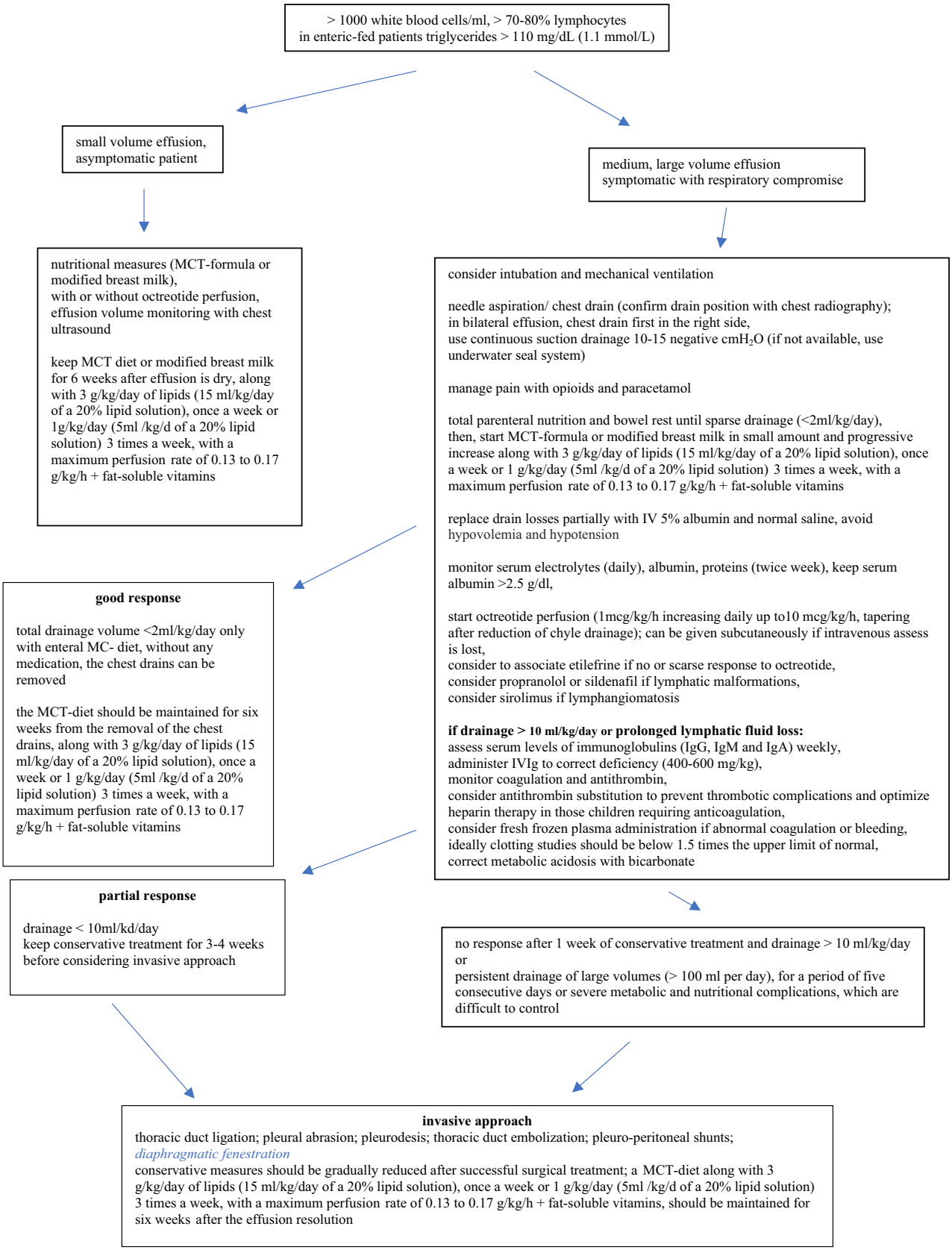
Along with these steps, it is important to avoid, or at least minimise, the risk of malnutrition, hypoproteinaemia, electrolyte imbalance, metabolic acidosis, lymphocyte depletion, hypogammaglobulinemia, immune deficiency, and infections.[1]

