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CONGENITAL CHYLOTHORAX OF THE NEWBORN: DIAGNOSIS AND TREATMENT IN THREE PICTURES

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ABSTRACT

There is general agreement regarding the evident need for an international, multicenter trial including long-term follow-up to establish the correct criteria for diagnosing and managing congenital chylothorax. In an attempt to identify these criteria, which could then be used to draft a prospective multicenter trial, we propose three flow-charts showing three algorithms that could be used to: 1) obtain a definitive diagnosis of pleural chylous effusion; 2) specifically focus on chyle leakage evolution and etiology of chylothorax; and 3) focus on the management of congenital chylothorax. The aim of the algorithms we propose is to build the basis on which a strongly needed multicenter trial might be structured.

Keywords: congenital chylothorax, newborn, algorithm, diagnosis, therapy

The thoracic duct originates from the cisterna chyli at the level of the first and second lumbar vertebrae, lateral to the aorta. The thoracic duct can have a variable course generally running between the aorta and azygos vein, crossing the body to the left side at the level of the fifth-sixth thoracic vertebrae, and ending at the level of the junction of the left subclavian and internal jugular veins (1).

Chylothorax is an accumulation of chyle in the pleural space that occurs in patients during enteral feeding. In general, chylothorax may be caused by intrinsic abnormalities of the lymphatic system, or damage or disruption of the thoracic duct via trauma, surgery, malignancy, or by cardiovascular disease. In the neonate, the focus of this article, chylothorax is recognized as the most common cause of pleural effusion. It may be linked to congenital duct defects, either isolated or associated with generalized lymphatic vessel dysplasia, or more rarely, the result of direct trauma at birth (2).

Accumulation of fluid in the visceral compartment during the neonatal period is rare and data on pathogenesis and treatment modalities are limited and contradictory. Leakage may manifest as a chylothorax (thoracic cavity), chylous ascites (peritoneal cavity), chylopericardium (pericardiac cavity), or in various combinations (2,3). During the intrauterine period, occurrence of these conditions singly or in combination may lead to hydrops formation (4). The reported incidence of congenital chylothorax ranges from 1:8,600 to 1:10,000 live births (2). There is general agreement concerning the need for an international multicenter trial including long-term follow-up to establish the best criteria for diagnosing and managing congenital chylothorax (2,3). To date, no

