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Original article

Neonatal pleural effusions in a Level III Neonatal Intensive Care Unit

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Abstract

Pleural effusions are rare in the newborn. Still, being familiar with this condition is relevant given its association with a wide range of disorders. Only two large series of cases on this matter have been published, with no solid conclusions established. The aim of this study is to determine the etiology, management and prognosis of pleural effusions in a population of high-risk neonates.

The authors performed a retrospective study in the Neonatal Intensive Care Unit of "Hospital de São João", Porto (Portugal), between 1997 and 2014, of all newborns with the diagnosis of pleural effusion, chylothorax, hemothorax, empyema, fetal hydrops or leakage of total parenteral nutrition (TPN).

Eighty-two newborns were included, 48 males and 34 females. Pleural effusions were congenital in 19 (23.2%) newborns and acquired in 63 (76.8%). Fetal hydrops was the most frequent cause (15 cases, 78.9%) of congenital effusions while postoperative after intrathoracic surgery was the most common cause (39 cases, 61.9%) of acquired effusions, followed by leakage of TPN (13 cases, 20.6%). Chylothorax was the most common type of effusion (41.5% of cases). Pleural effusions after intrathoracic surgery were mainly (64.1%) chylothoraces. Regarding use of octreotide for treatment of acquired chylous effusions, the comparative analysis showed no statistical differences between the group of alive newborns who received octreotide and the group who did not. Twenty-seven (32.9%) newborns died; the causes of death were related to underlying diseases and not to the pleural effusion. Clinical outcome is generally good, except in hydropic neonates. Blood albumin level appears to be predictive of prognosis and further investigation on its clinical significance should be encouraged.

Keywords

Pleural effusion, newborn, chylothorax, hydrops fetalis, serum albumin, prognosis.

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Introduction

The pleural space exists between the parietal pleura of the chest wall and the visceral pleura of the lung. Both pleural surfaces filter fluid into the pleural space and the lymphatics are responsible for most of the fluid reabsorption [1]. Pleural effusion, defined as fluid accumulation in the pleural space, can occur if the rate of filtration increases, or if the rate of lymphatic clearance decreases, or if both of these mechanisms are present [2].

Pleural effusions are rare in the neonate [3]. Nevertheless, being familiar with this condition is relevant because of its association with a wide range of disorders. It has generally a favorable prognosis, except in hydropic neonates. [4]. Effusions may be diagnosed antenatally or they can appear at any time during the neonatal period. They may be asymptomatic or present with respiratory distress [2].

Several causes have been described in the literature, including congenital and acquired chylothoraces, fetal hydrops, and parapneumonic effusions [4]. There are also reports of hemothorax and leakage of parenteral nutrition, which are usually iatrogenic complications [3, 5]. Still, information on the relative frequencies of these disorders as causes of pleural effusions is sparse.

Treatment options and clinical outcomes are also poorly described. Guidelines for management of pediatric chylothorax have been proposed [6, 7] but only one publication presents specific guidelines for the neonatal period [8]. Moreover, new therapeutic approaches have been developed and no prospective or randomized trials have yet been performed [9].

There are only two recent publications reporting large series of pleural effusions in the fetus and newborn and no solid conclusions have been established so far [3, 10]. Therefore, the aim of this study is to investigate etiology, clinical management and prognosis of neonatal pleural effusions in a tertiary Neonatal Intensive Care Unit (NICU).

Material and methods

All newborns admitted to the NICU of "Hospital de São João", Porto (Portugal), between 1997 and 2014, with the discharge diagnosis of pleural effusion, chylothorax, hemothorax, empyema, fetal hydrops or leakage of total parenteral nutrition (TPN) were included. Our NICU is a Level III unit and a reference center for cardiothoracic surgery. All the data were obtained by a retrospective search from the hospital computer database and medical records.

Demographic data and information regarding pregnancy and delivery were recorded. Pleural effusion characteristics were also collected: congenital or acquired, laterality, volume, clinical presentation, other associated effusions, prenatal diagnosis, gestational age at diagnosis, duration of the effusion and biochemical, cytological and bacteriological analysis of the fluid. In addition, data regarding treatment and neonatal morbidity and mortality were collected.

Pleural effusions were diagnosed by chest radiography (standard supine anteroposterior projection) and/or chest ultrasound and they were classified as: small – if they were apparent in not more than a quarter lung field; moderate – if apparent in a quarter to half lung field; large – if apparent in more than half lung field; massive – if apparent around the entire lung with mediastinal shift [3]. Although chest ultrasound outperforms the radiograph in ruling in and out pleural effusions in the adult, comparative studies have not yet been published for the neonate and child. Still, experienced pediatric clinicians are increasingly resorting to the aid of ultrasound for the diagnosis of neonatal pleural effusions, adapting it to their specific clinical issues [11, 12]. In our clinical practice, we quantify the pleural effusion as: small (< 10 mm), moderate (10-30 mm) and large (> 30 mm)), measured at the posterior pleural costophrenic recess with the patient in supine position. Type of effusion was assessed based on biochemical and cytological analysis of the fluid. Etiology of the effusion was established according to the clinical setting and medical history.