2.2 | Nutritional measures

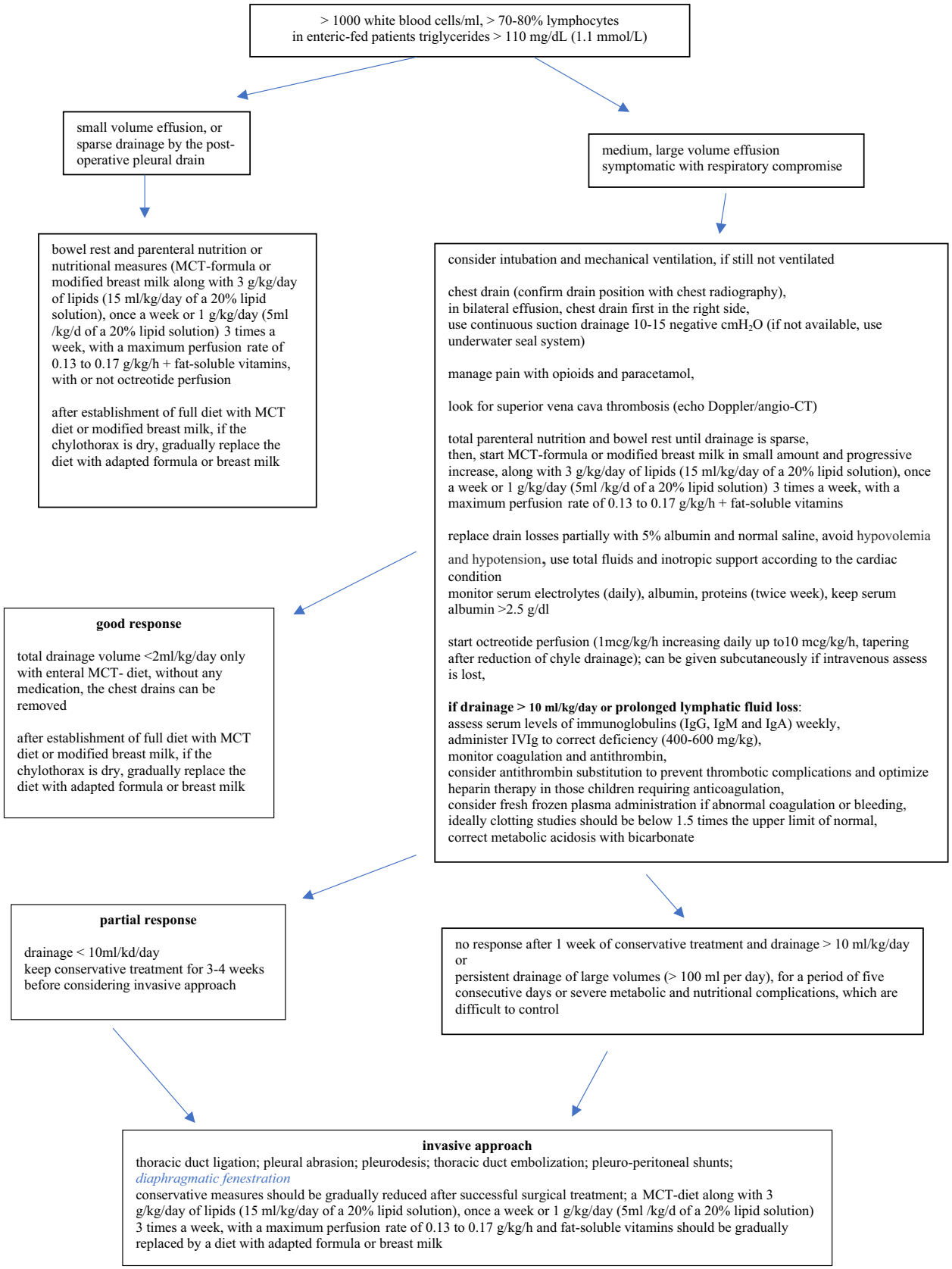
Lymph in the thoracic duct transports nutrients including chylomicra, several proteins, cells, hormones, electrolytes, bicarbonate, and fluid. The aim of nutritional therapy is to minimise intestinal flow, both by using a parenteral route for feeding with no enteral feeds or using a diet with medium-chain triglycerides (MCT) as a lipid source (RG I).[1,27] Total parenteral nutrition and bowel rest along with octreotide perfusion, followed by reestablishment of feeds using an MCT-based milk formula, has been used in our unit for several years.[28] A formula containing MCT as a lipid source (Monogen®, Portagen®, or Enfaport®), or fat-modified breast milk with or without association with a pharmacological agent, is another possible strategy.[27]