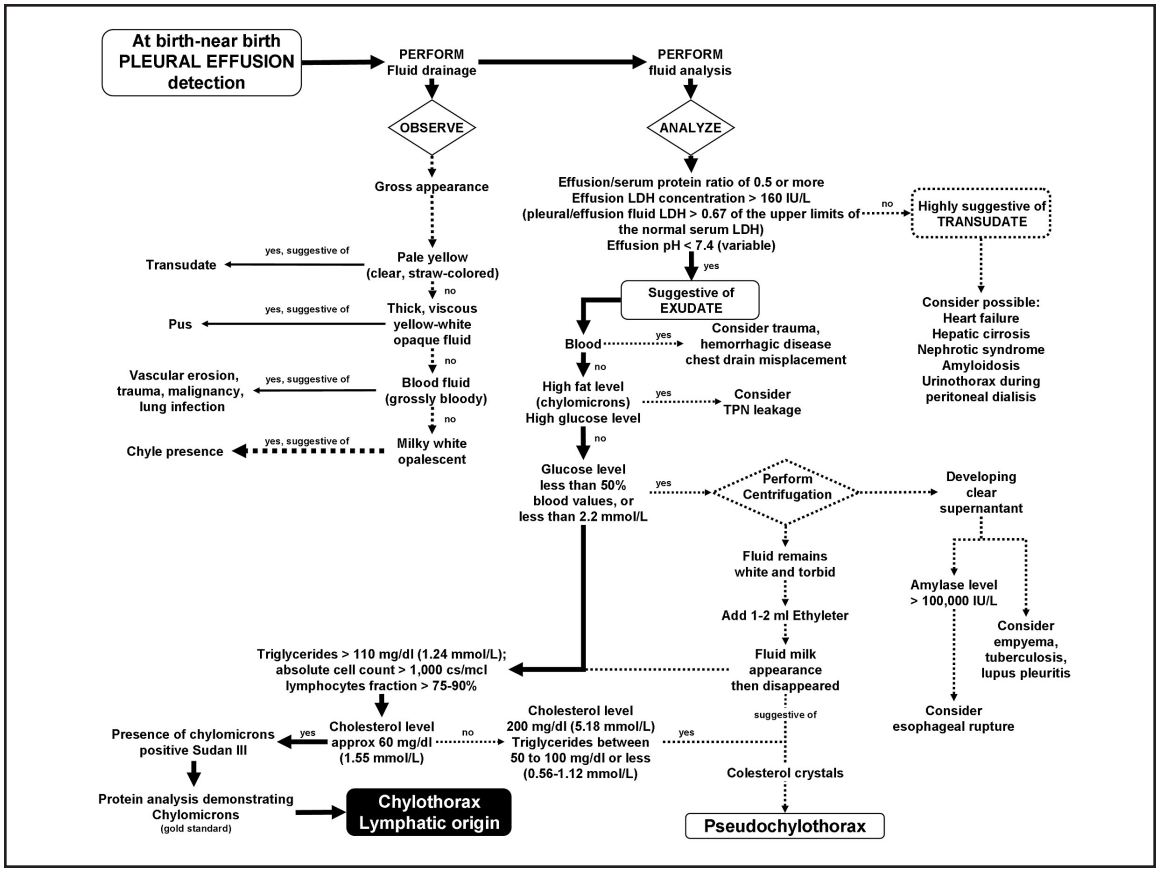

Fig. 1. Diagnosis.

standardized approach has been evaluated prospectively and there is no evidence that any specific approach results in improved outcomes (2,3). The observational design and small sample size of various published studies prevent any firm conclusions from being made (2,4).

We recently published our experience in diagnosing and managing congenital chylothorax of the newborn (2) and the management of chylothorax was recently reviewed (1). We have also reviewed the physiological and pathophysiological dynamics of pleural effusion of chylothorax in the newborn, with particular emphasis on the role of the lymphatic system (4), pointing to the presence of increased transpleural filtration pressure, impaired lymphatic drainage, and increased permeability as the mechanisms possibly leading to chylothorax formation. While suggestions regarding the diagnostic and therapeutic possibilities are available, agreement on diagnosis and in particular on treatment is currently under debate. Thus, pinpointing the exact diagnoses and choosing the most appropriate therapy is currently challenging (2,5).

In an attempt to establish the diagnostic and management criteria for congenital chylothorax on which future prospective multicenter trials could be drafted, we have developed three flow-charts (*three pictures*) we believe could be useful for diagnosing and managing congenital chylothorax of the newborn, with special attention to congenital chylothorax of lymphatic origin linked to

