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CONGENITAL CHYLOTHORAX: CURRENT EVIDENCE-BASED PRENATAL AND POST-NATAL DIAGNOSIS AND MANAGEMENT

L.C. De Angelis, T. Bellini, M.H. Witte, R.I. Kylat, M. Bernas, F. Boccardo, D. Paladini, G.M. Magnano, L.A. Ramenghi, C. Bellini

Department Mother & Child, Neonatal Intensive Care Unit (LCDA,TB,LAR,CB) and Fetal Medicine & Surgery Unit (GMM), IRCCS Istituto Gaslini, Genova, Italy; Departments of Surgery (MHW) and Pediatrics (RIK), University of Arizona College of Medicine, Tucson, Arizona, USA; Department of Medical Education (MB), TCU and UNTHSC School of Medicine, Fort Worth, Texas, USA; Department of Surgery (FB), University of Genova, Italy; Radiology Department (DP), IRCCS, Istituto Giannina Gaslini, Genova, Italy

ABSTRACT

Congenital chylothorax is an uncommon condition but represents the main cause of congenital pleural effusion during the neonatal period. It usually appears before birth, both as an isolated disorder or in association with hydrops fetalis, negatively affecting the subsequent neonatal outcome. Prenatal treatment is usually considered to ensure a satisfactory lung development in case of moderate to severe pleural effusion or in the presence of hydrops, although consensus on treatment timing and modalities has not been reached to date. Both medical and surgical therapeutic strategies are available to treat this condition and novel treatment options have been recently attempted with acceptable results in both prenatal and post-natal setting. The heterogeneous clinical presentation of congenital chylothorax together with its rarity, its numerous etiologies and the absence of a highly effective treatment renders the diagnostic and therapeutic approach difficult to standardize. In addition, adequate visualization of the lymphatic system is complex, especially in small neonates, although new promising techniques have been developed lately and may contribute to improved management of this serious but infrequent condition. This review focuses on the current evidence base for the diagnosis and treatment options for congenital chylothorax, suggesting a rational diagnostic and therapeutic approach both in the prenatal and in the neonatal period.

Keywords: congenital chylothorax, hydrops, fetal hydrothorax, lymphatic system, diagnosis, evidence-based management

CONGENITAL CHYLOTHORAX

Congenital chylothorax consists of a lymphatic fluid accumulation within the pleural space, which can occur prenatally or during the neonatal period (1). Lymph originates in the interstitial spaces within organs and is composed of cells, particles, lipids, proteins and peptides (2). Flowing into progressively larger lymphatic vessels and passing through one or more regional lymph nodes (3), lymphatic fluid reaches the cisterna chyli located between the aorta and the vena cava. Then it enters the thoracic duct located in the posterior right mediastinum between the aorta and the azygos vein, crosses the aortic arch and eventually reaches the blood circulation between the jugular and the left subclavian veins.

Any pathologic process that causes damage or obstruction to the lymphatic system may lead to a leakage of lymph, which can variably fill the pleural space or the peritoneal cavity causing chylous ascites. Whereas congenital chylothorax is a rare condition, it represents the most common cause of congenital pleural effusion during the neonatal period (4). The reported incidence of congenital chylothorax is about 0.4 - 1.7:10,000 live births with a male:female ratio of 2:1 (5,6). It is often bilateral, but the right side is more frequently involved due to the usual localization of the thoracic duct largely in the right mediastinum. Congenital chylothorax is caused either by anomalies in lymphatic development or other conditions that affect the structure and/or function of the lymphatic system, leading to chylous fluid leakage (7-9). Though in some cases a specific cause is not found, congenital chylothorax has been associated with genetic syndromes in which a degree of lymphatic dysplasia is present and with congenital anomalies involving the thoracic region (10-14). Main conditions associated with congenital chylothorax are shown in *Table 1*.

TABLE 1
Conditions Associated with Anatomical or Functional Anomalies of the Lymphatic Drainage System, Which can Result in Congenital Chylothorax

Conditions associated with congenital chylothorax
Anomalies of the lymphatic system
Mediastinal lymphangioma
Congenital pulmonary lymphangiectasia
Lymphatic dysplasia syndrome
Congenital atresia of the lymphatic duct
Intestinal lymphangiectasia
Thoracic anomalies
Congenital pulmonary malformations
Congenital diaphragmatic hernia
H-type tracheoesophageal fistula
Mediastinal tumors or cysts
Congenital heart defects
Superior vena cava obstruction
Bilateral agenesis of superior vena cava
Genetic syndromes
Noonan's syndrome
Trisomy 21
Turner syndrome
Ehlers Danlos disease
X-linked myotubular myopathy
Hennekam syndrome
Missense mutation in integrin $\alpha 9\beta 1$
Gorham-Stout syndrome
Yellow nail syndrome

CLINICAL FEATURES AND PROGNOSTIC FACTORS OF CONGENITAL CHYLOTHORAX

Most cases of congenital chylothorax are diagnosed during pregnancy, more frequently during the third trimester (15). As the fetus is not fed in utero and the mean percentage of blood lymphocytes is normally >80%, congenital chylothorax is rather called "hydrothorax" prenatally (16).

When occurring early during fetal development it may have detrimental consequences on lung growth, leading both to pulmonary hypoplasia and to pulmonary hypertension. In addition, the mass effect caused by the pleural effusion may compromise venous return, causing cardiac failure (17,18).