Total parenteral nutrition and bowel rest decrease chyle flow in patients who fail to respond to the MCT diet.[28]

Within 1 week, drainage should be lower than 10 ml/kg/day; otherwise, more invasive measures should be adopted.[5] When the total drainage volume reduces to 2 ml/kg/day with only enteral MCT diet, and without any medication, the chest drains can be removed. The MCT diet should be maintained for 6 weeks after the removal of the chest drains, along with weekly perfusion of a 20% lipid solution and fat-soluble vitamins, to avoid deficiencies in these essential nutrients (RG I).[28] This 20% lipid perfusion, which uses different types of lipid solutions as the injectable lipid emulsion (ILE) (medium-chain triglycerides/soybean oil ILE or 20% olive oil/soybean oil-based ILE or an oil-based a composite ILE



FLOWCHART 1 Congenital chylothorax approach [Color figure can be viewed at wileyonlinelibrary.com]



FLOWCHART 2 Posttraumatic chylothorax approach [Color figure can be viewed at wileyonlinelibrary.com]

with fish oil), at a dose of 3 g/kg/day of lipids (15 ml/kg/day), once a week or at 1 g/kg/d lipid (5 ml/kg/d) three times a week, with a maximum perfusion rate of 0.13–0.17 g/kg/h, provides essential fatty acids that are not present in the MCT-diet.[29] We add liposoluble vitamins to the lipid solution. Vitamin K can be administered directly into the central catheter or added to the lipid solution along with other liposoluble vitamins. If vitamins are administered only once a week, the doses are five to seven times the recommended daily dose.

A challenge of the enteral diet of patients with chylothorax is to offer a long-chain triglyceride-free supply, and to ensure adequate nutrition for their weight growth and development. Thus, to complement conservative treatment, enteral dietary schemes must be created and adapted to the conditions of each service, clinical conditions, and the food tolerance of each patient.[28,30,31]

Breast milk can be centrifuged and converted into low-fat breast milk, which can be supplemented with MCT.[31–34] In a study by Di Lauro et al.,[31] there were no statistically significant differences in the duration or volume of chest drainage between patients who respectively received MCT and low-fat breast milk.[31] The accuracy of a creamatocrit in determining the total lipid content of a breast milk sample is approximately 90%, making it an accessible methodology that is fast and easy to use.[35,36] The removal of the fat layer from cold, centrifuged mother's milk using a syringe is more effective than the use of a spoon or spatula; it leaves about 34% less lipid residue in low-fat breast milk.[32] Breast milk has a variable amount of somatostatin in its composition, which is advantageous in reducing chylo drainage.[37] The concentration of proteins in low-fat breast milk is not influenced by centrifugation or manipulation.[38] A therapeutic scheme with protein supplementation should be recommended to patients who need more calories per ml and more protein to replace the losses of pleural drainage (RG IIa).[39]