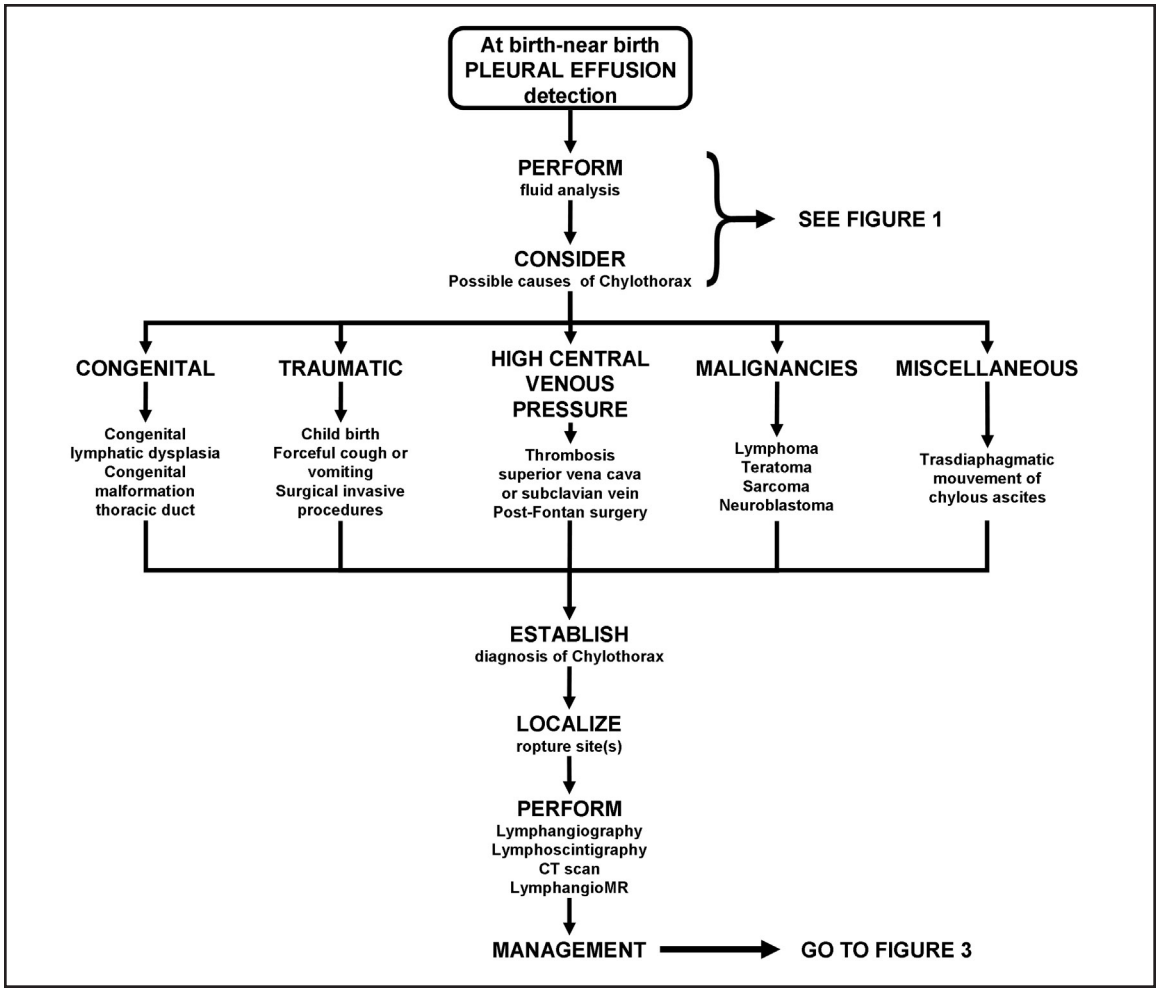

Fig. 2. Etiology.

congenital lymphatic dysplasia. The article is structured in a simple manner, using the three different flow-charts (*Figs. 1-3*) and providing a specific comment for each one. In summary, *Fig. 1* shows the algorithm that should be used to obtain a definitive diagnosis of pleural chylous effusion, with attention to rarely reported analyses; *Fig. 2* shows a simplified etiology of chylothorax, keeping in mind that two major mechanisms are usually involved i.e., disrupted development of the native lymphatic system or a functional obstruction to chylous flow; and *Fig. 3* shows the recommended management considering both responders and non-responders. As reported above, the aim and the hope of the algorithms we propose is to be of service towards building the basis on which the highly essential multicenter trial might be conceived.

Performing thoracentesis is mandatory for chylothorax and in general, for the presence of pleural effusion during the neonatal period in order to obtain fluid for analysis. Simple observation of the gross appearance of the fluid is very important; a milky white appearance of non-clotting fluid is highly indicative of chyle – however, this is true only if the patient is being enterally fed (5). The presence of transudate, pus, or blood is a rare event during the neonatal