Chylothorax was defined according to the criteria proposed by Buttiker et al.: an absolute white cell count > 1,000 cells/μL with a lymphocyte fraction > 80% and triglyceride levels > 110 mg/dL in pleural fluid (provided there was minimal fat enteral intake) [6] and treated according to the published guidelines [8]. Transudates were effusions with a total protein level < 3.0 g/dL or a pleural/serum protein ratio < 0.5, and a total leukocyte count < 1,000/mm^3 with predominance of mononuclear cells. Exudate was defined by the presence of at least one of the following: protein level > 3.0 g/dL with pleural/serum protein ratio > 0.5; pleural fluid lactic dehydrogenase (LDH) values > 200 IU/L; or a pleural-to-serum LDH ratio > 0.6 [13]. Empyema was defined as an exudative effusion presenting with purulent appearance and a total leukocyte count > 5,000/mm^3 with predominance of polymorphonuclear cells (PMNs). Hemothorax was diagnosed based on the presence of blood in the pleural space [13]. Leakage of TPN was considered in neonates with a central venous catheter that presented a pleural fluid with a low leukocyte count and high concentrations of both glucose and potassium [5].

Fetal hydrops was defined as an excessive fluid accumulation within the fetal extravascular compartments and body cavities, characterized by generalized skin thickness of > 5 mm, placental enlargement, pericardial or pleural effusion, or ascites [14].

Gestational age was assessed by post-menstrual age, ultrasound examination [15] or the New Ballard Score (in the absence of obstetrical indexes) [16]. Small for gestational age was defined as a birth weight below 3rd percentile of Fenton's fetal growth charts [17].

Hyaline membrane disease was defined based on the European guidelines [18]. The diagnosis of bronchopulmonary dysplasia was made according to the NIH Consensus definition [19]. Hemodynamically significant patent ductus arteriosus was diagnosed according to SIBEN consensus [20]. The diagnosis and staging of necrotizing enterocolitis was established based on Bell criteria [21]. Intraventricular hemorrhage was classified according to Papile [22] (before 2010) and Volpe [23] (after 2010). Cystic periventicular leukomalacia was classified according to de Vries and Rennie [24]. Staging of retinopathy of prematurity was done according to the international classification [25]. Proven neonatal sepsis was defined as any systemic infection documented by a positive blood culture. Pneumonia was diagnosed based on clinical, radiological and bacteriological parameters. Hypoalbuminemia was defined by a blood albumin level < 35 g/L [2].

The statistical analysis was performed using SPSS for Windows, version 20. Continuous variables were characterized by mean (± standard deviation) or median (medium-maximum) if they had symmetric or asymmetric distribution respectively and categorical variables by absolute and relative frequencies. To compare continuous variables non-parametric tests (Mann-Whitney U test or Kruskal-Wallis test) were used if they had two or more than two categories, and Chi-square or Fisher's exact test to compare categorical variables, the latter for expected values less than 5. A multivariate analysis by logistic regression was performed to evaluate predictive factors for death. A p value less than 0.05 was considered statistically significant.

Results

During the 18 years of the study period, about 7,200 newborns were admitted to the NICU and 82 neonates with pleural effusion were retrieved and studied. The incidence of effusions in our series was 110 per 10,000 neonates. Demographic and clinical data are summarized in **Tab. 1**. Pleural effusions were congenital in 19 (23.2%) neonates and acquired

Table 1. Demographic and clinical data of the newborns with pleural effusion (n = 82).

Gender, n (%)	
Male	48 (58.5)
Female	34 (41.5)
Birth weight (g), mean (± SD)	2,476 (± 941)
Small for gestational age, n (%)	9 (11)
Gestational age (weeks), mean (± SD)	35 (± 4.3)
Surveillance during pregnancy, n (%)	81 (98.8)
Parity, n (%)	
Single	72 (87.8)
Multiple	10 (12.2)
Prenatal period	
Steroids use, n (%)	27 (32.9)
Full cycle, n (%)	16 (59.3)
Polyhydramnios, n (%)	16 (19.5)
Fetal hydrops, n (%)	15 (18.3)
Delivery, n (%)	
Vaginal	25 (30.5)
C-section	57 (69.5)
Apgar score, n (%)	
1st minute < 7	39 (48.1)
5th minute < 7	21 (26.3)
Resuscitation, n (%)	45 (61.6)
Endotracheal tube	42 (93.3)
Associated congenital malformations, n (%)	53 (65.5)
Chromosomal anomalies, n (%)	4 (8)
Dysmorphic syndrome, n (%)[a]	4 (5)
NICU stay (days), median (min-max)	26 (0-167)
Deceased, n (%)[b]	27 (32.9)
Autopsy	19 (70.4)