2.3 | Pharmacological agents

Several pharmacological agents have been used in the treatment of chylothorax, with the aim of reducing thoracic lymphatic flow. **Somatostatin** has been used successfully, but its use has been replaced by octreotide.[40–42]**Octreotide** is a synthetic analogue of the natural hormone somatostatin, with a more powerful and long-lasting action and fewer side effects.[43] Among several gastrointestinal actions, octreotide reduces splanchnic blood flow, fat absorption, and lymphatic flow in the thoracic duct.[43,44] It has been used to treat chylothoraces in infants and neonates since 2001.[45–48] In 2010, a *Cochrane* review with the objective of assessing the efficacy and safety of octreotide in the treatment of chylothorax in neonates did not find any randomised trial, but analysed 19 case reports of 20 neonates with chylothorax treated with octreotide, either intravenously or subcutaneously. Although the majority of the reports described successful use, the authors did not recommend its use.[49] A systematic review in 2018 that included only single case reports and case series concluded that octreotide is relatively safe and effective, and should be considered as an adjunctive treatment in term and preterm neonates with acquired and CC.[50] Currently, octreotide is the pharmacological agent that provides the most robust evidence for the treatment of chylothorax in neonates (LoE B). Some clinicians use octreotide as a second-line treatment after total parenteral nutrition failure before considering surgical treatment. At our centre, we use octreotide since the beginning of treatment together with nutritional measures, with good results.

Etilefrine, a sympathomimetic drug that causes contraction of smooth muscle fibers in the thoracic duct has been used, in combination with octreotide or not, in adult and neonatal patients with postoperative chylothorax.[51–54] Although experience with etilefrine is limited, it can be a novel option in the conservative treatment of neonatal chylothorax. Prospective trials are needed to establish its efficacy and safety (LoE C).

Midodrine, an oral selective alpha-1adrenoreceptor agonist, is a vasopressor that may be used as an adjunctive therapy to contract lymphatic vessels in patients with chylothorax.[55] It has been successfully used in adults,[56,57] a 4-year-old girl,[58] and a neonate[59] (LoE C).

Propranolol has been used in neonates to treat chylothoraces associated with lymphatic malformations; descriptions of propranolol use are limited to case reports and small case series with variable degrees of success (LoE C).[60–63] The effects of propranolol may be caused by the suppression of proangiogenic factors, which are also lymphangiogenic factors (VEGF1, bFGF, and MMP-2), in the short term, and by the increase in the apoptosis of endothelial cells in the long term.[64]

Sildenafil, an inhibitor of phosphodiesterase-5 used to treat pulmonary arterial hypertension, reduces lymphatic endothelial proliferation as well as new lymphatic vessel growth. It has been used in the treatment of lymphatic malformations since being used to treat an infant with pulmonary hypertension in the setting of a lymphatic malformation[65] (LoE C). An association between sildenafil and retinopathy of prematurity has been reported, with conflicting results.[66–68] Large cohort studies are needed to confirm this association.

Sirolimus, an inhibitor of the mammalian target of rapamycin, a kinase overexpressed in cutaneous vascular malformations, has antiangiogenic properties that mitigate VEGF.[69] It is an immunosuppressant drug that has been used in cases of lymphangiomatosis.[70]

The pharmacological agents used to treat chylothorax in neonates, as well as doses and adverse effects are summarised in Table 2.[54,59,63,71,72]

2.4 | Additional therapies

Lymphatic fluid loss is associated with the loss of key elements such as lymphocytes and small molecular weight proteins, including immunoglobulins and coagulation factors.[5,16] Therefore, in patients with prolonged lymphatic fluid loss, immunodepression and coagulation disorders have become a serious concern. Persistent chylothorax is associated with lymphopenia, and the degree of lymphopenia correlates with a longer duration of chylothorax but not with the quantity of drainage.[17,73–75]

TABLE 2 Pharmacological agents used to treat chylothorax in neonates[54,59,63,71,72]