In case of massive lymph effusion hydrops fetalis may develop (4), and this condition is associated with fetal demise in a large proportion of cases especially if diagnosed during early pregnancy (19). The natural history of congenital hydrothorax is extremely variable. Spontaneous regression has been reported in 22% of cases, with a nearly 100% survival rate (20), while severe conditions, mostly when associated with hydrops, may lead to high morbility and mortality (21). Poor prognosis is related to bilateral pleural effusion, hydrops, polyhydramnios, progressive fluid accumulation with mediastinal shift and early gestational age at diagnosis (less than 30 weeks of gestational age) (22-25). Prenatal treatment has been shown to improve neonatal survival

significantly in fetuses with hydrops or progressive effusion (26), yet perinatal mortality remains high, varying between 22% and 53% (27).

Neonates with congenital chylothorax often show respiratory distress at birth due to lung hypoplasia and/or due to premature birth associated with prenatal intervention (28). Poor cardiovascular function and generalized edema may be present in more severe cases, and percutaneous evacuation of chyle is associated with fluid, protein including immunoglobulin and T lymphocyte depletion, which increases the risk of neonatal infections (29,30).

PRENATAL DIAGNOSIS OF CONGENITAL CHYLOTHORAX

Diagnosis of fetal hydrothorax is made when a monolateral or bilateral pleural effusion is detected by ultrasound *(Fig. 1)*.

In the case of two or more fluid collections, including ascites, pleural or pericardial effusion, and generalized subcutaneous edema, a diagnosis of hydrops should be made (31). Fetal primary hydrothorax is caused by an anomalous development of the lymphatic system, while secondary forms are associated with a number of conditions characterized by an imbalance in the regulation of fluid movements between the blood vascular space and the interstitium (32) *(Fig. 2)*.

Once a pleural effusion is detected, a comprehensive prenatal evaluation is necessary to determine the etiology, predict the prognosis and establish a treatment strategy. A diagnostic work-up of fetal hydrothorax is presented in *Table 2* (33).

MANAGEMENT OF PRENATAL CONGENITAL CHYLOTHORAX

Once other causes of secondary pleural fluid effusion are excluded, treatment of fetal primary hydrothorax should be considered in utero in order to decompress the pleural space and reduce the intrathoracic pressure, restoring normal lung development and fetal hemodynamics (34). Fetal intervention has been associated with a higher survival of preterm infants with congenital chylothorax (35), and it increased Apgar scores, reduced ventilator days, and decreased complications in neonates with hydrops fetalis (36). Lack of consensus exists on what is the preferable therapeutic strategy in these patients as no randomized studies have been conducted to date due to the rarity of this condition and the marked heterogeneity of the disease. Gestational age, severity, and progression of pleural effusion and concomitant presence of secondary fetal consequences (e.g. hydrops, pulmonary hypoplasia, mediastinal shift) are usually considered to decide on the best treatment option (37). Conservative management and close follow-up with serial ultrasounds should be considered in case of small to moderate unilateral effusion without hydrops, as spontaneous resolution may occur (26). Conversely, in case of large or progressive pleural effusion or hydrops, prenatal interventions include thoracocentesis (either single or repeated) (17), pleuroamniotic

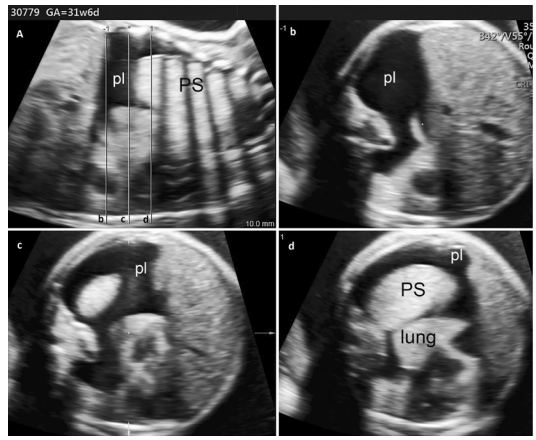

Fig. 1. Pulmonary sequestration complicated by severe hydrothorax in a 31+6 weeks fetus. A: sagittal section showing right hydrothorax (pl) associated with a large pulmonary extra-lobar sequestration (PS). Downward displacement of the diaphragm caused by the effusion is noted. Plane section levels b, c and d are shown; b, c: evidence of pl in transversal sections; d: upper transverse section showing PS, severe hydrothorax, and compressed right lung.

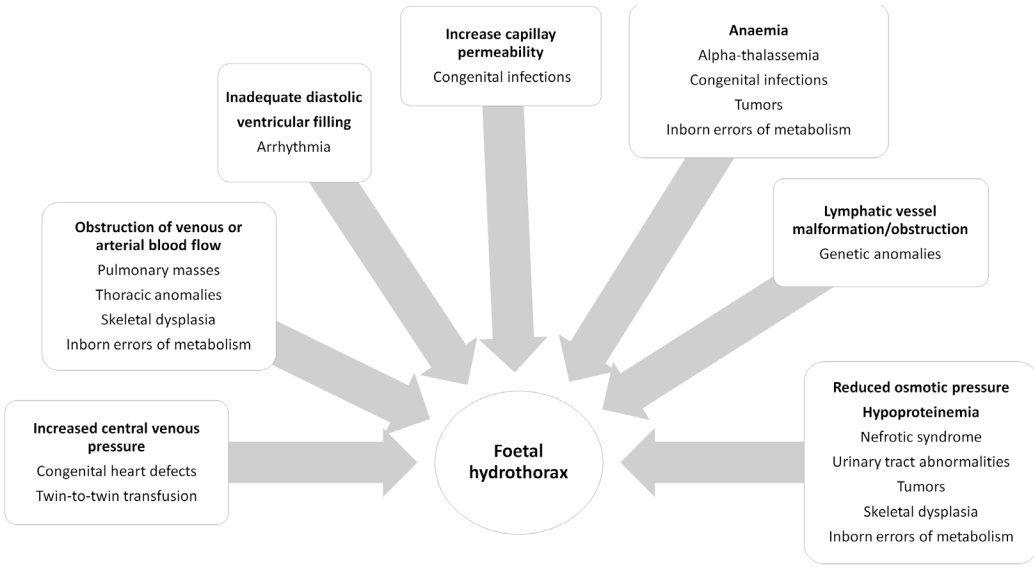

Fig. 2. Pathological conditions associated with the development of fetal hydrothorax.