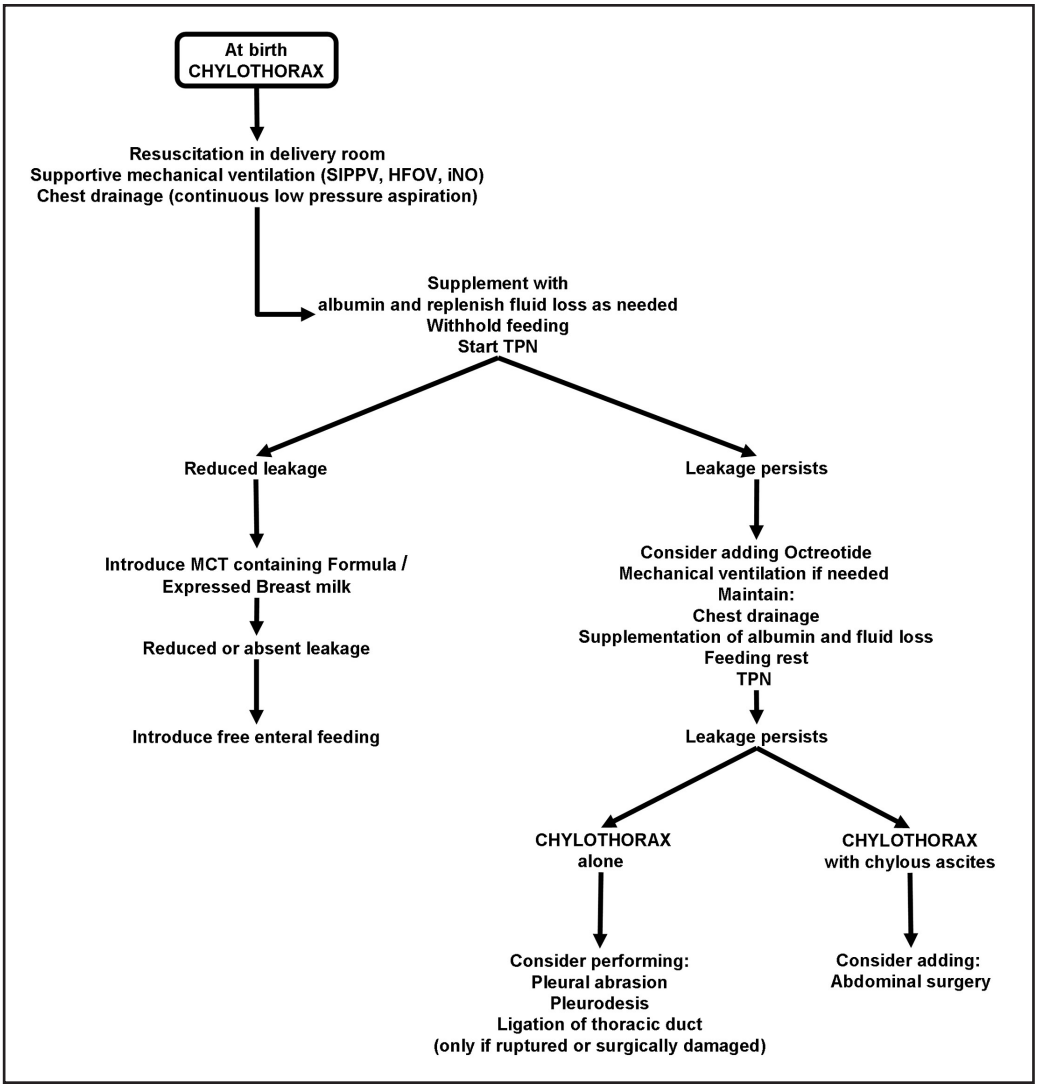

Fig. 3. Treatment.

period, but it should be considered in differential diagnosis. Analysis of milky fluid is a key step towards diagnosing chylothorax. In *Fig. 1*, the path to reach a diagnosis of congenital chylothorax of lymphatic origin is clearly indicated by bold continuous arrows. If a preliminary analysis of pleural effusion fluid demonstrates the presence of an effusion/serum protein ratio of 0.5 or more, effusion LDH concentration >160 IU/L (pleural/effusion fluid LDH >0.67 of the upper limits of the normal serum LDH), and effusion pH <7.4, then the presence of exudate is highly likely (5). These data are far from being conclusive in proving lymphatic origin. The presence of chylomicrons and triglycerides >110 mg/dl (1.24 mmol/L) and absolute cell count >1,000 cs/mcl with a lymphocyte fraction >75-90% is highly indicative of lymphatic origin. Proof of the presence of chylomicrons is obtained after staining pleural drainage with Sudan III (6). This staining method requires special cytological preparation of the pleural fluid that may not