NICU: Neonatal Intensive Care Unit; [a]Down's syndrome (2), DiGeorge syndrome (1), Klippel-Feil syndrome (1); [b]multiorganic failure (8), sepsis (7), extensive hemorrhagic disorders (6), congestive heart failure (2), pulmonary hypoplasia (2), fetal arrhythmia (1), alveolar capillary dysplasia (1).

in 63 (76.8%). The etiologies of each category are described in **Tab. 2**.

We observed 15 cases of congenital pleural effusion with fetal hydrops. Five (33.3%) of them were chylothoraces, 9 (60%) were transudates and 1 (6.7%) was of unknown type. Out of the 9 transudates, 5 (55.6%) were caused by fetal arrhythmia, 1 (11.1%) by twin-to-twin transfusion syndrome, 1 (11.1%) by hemochromatosis, 1 (11.1%) by congenital nephrotic syndrome and 1 (11.1%) was idiopathic.

Regarding acquired effusions, 39 (61.9%) were iatrogenic after intrathoracic surgery. As mentioned above, our NICU is a reference center for cardiothoracic surgery. The association was found for surgical interventions on three types of major congenital malformations: congenital heart disease (CHD), diaphragmatic hernia and esophageal atresia. These postoperative effusions were chylothoraces in 25 (64.1%) cases.

Extravasation of TPN was identified in 13 newborns (20.6% of the acquired effusions). They were unilateral in 8 (61.5%) cases and of moderate volume in 5 (38.5%). Four of them had spontaneous resolution of the effusion after catheter removal, with no need for further intervention. The median duration of effusions in this group was 2 days (range, 1-6 days). Two of the newborns died.

Three newborns developed parapneumonic effusions; fluid analysis was consistent with empyema in all of them.

Of the 3 cases of hemothorax, 1 was congenital and occurred in a newborn with a paravertebral neuroblastoma associated with disseminated intravascular coagulation. The other 2 were acquired; 1 in a newborn performing anticoagulation therapy for extracorporeal membrane oxygenation (ECMO) and the other as a complication of cardiac catheterization with pulmonary hemorrhage. In this group the median duration of the effusions was 2 days (range, 1-14 days) and all of them died.

Chylothorax was the diagnosed type of effusion in 34 (41.5%) neonates. Other types were: 23 (28.0%) transudates, 7 (8.5%) exudates, 13 (15.9%) cases of fluid consistent with TPN, 3 (3.7%) cases of fluid consistent with blood (hemothorax) and 2 (2.4%) unknown. **Tab. 3** shows pleural effusion characteristics and demographic/clinical data of the following three types: chylothorax, transudates, exudates.

Chylous effusions are described in more detail in **Tab. 4**. Twelve neonates with chylothorax

Table 2. Etiologies and types of pleural effusions.

Etiology, n (%)		Type, n (%)					
		Chy	Trans	Exu	TPN	Hem	Unk
Congenital	**19 (23.2)**	**7 (36.8)**	**10 (52.6)**	**0**	**0**	**1 (5.3)**	**1 (5.3)**
Fetal hydrops	15 (78.9)	5 (71.4)	9 (90)	-	-	-	1 (100)
Isolated congenital chylothorax	2 (10.5)	2 (28.6)	-	-	-	-	-
Congestive heart failure	1 (5.3)	-	1 (10)	-	-	-	-
Coagulopathy and intrathoracic neoplasm	1 (5.3)	-	-	-	-	1 (100)	-
Acquired	**63 (76.8)**	**27 (42.9)**	**13 (20.6)**	**7 (11.1)**	**13 (20.6)**	**2 (3.2)**	**1 (1.6)**
Postoperative (after intrathoracic surgery)	39 (61.9)	25 (92.6)	9 (69.2)	4 (57.1)	-	1 (50)	-
Congenital heart disease	15 (38.5)	13 (52)	-	1 (25)	-	1 (100)	-
Congenital diaphragmatic hernia	16 (41)	6 (24)	9 (100)	1 (25)	-	-	-
Esophageal atresia	8 (20.5)	6 (24)	-	2 (50)	-	-	-
Leakage of TPN	13 (20.6)	-	-	-	13 (100)	-	-
Pneumonia	3 (4.7)	-	-	3 (42.9)	-	-	-
Compression by intrathoracic tumor	1 (1.6)	1 (3.7)	-	-	-	-	-
Complication of pneumothorax drainage	1 (1.6)	1 (3.7)	-	-	-	-	-
Superior vena cava syndrome	1 (1.6)	-	-	-	-	-	1 (100)
Coagulopathy by thrombolytic therapy	1 (1.6)	-	-	-	-	1 (50)	-
Nephrotic syndrome	1 (1.6)	-	1 (7.7)	-	-	-	-
Congestive heart failure and hypoproteinemia	1 (1.6)	-	1 (7.7)	-	-	-	-
Congestive heart failure and nephrotic syndrome	1 (1.6)	-	1 (7.7)	-	-	-	-
Unknown	1 (1.6)	-	1 (7.7)	-	-	-	-