shunting (38,39) and intrauterine pleurodesis with OK-432 (40). In addition, in case of polyhydramnios, multiple amniodrainage may be considered (41). Thoracocentesis is often performed as initial treatment but in most cases a rapid fluid re-accumulation is observed and repeated thoracocentesis or pleuroamniotic shunt becomes necessary. Decompression of thoracic structures following thoracocentesis has both therapeutic and diagnostic value: it may reveal pulmonary hypoplasia in case of failed lung expansion and may improve heart defect detection once the mediastinum returns to a correct position (42). As the rate of success with a single thoracentesis is relatively low, pleuroamniotic shunt, consisting of a permanent communication between the pleural space and the amniotic cavity, has been proposed as first-line treatment in primary severe fetal hydrothorax (43-45) *(Fig. 3)*.

Although no randomized trials comparing different interventions for fetal pleural effusion have been performed, data from retrospective analysis of large case series suggest pleuroamniotic shunting as a more effective treatment compared to repeated thoracocentesis for hydropic fetuses. Despite the good level of tolerance by both mother and fetus, shunt placement is burdened by several complications: immediate fetal demise following shunt placement has been reported up to 11% (39). Shunt dislocation varies from 20% to 65% among studies and is sometimes associated with a lateral or antero-lateral shunt insertion *(Fig. 4)*. Preterm delivery and premature rupture of membranes remains a common complication of prenatal intervention with a survival rate of 66% in premature birth and 100% in full-term delivery (16,46,47).

Chest wall deformity has been described as a complication of thoracoamniotic shunt placement, especially if performed before 20 weeks of gestation (48). Interval between thoracoamniotic shunting and birth appears to be crucial; the longer the interval, the more likely is the reversal of antenatal hydrops and subsequent neonatal survival (28).

Recently, intrauterine pleurodesis with OK-432, a sclerosant commonly used in adults and children with lymphangioma, has been shown to be effective in fetuses with early hydrothorax (< 21 weeks gestation), and it may

TABLE 2
Diagnostic Procedures Suggested in Fetal Hydrothorax

Examinations	Comments	References
Detailed maternal history	- Ethnicity and risk of specific genetic disorders (e.g. hemoglobinopaties) - Underlying pathologies (e.g. collagen-vascular diseases, organ transplant, disthyroidisms, blunt abdominal trauma, viral infections, jaundice in other family members) - Medications and exposure to teratogenic substances - Previous pregnancies (e.g. genetic or chromosomal abnormalities, inborn errors of metabolism, congenital malformations, jaundice, congenital heart defects, fetal demise, polyhydramnios).	(103) (104)
Maternal blood testing	- Blood cell count - blood group and Rh (plus the partner's one if available) - Hb electrophoresis, erythrocyte enzymes (G6PD, pyruvate kinase, and glucose phosphate isomerase) - Kleihauer-Betke test - serum alpha-fetoprotein - anti-SSA/SSB antibodies - toxoplasma gondii, rubella virus, cytomegalovirus, herpes simplex virus, enterovirus, syphilis, varicella-zoster virus, Lyme disease, HIV, parvovirus B19 - Genetic testing for inborn error of metabolism	(105) (106)
Fetal imaging	- Detailed morphologic obstetric ultrasound study in a tertiary center (assessment of the fetal venous and arterial circulations, venous and arterial MCA Doppler) - Fetal echocardiogram - Exclude Twin-to-twin transfusion syndrome - Fetal MRI	(107) (108)
Amniocentesis	- Karyotype - Chromosomal microarray - Inborn errors of metabolism gene mutations - Culture/PCR for infective agents (where indicated, based on maternal serology) - DNA extraction for alpha-thalassemia	(109) (110)
Fetal blood testing (in case of concomitant intrauterine transfusion)	- Karyotype - Fetal complete blood count - Hemoglobin electrophoresis - Congenital infections - Fetal albumin - Inborn errors of metabolism assessment*	(111) (112)

*Hydrops fetalis has been described in lysosomal storage diseases including Gaucher disease type II, Morquio disease, Hurler syndrome, Sly syndrome, Farber disease, GM1 gangliosidosis, I-cell disease, Niemann-Pick disease type A and type C, infantile sialic acid storage disorder, alphaneuroaminidase deficiency, multiple sulfatase deficiency, and Wolman disease. Consider also nonlysosomal diseases, including glycogenosis type IV, long-chain hydroxy-acylCoA dehydrogenase deficiency, CDG type1a, CDG type I/IX, hypothyroidism, Carnitine deficiency, and Smith-Lemli-Opitz syndrome

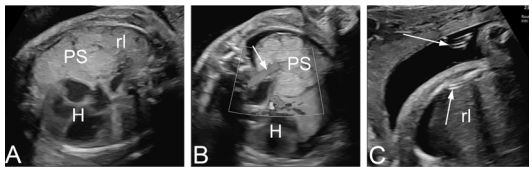

Fig. 3. The same fetus as in Figure 1 with pulmonary sequestration complicated by severe hydrothorax treated with thoraco-amniotic shunt. A: pleural effusion is completely drained into the amniotic fluid. The right lung (rl), the heart (H), and pulmonary sequestration (PS) are visible; B: Color Doppler imaging shows the vascular pedicle with the afferent artery originating from the thoracic aorta (arrow); C: correct position of the thoraco-amniotic shunt with one end visible in the pleural space and the other within amniotic cavity (arrows).