be easily available. In 1980, Staats et al (5) conducted a study in which they demonstrated that lipoprotein electrophoresis is the gold standard test for distinguishing chylous from non-chylous effusions. Triglyceride concentration in the fluid is a simpler method but it will result positive only if the concentration is above 1.24 mmol/L (concentrations between 0.56 and 1.24 mmol/L are considered equivocal). It has been previously shown that an analysis of pleural effusion fluid showing a triglyceride value less than 50 mg/dL (0.565 mmol/L) has no more than a 5% chance of being chylous, while if the triglyceride levels are between 55 and 110 mg/dl (0.621-1.24 mmol/L), a lipoprotein analysis is indicated to detect the presence of chylomicrons in the pleural fluid (1,5-7). Other characteristics of the pleural fluid from chyle leak are the abundance of T lymphocytes, along with products that are usually transported by lymphatics such as proteins (immunoglobulins, clotting factors), vitamins, electrolytes, and other products of digestion (7). Previously an attempt at guidelines for diagnosis and management has been reported in a small population (39 children) (8), showing that in 36 (92%), total cell count was >1,000 cell/µL and >90% of these were lymphocytes; however, this was before more sophisticated imaging has become available, and our aim is more closely focused on newborns.

The etiology of chylothorax can be simplified into one of two major mechanisms: disrupted development of the native lymphatic system, or a functional obstruction to chylous flow. Lymphangiomatosis and lymphangiectasia are examples of a possible disrupted or abnormal development of the lymphatic system, where functional obstructions may arise from complications of thoracic surgical procedures, pleural and mediastinal malignancies or from a pathological increase in systemic venous pressure related to congenital heart disease (1,4,9). How or when certain disruptions or failure of interruptions occur in the development of the lymphatic system is unclear. Lymphatic congenital anomalies include a variety of developmental and/or functional defects affecting the lymphatic vessels: sporadic and familial forms of primary lymphedema, secondary lymphedema, chylothorax and chylous ascites, lymphatic malformations, and overgrowth syndromes with a lymphatic component, and chromosomal anomalies and trisomies. In the case of lymphangiomatosis, sequestration of lymphatic tissue due to insufficient lymph drainage is believed to be the involved mechanism. In lymphangiectasia, there is an over-abundance of subpleural and interlobular lymphatic vessels and an associated inability of the body to adequately drain lymph effectively (1,10). Complex surgery is often hampered by mechanical injury to the lymphatics, in particular during correction of congenital heart malformations in the neonatal period. Chylothorax is a relatively common complication of corrective surgery for tetralogy of Fallot, which involves total anomalous pulmonary venous return and transposition of the great vessels. Any post-surgical disruption along any portion of the thoracic duct or its smaller tributaries may contribute to the formation of a chylothorax. Lastly, malignancies such as neuroblastoma and lymphomas may also contribute to the development of chylothorax in the newborn, acting as a mass at the level of the mediastinum or by the direct invasion into lymphatic vessels. Any increase in systemic venous pressure will result in higher lymphatic pressure thus leading to fluid leakage (1,4,9). Imaging studies are useful for establishing the diagnosis. Chest radiography is an old exam that is still useful for demonstrating a pleural effusion. Computed tomography helps identify both location and causes of the chylous leak at the retroperitoneal or mediastinal level, and thus lymphan-gioleiomyomatosis, thoracic lymphangiectasia, lymphangiomatosis or giant lymph node hyperplasia (1,11). Lymphangiography, which is not easy to carry out in the neonatal age, and lymphoscintigraphy are important tools in the

diagnostic work-up (1,11-14). The sensitivity and specificity of magnetic resonance (MR) lymphangiography vs lymphoscintigraphy to establish abnormal lymph vessels and an abnormal pattern of lymphatic drainage was recently evaluated (15). It was found that both techniques show clear concordance and good performance in evaluating the pattern and delay of lymphatic drainage.