Pharmacological agent (LoE)	Characteristics	Dosage	Adverse effects
Octreotide (LoE B)	A long-acting analogue of the natural hormone somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.	Start with 1 mcg/kg/hour IV continuous infusion. Titrate upward as necessary based on reduction in chyle production to a maximum dose: 10 mcg/kg/hour. Dosage increases of 1 mcg/kg/hour every 24 h have been used. To stop treatment, infusion is decreased gradually over 2–7 days. Can also be used subcutaneously or IV in divided doses, every 6 h.	Vomiting, diarrhea, abdominal distention, steatorrhea and hyperglycemia may occur. Pulmonary hypertension has been reported in treated former premature infants with chronic lung disease. Necrotizing enterocolitis has been reported in term neonates receiving octreotide for the treatment of hyperinsulinemic hypoglycemia (6 cases) and chylothorax (2 cases).
Etilefrine (LoE C)	A sympathomimetic amine, cardiac stimulant used as an anti-hypotensive	Two cases described in neonatal literature (54). Doses used: 0.5–1 mcg/kg/h Monitor blood pressure and heart rate. Weaned progressively from 0.5 to 0.2 mcg/kg/h, based on reduction in chyle production.	Palpitations, arrhythmias, chest pain, hypertension.
Midodrine (LoE C)	An agent that exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar, venous and lymphatic vasculature, producing an increase in vascular tone and elevation of blood pressure.	One case described in literature (59): Started at a daily dosage of 0.5 mg (oral); confirming that no adverse effects were observed, the dosage was increased to 1 mg/day.	Headache, feeling of pressure/fullness in the head, vasodilation/flushing face, scalp tingling, confusion/thinking abnormality, dry mouth, nervousness/anxiety and rash. Systemic arterial hypertension may occur; close monitoring of blood pressure is essential.
Propranolol (LoE C)	Nonselective β-adrenergic-receptor blocking agent Used to treat hypertension, tachyarrhythmias and infantile hemangiomas. Has been used in neonates to treat **chylothoraces associated with lymphatic malformations.**	**Term neonates**: 1–4 mg/kg/day, oral route (most reported patients received 1–2 mg/kg/day) divided every 8 h **Preterm neonates**: starting dose 0.1–0.5 mg/kg/day, titrate to a max dose 2 m/kg/day, divided every 8 h	Bradycardia, hypotension, bronchospasm, hypoglycemia Contraindicated in patients with cardiogenic shock, sinus bradycardia greater than first degree block, reactive airway disease, or diminished myocardial contractility. A withdrawal syndrome (nervousness, tachycardia, sweating, hypertension) has been associated with sudden cessation of the drug.
Sildenafil (LoE C)	Inhibitor of phosphodiesterase-5 used to treat pulmonary arterial hypertension. Has been used to treat chylothoraces associated with lymphatic malformations.	Oral route: 2–4 mg/kg/day divided three times daily, titrated to achieve concentrations 5–15 ng/ml.	Systemic hypotension; one case report of bleeding after circumcision in a neonate receiving chronic therapy; transient impairment of colour discrimination in adults; concern that it could increase the risk of severe retinopathy of prematurity in extremely premature infants; retinal vascularization must be established before sildenafil is used in extremely preterm infants.
Sirolimus (LoE C)	Inhibitor of mammalian target of rapamycin (mTOR) used to treat diffuse lymphangiomatosis and a variety of lymphatic and vascular anomalies.	0.8–1.6 mg/m^2/day divided twice daily	Bone marrow, gastrointestinal and metabolic toxicity; risk of infections

Abbreviations: GnRH, gonadotropin hormone-releasing hormone; IV, intravenous; LH, luteinizing hormone; LoE, level of evidence.

Absolute counts of circulating B-cells and T-cells are both decreased, but there appears to be a selective loss of T cells, particularly CD4+ T cells, and retention of NK cells, resulting in a normal NK cell count.[73,74] Orange et al. studied the proportions of naive and memory T-cell subpopulations in a small sample of patients with chylothorax and found a selective loss of naive T-cells in chyle. However, despite the low number of peripheral circulating lymphocytes, most case series do not find a significant increase in infections characteristic of T-cell deficiency.[17,74,75] This might be related to the fact that peripheral lymphopenia does not accurately reflect total body lymphocytes, and to the altered profile of relative lymphocyte count due to selective loss or retention of certain subpopulations. Therefore, in patients with chylothorax, the absolute number of peripheral circulating lymphocytes may not be an indicator of immunologic competence.[74,75]