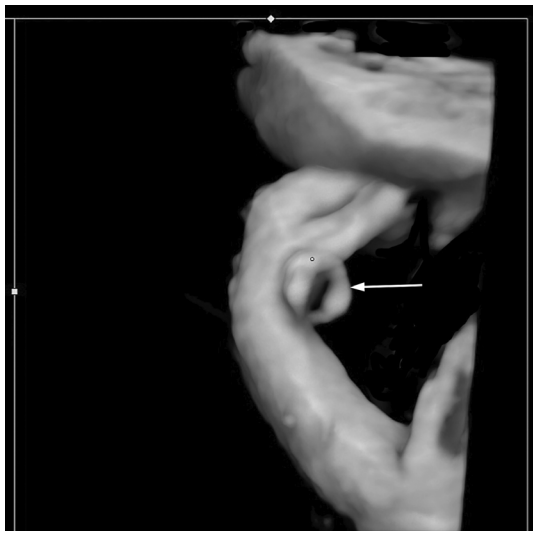

Fig. 4. A three-dimensional reconstruction of a shunt extremity (white arrow) surrounded by a fetal arm in a case of a 30+3 week fetus with hydrothorax treated with a thoraco-amniotic shunt laterally inserted. The shunt appeared to be dislocated and tightened in the fetal hand at the follow-up ultrasound scan evaluation.

reduce the risk of premature membrane rupture associated with prenatal intervention as the needle needed for injection is considerably thinner (49,50). Although promising, further studies are needed to assess efficacy and safety of this procedure.

Maternal dietary treatment with a low-fat, high medium-chain triglyceride diet has been suggested to reduce the amount of pleural fluid accumulation in cases of fetal chylothorax, delaying the need for thoracentesis (51). It may be considered both in conservative management and in combination with surgical treatment (52).

POST-NATAL DIAGNOSIS OF CONGENITAL CHYLOTHORAX

Most cases of congenital chylothorax are detected prenatally, however fluid drainage is mandatory to confirm the chylous nature of pleural effusion. In newborns enterally fed, a milky white opalescent appearance of drained fluid is suggestive of chylous effusion. The presence of an effusion/serum protein ratio of 0.5 or more, effusion LDH >160 IU/L and effusion pH <7.4 is suggestive of exudate, and the lymphatic origin of pleural fluid is confirmed by the presence of chylomicra and triglycerides >110 mg/dl (1.24 mmol/L) and absolute cell count >1,000 per mL with a lymphocyte fraction >80% in exudate cases (53,54).

Once the presence of chylothorax is confirmed after birth, diagnostic work-up should be performed to find the etiology and establish a targeted therapy when available (55). A diagnostic flow-chart is proposed in *Fig. 5*.

A meticulous blood examination panel, customized in accordance with the diagnostic hypotheses, should be performed soon after birth, while imaging studies are necessary to evaluate cardiopulmonary, thoracic and cerebral anatomy and function *(Fig. 6)*.

Karyotype and specific genetic mutation analysis are mandatory in case a syndromic or genetic condition is suspected *(Table 3)*. Lung biopsy with subsequent histological and immunohistochemical studies should be performed to confirm the diagnosis of congenital pulmonary lymphangiectasia (56).

In addition, lymphatic system imaging procedures are often needed to outline abnormal lymphatic drainage patterns and to identify the site of chyle leakage. Many techniques have been proposed to investigate