The management of congenital chylothorax has focused on the treatment of respiratory compromise, nutritional support, and closure of the chylous leak. Appropriate cardiopulmonary support may include endotracheal intubation and mechanical ventilation in infants who present with severe respiratory failure. Both conventional and high-frequency ventilatory modes have been used successfully (1,2). In addition to confirming diagnosis, initial thoracentesis is useful for draining chyle from the involved hemithorax, thus allowing for better lung expansion and ventilation. A thoracostomy tube is placed for continuous drainage if the chyle reaccumulates and may require intermittent or continuous aspirations to keep the pleural space empty (1,2,9). Debate is still ongoing regarding the optimal duration of conservative management, taking into account that the longer the duration, the greater the risk of severe immunological and nutritional disorders. Nutritional support directly influences the amount of chyle formation. The diet may be managed with the use of enteric rest with parenteral nutrition, or enteral nutrition with medium-chain trigylceride (MCT) feedings or dedicated formulas (1,2). Medium chain triglycerides are directly absorbed into the portal system, bypassing the intestinal lymph system, and thus reducing chyle production. If the amount of chyle production remains high even during MCT administration, total parenteral nutrition is mandatory (2,3,6). No differences in lymph production have been observed during breast or formula feedings. Protein replacement, adequate caloric intake, and electrolyte supplementation are all part of standard conservative management. The neonate with chylothorax is at risk for coagulopathy and immunodeficiency due to the possible lack of prothrombin, fibrinogen, immunoglobulins, and lymphocytes in the chylous pleural effusion. Continuous monitoring of serum electrolytes, lymphocyte count, albumin, immunoglobulins, and clotting factors is an important part of the management procedure (1-3,6). Surgical intervention is an option if conservative management fails. On the basis of the available literature (3,6,8), indications for surgical intervention include an unresponsive daily loss of chyle exceeding 100 ml/day for a 5-day period, or chyle production failing to diminish after a 14-day period, or nutritional complications linked to parenteral nutrition. It must be taken into account that there is no general agreement regarding which parameters define failure of conservative management; we are usually very cautious considering that spontaneous resorption of chyle pleural leakage during the first months of life is possible (2,4). Surgical procedures for refractory chylothorax include thoracotomy and thoracic duct ligation, apical pleurectomy, pleural abrasion, chemical pleurodesis, or pleural-to-peritoneal shunts.

Octreotide treatment might be considered conservative and clinically effective medical therapy. The mechanism of action of Octreotide is believed to involve a reduction of the intestinal absorption of fats, thus it decreases gut motility (1,2). It is described in the treatment of a variety of conditions, including acromegaly, secretory diarrhea, esophageal varices, breast cancer, cryptosporidiosis, Cushing's syndrome, insulinomas, small bowel fistulas, post-gastrectomy dumping syndrome, chemotherapy-induced diarrhea, Zollinger-Ellison syndrome, and severe neonatal hypoglycaemia. Despite the availability of several articles in the literature describing the use of Octreotide in chylothorax of the newborn, to date no definitive data are available on its efficacy and safety, and prospective trials are lacking (1-3).

CONCLUSION

Congenital chylothorax of the newborn represents a diagnostic and management challenge. Agreement on the biological parameters that need to be obtained by pleural fluid analysis and leading to a diagnosis of chylothorax is generally achieved, as shown in *Fig. 1*. Recent available instrumental techniques, such as lymphangiography, lymphoscintigraphy, CT scan, and lymphangioMR, together with available prenatal studies (16,17) allow us to obtain an ever increasing number of definitive diagnoses, as shown in *Fig. 2*. The weakest area remains treatment; although some landmarks are now generally accepted, such as the value of MCT use, a great deal of work still needs to be done to reach definitive guidelines for the use of Octreotide or for surgical indications. As we in 2012 (2) and Bialkowski et al in 2015 (3) concluded, prospective trials for congenital chylothorax of the newborn are needed, but not yet available. *Fig. 3* displays indications that reach a high degree of confidence by literature evaluation, but these still must be considered as guidelines lacking definitive scientific strength.

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