Low serum immunoglobulin levels have been documented in patients with chylothorax (decreased levels of immunoglobulin G (IgG), and in some cases, even of IgM and IgA), and hypogammaglobulinemia correlates with a higher volume of lymphatic drainage.[74–76] Treatment of secondary immunodeficiency with intravenous immunoglobulin (IVIg) is a common practice in these children.[75–77] However, robust evidence for its effectiveness is lacking. In a small retrospective cohort study on the role of IVIg, Hoskote et al. reported that the administration of IVIg did not influence the risk of bloodstream infection (BSI) or hospital survival.[75] These results are supported by other small case series.[74] In addition, Orange et al.[74] demonstrated in a small sample of children with chylothorax that hypogammaglobulinemia-specific antibodies induced by previous immunisation remained within the protective range. However, children with chylothorax have an increased risk of BSI, and although current evidence does not support routine administration of IVIg in infants with infection, studies evaluating infants with chylothorax are lacking.[17,75,78] It is advised that lymphocyte count and serum immunoglobulins in patients with prolonged and/or high-volume drainage be monitored and that the administration of IVIg (RG IIa) be considered.

Patients with chylothorax may also present with coagulation disorders.[6,77,79] The loss of large amounts of coagulation proteins including fibrinogen and prothrombin increases the risk of haemorrhagic complications.[79] The loss of a coagulation inhibitor, namely antithrombin (AT), has also been described, potentially predisposing these children to an increased risk of thrombosis.[79] Although some authors have described the use of FFP for the replacement of chylous losses,[73] there are no specific indications for FFP administration in children with chylothorax; therefore, standard indications should be applied. Bernet-Buettiker et al.,[79] based on their findings of reduced AT activity, recommended that repeated antithrombin substitution be considered to prevent thrombotic complications and to optimise heparin therapy in children requiring anticoagulation. Thus, it is advised that coagulation and antithrombin in patients with prolonged and/or high-volume drainage be monitored and that antithrombin substitution be considered to prevent thrombotic complications and to optimise heparin therapy in children requiring anticoagulation (RG IIa).

Continuous drainage of a large amount of lymphatic fluid leads to bicarbonate loss, with consequent reduction in plasma bicarbonate and metabolic acidosis.[80–82] Replacement of fluid losses with solutions containing bicarbonate may be necessary.[80] Blood gas acid–base metabolism should be monitored in patients with prolonged and/or high-volume drainage, and solutions containing bicarbonate should be administered in case of metabolic acidosis (RG IIa).

2.5 | Invasive treatments

When medical approaches fail to resolve chylothorax, surgical approaches present themselves as the next step in the therapeutic algorithm. There is a lack of consensus on the exact timing for declaring failure of medical treatment and proceeding to invasive procedures. A majority of clinicians recommend a period of three to 4 weeks of conservative management before escalating treatment (RG IIa). Persistent drainage of large volumes (>100 ml per day) for a period of five consecutive days, or severe metabolic and nutritional complications that are difficult to control, may lead to an earlier choice of surgical treatment (RG I).[28,83,84] Successful surgery can shorten hospitalisation and reduce the risk of malnutrition and immunosuppression.[23,85] Conservative measures should be gradually reduced after successful surgical treatment. In cases of CC, an MCT-diet along with a 20% lipid solution and fat-soluble vitamins should be maintained for 6 weeks after effusion resolution.[28]

Thoracic duct ligation is one of the most widely used surgical treatments and can be up to 95% effective.[5,85–87] The main difficulty in this procedure involves identifying the leakage site to be clamped, which can be facilitated by lymphangiography and enhanced by the perioperative enteral administration of cream or olive oil.[84,85] Even so, if the duct cannot be identified, mass ligation of the site where the thoracic duct is supposed to enter the thorax is indicated.[85] The surgical approach in neonates is mainly thoracotomy, but a thoracoscopic approach has also been described.[88]

Pleurodesis aims to obliterate the pleural space by instilling an irritating chemical or biological agent that induces inflammation.[23,89,90] Some of the agents used in neonates are talc, povidone-iodine, tetracycline derivatives, fibrin glue, hypertonic glucose, and *Streptococcus pyogenes* A3 (OK-432).[89–92] Povidone-iodine pleurodesis is safe, effective, and minimally invasive, with a high success rate and few complications. Side effects include allergic reactions, cardiopulmonary failure, thyrotoxicosis, and nephrotoxicity.[90–95] Use of fibrin glue has been described in neonatal patients, but is mainly associated with persistent pneumothorax.[96,97] Recent reports have suggested pleurodesis with OK-432 as an alternative therapeutic option, even in foetuses and preterm infants with bilateral pleural effusion.[98–101]