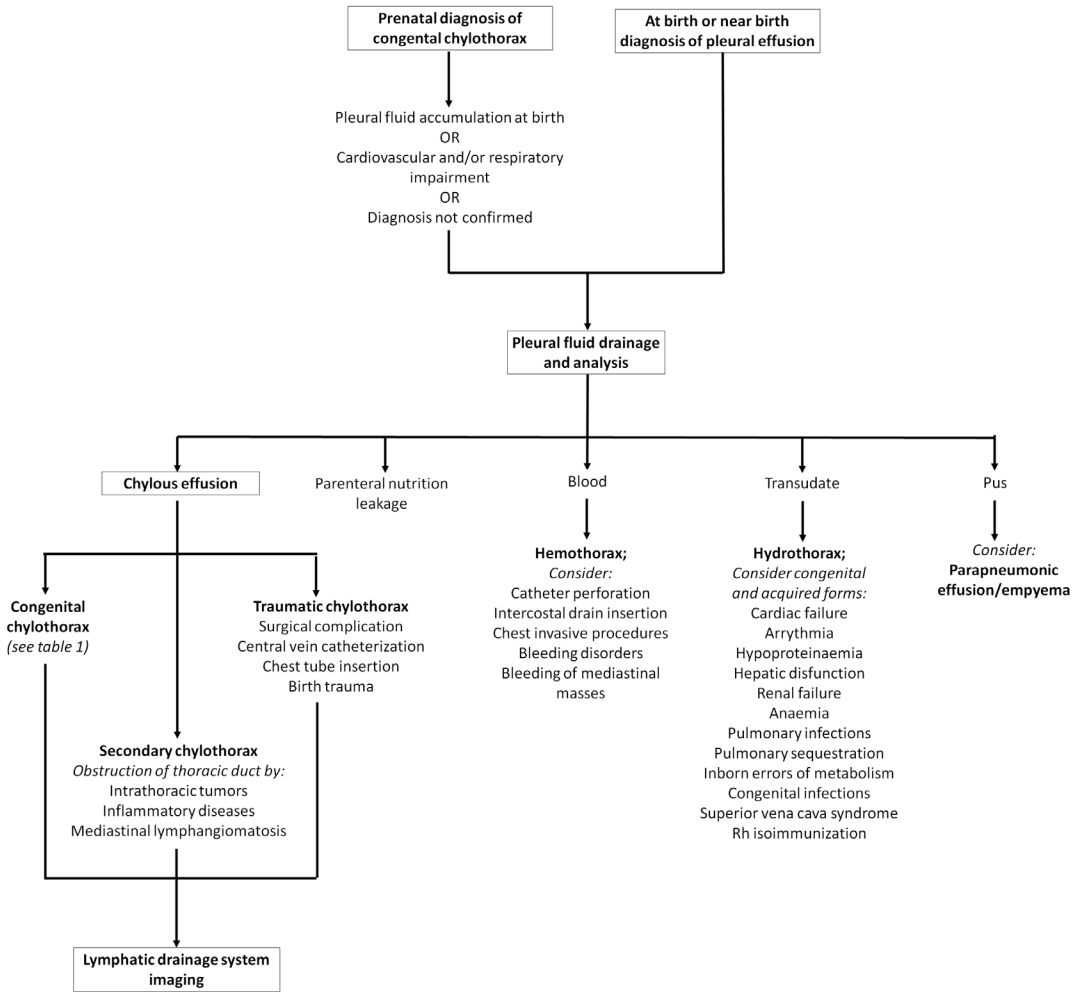

Fig. 5. Diagnostic algorithm of the management of neonatal pleural effusion detected prenatally or after birth.

anatomy and function of both central conducting lymphatics, including retroperitoneal lymphatic channels, cisterna chyli, and thoracic duct as well as peripheral lymphatic vessels, although no standardized procedure has yet been established in newborns and infants (57). Key diagnostic techniques are summarized in *Table 4*.

In case of prenatal etiological diagnosis and complete or nearly complete resolution of pleural effusion due to in utero treatment, associated with clinically stable cardiovascular and respiratory conditions, conservative management and close follow-up may be cautiously considered during the neonatal period (41). When pleural effusion is detected at birth or near birth, fluid drainage must be performed both for diagnostic and therapeutic purposes, and acquired causes of chylothorax should be considered.

MANAGEMENT OF POST-NATAL CONGENITAL CHYLOTHORAX

Post-natal management of congenital chylothorax is challenging, both for the heterogeneity of clinical course and because the optimal treatment has not been established de-

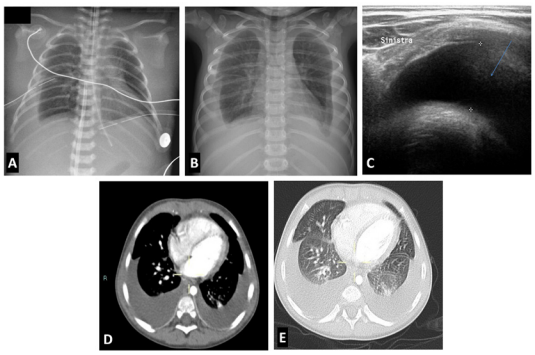

Fig. 6. Chest imaging techniques to assess the presence and severity of pleural effusion.

A: Presence of bilateral thoracic drainage with satisfactory lung expansion. Mild right pleural effusion; B: subsequent control 24 hours after thoracic drainage removal shows bilateral effusion associated with vascular and interstitial congestion; C: ultrasonographic appearance of pleural hypoechoic effusion in a transverse section of the left hemithorax; D, E: axial sections of contrast computed tomography imaging showing bilateral pleural effusion and vascular congestion; (D) parenchymal and (E) mediastinal windows.

TABLE 3
Main Diagnostic Procedures Suggested after Birth for the Management of Congenital Chylothorax*

Main diagnostic procedures suggested for congenital chylothorax
Pleural fluid analysis
Blood exams
Complete blood count
Coagulation tests
Hepatic and renal function
Direct Coomb test
Markers of acute infection
TORCH serologies
Genetic analysis
Karyotype analysis
Research of specific gene mutations including metabolic disorder
Structural and functional echocardiography
Electrocardiography
Cranial ultrasound
Chest and total body imaging
Chest X-Ray
Computed tomography
Magnetic resonance

*Diagnostic modalities and timing should be tailored on the basis of diagnostic suspect and therapeutic management needed by the patient.

spite the wide variety of available treatments. A post-natal therapeutic algorithm currently used in the Gaslini Unit is suggested in *Fig.* 7.

Perinatal asphyxia and respiratory insufficiency are major symptoms of congenital chylothorax at birth, especially in cases of severe pleural effusion and/or hydrops, and vigorous resuscitation is frequently necessary soon after birth (58). Thoracocentesis performed in the delivery room may guarantee an adequate lung expansion while intubation and mechanical ventilation may improve respiratory function.

Once the neonate is admitted in the neonatal intensive care unit, supportive management consists of respiratory and cardiovascular support, pleural drainage, nutritional management and pain therapy.

While both conventional and high frequency ventilation have been employed in infants with pleural effusion without conclusive data regarding the superiority of one modality or another, the latter may improve lung opening and volume maintenance, which may prevent further pleural fluid accumulation (59,60). Together with fluid and electrolyte replacement, transfusion with fresh frozen plasma or albumin should be considered in order to maintain an adequate oncotic pressure in the blood vascular compartment as hypoproteinaemia can frequently occur in these patients.

Neonates with prolonged pleural effusion congenital chylothorax are at higher risk of infection, due to both hypogammaglobulinemia and leukopenia, and may benefit from intravenous immunoglobulin infusion (30).

Nutritional Management

The aim of nutritional therapy is to minimize intestinal lymphatic flow, both by using the parenteral route for feeding and by modifying the fat content of enteral feeds. Total parenteral nutrition may be indicated in case

TABLE 4
Main Imaging Techniques Which can be Used to Evaluate Peripheral and Central Lymphatic Vessels*

Procedure	Main information provided	Description	Comments	References
Pedal lymphography	Visualization of peripheral lymphatic channels and central lymphatic system for both diagnosis and interventional procedures.	It requires the cannulation of peripheral lymphatic channels in foot dorsum through a surgical incision and the infusion of an oil-based contrast medium.	Replaced by intranodal lymphography to study central lymphatic vessels. It is technically difficult, invasive and requires protracted general anaesthesia. It is associated with significant complications including respiratory compromise due to oily pulmonary emboli.	(113)
Intranodal Lymphangiography	It replaced pedal lymphangiography for the visualization of central conducting lymphatics. It provides quick and reliable access to the central lymphatic ducts for interventional procedures. It provides limited information about the relationship of lymphatics with surrounding structures.	It is a fluoroscopic lymphangiography performed after US-guided intranodal injection of oil-based contrast material.	It shows a higher success rate than pedal lymphangiography, it is faster and generally well tolerated. It exposes to ionizing radiation and there is a possible risk for systemic embolization in infants with right-to-left shunts. Lack of indications about contrast agent dosage in infants may reduce the sensitivity of the exam.	(114) (115) (116)
Interstitial lymphoscintigraphy	It provides dynamic information and quantitative information of lymph flow but lacks anatomical resolution. It can be used for monitoring treatment efficacy and disease evolution.	Intradermal injection of technetium-99m and detection of its distribution with a gamma camera.	Minimally invasive and well tolerated. None or only mild sedation required. The poor anatomical resolution limits its role in both diagnostics and pre-procedural planning.	(117) (118) (119)
Indocyanine green lymphography	It evaluates the presence and the severity of lymphatic dysplasia, providing a clear picture of the lymphatic superficial vessels in the extremities.	It consists in intradermal injections of indocyanine green as contrast agent and detection of its distribution pattern with an infrared camera system;	Minimally invasive, no sedation required; Bedside procedure.	(120) (121) (122)
Non-contrast T2-weighted MR lymphangiography	It visualizes parts of the peripheral and segments of the central lymphatic anatomy, including the thoracic duct.	It is performed using the three-dimensional heavily T2 weighted imaging and axial and coronal fat-saturated T2 weighted imaging with fast spin-echo sequences.	It doesn't provide information about lymphatic flow. Small lymphatic ducts are hardly visualized due to the lack of contrast agent. Its use in diagnostic and interventional lymphangiography is limited.	(123) (124)
Procedure	**Main information provided**	**Description**	**Comments**	**References**
Dynamic intranodal MR lymphangiography	It provides fast and reliable enhancement of the central lymphatic ducts and shows both central lymphatic anatomy and dynamic flow with good temporal and spatial resolution.	It is performed by using T1-weighted three-dimensional gradient sequences after ultrasound-guided groin intranodal injections of gadolinium-based contrast agent.	It's becoming a modality of choice for both diagnosis and pre-procedural interventional planning. Minimally invasive and well tolerated. Mild sedation is required.	(126) (127) (128) (129)

*The procedure performed should be selected on the basis of the main diagnostic question and the possible subsequent treatment; MR: Magnetic Resonance