Mechanical pleurodesis, without instillation of chemical agents, using only mechanical friction of the pleura, via thoracoscopy or thoracotomy, has been shown to be effective and safe in refractory chylothorax.[23]

Thoracic duct embolisation is a minimally invasive percutaneous procedure that constitutes an alternative to thoracic duct ligation.[102,103] Classically, the procedure involved bilateral pedal lymphangiography, but the main technical advance that allowed the application in younger patients, including neonates, was intranodal lymphangiography as a way to opacify the lymphatic system.[104] Contraindications to lymphangiography include the presence of a right-to-left cardiac shunt and severe lung disease.[105,106] Lipiodol® (poppy seed oil) injection, which produces an inflammatory process and occludes the chyle leak,[107] was successfully used in a former 35-week male infant at 2 months old with a refractory chylothorax.[108]

Pleuroperitoneal shunts have been described since 1983 in neonates and small infants up to 3 months of age, with weights between 800 and 3300 g.[109–112] The procedure appears to be effective, safe, easy to perform, and well-tolerated by the patient. However, the need to maintain the shunt can last for several weeks to months, with an increased right atrial pressure >25 mmHg being considered a contraindication.[102] Meanwhile, this method quickly and effectively restores pulmonary, nutritional, metabolic, and immunological stability.[109,111,113]

Diaphragmatic fenestration can be an effective and safe therapeutic strategy consisting of excising a circular, central portion of the diaphragm, and suturing a fenestrated prosthesis into this surgically created defect.[23,87]

SVC thrombectomy or bypass is indicated in a subgroup of patients with chylothorax associated with thrombosis of this blood vessel. Increased thoracic duct pressure secondary to high pressure in the SVC has been proposed as a mechanism underlying chylothorax.[114–120] Furthermore, patients with chylothorax have an increased risk of thrombosis.[79,121] A large retrospective cohort study of paediatric patients with chylothorax after cardiac surgery demonstrated that 52% had confirmed venous thrombosis. A longer central venous catheter indwell time was associated with chylothorax and thrombosis.[122] Further prospective studies are necessary to clarify the association between chylothorax and thrombosis and to establish causality. Still, according to current evidence, prospective screening for upper venous system thrombosis using Doppler ultrasound and/or angio-CT should be considered in patients with non-CC, especially in postoperative chylothorax.[118,119,121,121,122]

In cases of SVC occlusion, some authors have described the construction of a Gore-Tex shunt between the upper venous system and the right atrium. This notable procedure has rarely been reported and is associated with high mortality.[87,123,124]

Lymphovenous anastomosis is a novel microsurgical technique that consists of anastomosis between the thoracic duct and the venous system. Access can be transabdominal or percutaneous and has been used successfully in young infants without the need for more invasive techniques.[23,125]

2.6 | Summary

The treatment strategy for neonatal chylothorax generally involves supportive management, and includes drainage as well as procedures to reduce chyle flow. A stepwise approach beginning with the least invasive method is recommended. Progression in the invasiveness of the treatment option is determined by the response to previous treatments. We have proposed a stepwise approach algorithm. Evidence-based treatment choices are critical.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Gustavo Rocha: conceptualization (lead); data curation (lead); formal analysis (lead); investigation (equal); methodology (lead); project administration (lead); writing original draft (equal); writing review & editing (lead). **Vanessa Arnet**: conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); writing original draft (equal). **Paulo Soares**: data curation (equal); formal analysis (equal); investigation (equal); writing original draft (equal). **Ana Cristina Gomes**: conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing original draft (equal). **Sandra Costa**: conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing original draft (equal); writing review & editing (equal). **Paula Guerra**: formal analysis (equal); writing original draft (equal). **Jorge Casanova**: writing review & editing (equal). **Inês Azevedo**: validation (lead); writing review & editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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