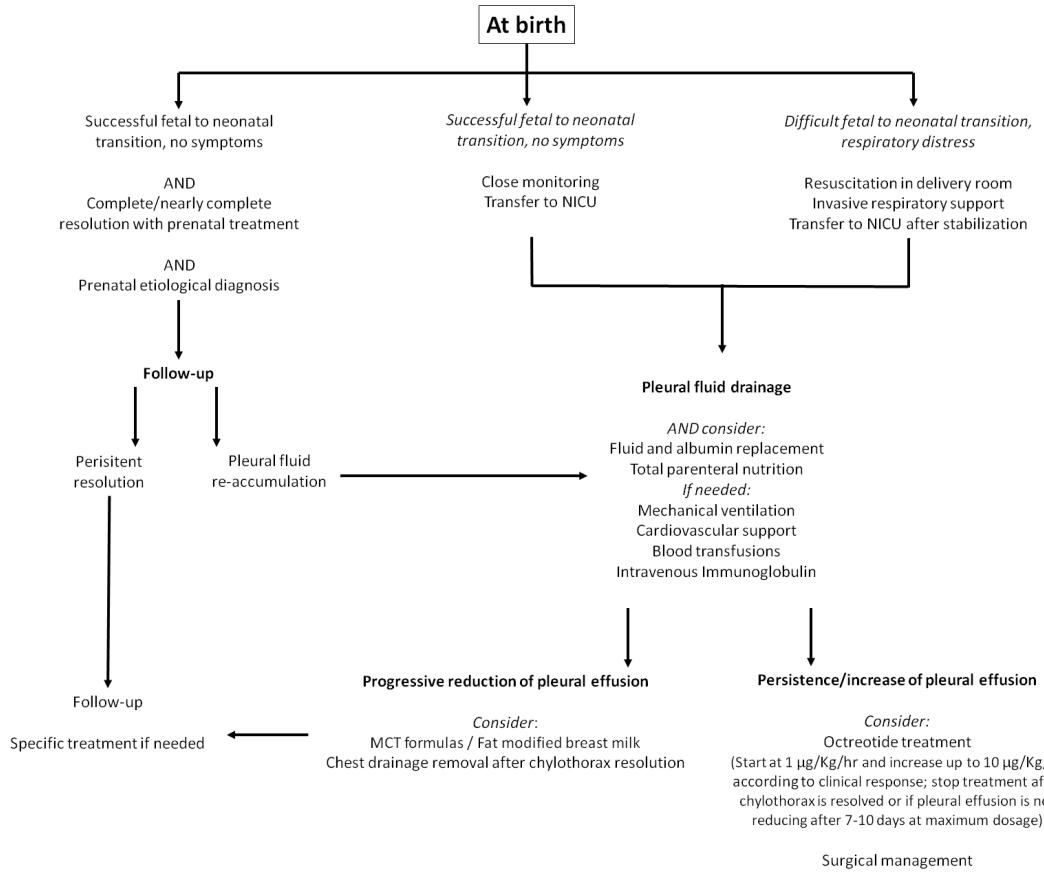

Fig. 7. Neonatal management algorithm for congenital chylothorax. MCT: medium chain triglycerides; NICU: Neonatal Intensive Care Unit. Modified from Bellini et al. 2016 (55).

of progressive and severe chylothorax or in intubated neonates (61) while medium chain triglyceride (MCT) formulas or fat modified breast milk have been shown to be effective in patients who can be orally fed (62,63). MCTs are directly absorbed into the portal venous system, drastically reducing both the fat content and volume of chylous effusion.

Infants who are fed with fat-modified breast milk may require additional fortification to support adequate growth (64).

Treatment with Octreotide

Octreotide, a somatostatin analogue, reduces lymphatic flow by causing mild vasoconstriction of splanchnic vessels, inhibits gastric, pancreatic, and intestinal secretions, and also reduces hepatic venous flow and intestinal absorption, which decrease the hydrostatic pressure driving chylous flow (65). Although octreotide is currently used as an additional treatment in neonatal congenital and post-operative chylothorax, no consensus has been reached on its use due to the lack of evidence about its efficacy and safety (66). Octreotide is usually administered as a second-line treatment after total parenteral nutrition failure and before considering surgical treatment. Marked variation among studies in octreotide regimen is reported, the commonest being intravenous infusion at a starting dose of 1 µg/Kg/hr, gradually increasing to 10 µg/Kg/hr according to therapeutic response. Although

heterogeneous definitions of octreotide efficacy have been reported, it generally refers to a significant reduction in chylous effusion within two weeks of drug administration. Octreotide has been reported to be effective in 47% of neonates with chylothorax from any cause with a slightly higher effectiveness in congenital forms and with a low incidence of side effects (67). Concerns remain about the possible onset of pulmonary hypertension and necrotizing enterocolitis in association with octreotide treatment (68-70). In addition, one case of severe hypotension following intravenous octreotide administration has been reported (71).

Other Emerging Medical Treatments

Sirolimus, also called rapamycin, is a macrolide compound naturally produced by several actinomycetes, possessing immunosuppressive, cytostatic, and antiproliferative properties (72). It inhibits the mammalian target of rapamycin (mTOR), a serine/threonine kinase which promotes cell growth, proliferation and survival (73,74). Besides its immunosuppressive and anti-neoplastic effects, sirolimus has played a role in treating lymphatic malformations through the inhibition of lymphangiogenesis secondary to decreased synthesis and augmented degradation of vascular endothelial growth factor (VEGF) receptor 3 (75). Only a few cases of lymphatic malformations treated with sirolimus in infants have been reported to date but based on published data most patients have shown at least a partial response with minor adverse effects (76). Although dose and duration of treatment in neonates and small children still remains to be determined, treatment with sirolimus may represent a promising therapeutic option in case of extensive lymphatic malformations associated with chylothorax (77,78).

Sildenafil is a selective inhibitor of phosphodiesterase type 5, which is responsible for cyclic guanosine monophosphate (cGMP) degradation. In the neonatal setting, it is a therapeutic option for the treatment of pulmonary arterial hypertension as cGMP accumulation leads to smooth muscle relaxation and vasodilation of the pulmonary vasculature (79).

Recently sildenafil has been proposed as a novel treatment for severe lymphatic malformations in children as lymphatic vessel growth and function is partly regulated by nitric oxide-induced production of cGMP, which is thought to facilitate lymphatic endothelial cell proliferation, migration and vessel formation (80-82). Since sildenafil prevents the degradation of cGMP, it may promote lymphatic vessel growth and/or remodeling, leading to a resolution of lymphatic obstruction and chylothorax. In 2015 oral sildenafil was reported to be effective for the first time in a case of a late preterm infant with chylothorax associated with congenital pulmonary lymphangiectasia (83). However, further evidence is needed both in the laboratory and the clinical setting before this treatment can be considered.

Chemical Pleurodesis

Chemical pleurodesis is performed by injecting substances into the pleural space which cause fibrous adhesions between the visceral and parietal pleura. Pleurodesis with povidone-iodine has been shown to be effective in 58-80% of neonates with chylothorax refractory to other medical treatments (71,84,85), but it has been associated with a number of complications including acute and chronic renal failure, hyperthyroidism, respiratory distress and cardiorespiratory failure (84). For these reasons its use in newborn infants should be cautiously considered (86).

Pleurodesis with intrapleural injection of OK-432 has been successfully attempted postnatally in a few infants with refractory chylothorax and although it seems to be safe and well tolerated (87-88), one case of life-threatening haemolytic anemia has been recently reported in a late preterm infant with persistent left chylothorax who received two doses of intrapleural OK-432 (89).

Surgical Management

Surgical treatment is usually reserved for infants with refractory chylothorax, defined as massive chyle leak (more than 50 mL/kg/day), or leak persistence, metabolic/nutritional complications, or overall clinical deterioration in spite of conservative treatment (5,90). While in post-surgical chylothorax, caused by iatrogenic rupture of thoracic duct, the more frequently chosen intervention is duct ligation as a surgical option (91), congenital chylothorax may pose more questions about about the choice of surgical approach. As no guidelines exist on operative management of congenital chylothorax and different options are available to treat this condition, optimal timing and type of surgical intervention should be evaluated according to such factors as age and size of the infant, severity of chylous leak, center specific surgical preference and length of attempted conservative management (92).

Pleuroperitoneal shunt has been reported to be an effective and well tolerated procedure in both term and preterm infants, yet the duration of shunt placement usually lasts from weeks to months. The external component is a potential source of infection, and obstruction or malfunctioning may require a further surgical intervention (93,94).

Mechanical pleurodesis is performed by gentle abrasion of the pleura to induce obliteration of the pleural space and may be performed both via thoracotomy and thoracoscopy. It has been demonstrated to be effective and safe in treating refractory chylothorax in infants, with a mean duration of post-operative chest tube drainage of nearly one week which allows a more rapid hospital discharge. However follow-up studies are needed to assess long term consequences of loss of sliding between the pleura and the lung (92,95).

Percutaneous thoracic duct embolization, consisting in a transcatheter embolization of the duct proximal to the chyle leak, is a less invasive procedure than thoracic duct ligation and has gained interest after intranodal lymphangiography replaced the more hazardous and technically difficult pedal lymphangiography (96). Small infant case series have shown this technique to be successful where conservative treatment and duct ligation have failed (97-99).

Thoracoscopic parietal pleural clipping has been successfully attempted in infants with refractory chylothorax in whom visualization of the thoracic duct and lymphatics was not possible (100).

Diaphragmatic fenestration, consisting of a circular excision of a portion of the diaphragm subsequently sutured to a fenestrated polytetrafluoroethylene patch, has been recently performed in a small cohort of infants with persistent chylothorax following cardiac surgery and shows promising results in terms of efficacy and safety (101).

Lymphovenous anastomosis is a new microsurgical technique in this setting consisting of an end-to-end or end-to-side thoracic duct-venous anastomosis through either transabdominal catheterization or percutaneous groin lymphatic access. It can rapidly restore a physiological lymphatic circulation, and it has recently been successfully attempted in two infants who failed traditional medical management and were unable to undergo alternative interventions (102).

FUTURE DIRECTIONS

Congenital chylothorax is a rare but severe condition with an elevated prenatal and postnatal morbidity and mortality. The heterogeneity of underlying etiology and the high variability of clinical manifestations make its diagnostic and therapeutic management challenging, both in the prenatal and in the neonatal period.

Fetal hydrothorax is the result of several conditions which vary in pathophysiology and clinical outcomes. Therefore an accurate diagnostic work-up is mandatory in order to determine the etiology and establish the subsequent treatment strategy. As no definite consensus exists on hydrothorax management, for every case a careful evaluation of potential options should be performed.

Different conservative approaches have

been proposed to treat this condition in the neonatal period, and several surgical options have been attempted with variable level of success and safety profile. Aside from supportive therapies, conservative treatments consist in dietary management including total parenteral nutrition, MCT formulas or fat-modified breast milk, treatment with octreotide and chemical pleurodesis. In some cases, dietary management alone is effective with a complete resolution of the chyle leak, but the persistence and the increase of pleural effusion necessitate additional treatment options.

Intravenous octreotide is extensively used regardless of chylothorax etiology as a second-line treatment after nutritional intervention failure and before considering a surgical management. Despite its extensive use, there is a wide variation in the treatment dose, duration and efficacy among the reported studies, and no consensus exists on optimal regimen or specific patient subgroups that could benefit most from the treatment. Conflicting reports also exist about efficacy and safety of chemical pleurodesis with povidone-iodine while a novel technique consisting of intrapleural injection of OK-432 has been successfully attempted even though safety needs to be further evaluated.

Recently, sirolimus has gained interest in the treatment of lymphatic malformations and although very few data exist on its application in the neonatal period, it seems to be a promising therapeutic option in selected cases in which congenital chylothorax is associated with extensive lymphatic malformations.

Surgical treatment is performed after a variable period in which conservative treatment turns out to be ineffective. New microsurgical and minimally invasive procedures have shown excellent results with a faster disease resolution and good safety profile but larger cohorts of patients are needed to confirm efficacy.

Although there is an urgent need to identify the optimal prenatal and post-natal management of congenital chylothorax, prospective multicentric trials involving a large sample size are hardly feasible due to the rarity of the condition and the heterogeneity of both presentation and etiology.

At the same time, published case reports and case series often lack detailed information about treatment regimen and duration, and efficacy is frequently scantly defined especially for conservative treatment. To enhance levels of evidence regarding congenital chylothorax management, we suggest continuing and meticulous case reports allowing improved comparison in systematic reviews. Finally, we believe shared diagnostic and therapeutic management between Neonatology Divisions and Fetal Medicine Services is of paramount importance to accelerate post-natal diagnostic work-up and select the most suitable and patient specific treatment plan.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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Carlo Bellini, MD, PhD
Neonatal Intensive Care Unit,
Department Mother & Child
IRCCS Gaslini
Largo G. Gaslini, 5
16147 Genoa, Italy
Tel: 0039-010-56362762
Email: carlobellini@gaslini.org