Chy: chylothorax; Trans: transudate; Exu: exudate; TPN: total parenteral nutrition; Hem: hemothorax; Unk: unknown.

Table 3. Pleural effusion characteristics and demographic/clinical data according to type.

	Chylothorax (n = 34)	Transudate (n = 23)	Exudate (n = 7)	P
Gender, n (%)				
Male	24 (70.6)	15 (65.2)	5 (71.4)	0.925[a]
Female	10 (29.4)	8 (34.8)	2 (28.6)	
Gestational age at birth (weeks), median (min-max)	37 (25-40)	37 (26-40)	38 (30-39)	0.840[b]
Birth weight (g), median (min-max)	2,708 (705-4,270)	3,045 (535-3,770)	2,663 (1,290-3,142)	0.261[b]
Small for gestational age, n (%)	4 (11.8)	2 (8.7)	0	0.859[a]
Parity, n (%)				
Single	30 (88.2)	22 (95.7)	6 (85.7)	0.561[a]
Multiple	4 (11.8)	1 (4.3)	1 (14.3)	
Type, n (%)				
Congenital	7 (20.6)	10 (43.5)	0	**0.042**[a]
Acquired	27 (79.4)	13 (56.5)	7 (100)	
Prenatal diagnosis, n (%)	6 (17.6)	4 (17.4)	0	0.776[a]
Gestational age at diagnosis (weeks), mean (± SD)	30 (23-35)	32 (30-37)	-	0.195[b]
Delivery, n (%)				
Vaginal	12 (35.3)	5 (21.7)	4 (57.1)	0.212[a]
C-section	22 (64.7)	18 (78.3)	3 (42.9)	
Apgar score, n (%)				
1st minute < 7	14 (41.2)	15 (65.2)	0	**0.006**[a]
5th minute < 7	8 (23.5)	9 (40.9)	0	0.088[a]
Endotracheal intubation at birth, n (%)	17 (56.7)	15 (71.4)	0	0.128[a]
Laterality, n (%)				
Unilateral	18 (52.9)	11 (47.8)	6 (85.7)	0.228[a]
Right	7 (38.9)	6 (54.5)	3 (50)	0.664[a]
Left	11 (61.1)	5 (45.5)	3 (50)	
Bilateral	16 (47.1)	12 (52.2)	1 (14.3)	0.228[a]
Volume, n (%)				
Small	7 (20.6)	12 (52.2)	4 (57.1)	**0.032**[a]
Moderate	21 (61.8)	6 (26.1)	3 (42.9)	
Large	6 (17.6)	5 (21.7)	0	
Respiratory distress, n (%)	26 (76.5)	13 (56.5)	7 (100)	0.059[a]
Other associated effusions, n (%)	10 (29.4)	14 (60.9)	2 (28.6)	0.058[a]
Ascites	9 (26.5)	13 (56.5)	1 (14.3)	**0.029**[a]
Pericardial	4 (11.8)	7 (30.4)	1 (14.3)	0.164[a]
Subcutaneous edema	8 (23.5)	11 (47.8)	0	**0.028**[a]
Associated congenital malformation, n (%)				
Heart disease	13 (38.2)	2 (8.7)	3 (42.9)	**0.009**[a]
Diaphragmatic hernia	6 (17.6)	9 (39.1)	1 (14.3)	
Esophageal atresia	6 (17.6)	0	2 (28.6)	
Others	1 (2.9)	1 (4.3)	0	
Chromosomal anomalies, n (%)	3 (12)	0	0	0.423[a]
Dysmorphic syndrome, n (%)	2 (6.3)	0	1 (14.3)	0.217[a]
Neonatal morbidity, n (%)				
Hyaline membrane disease	7 (21.2)	7 (31.8)	1 (16.7)	0.680[a]
Bronchopulmonary dysplasia	3 (8.8)	4 (17.4)	2 (28.6)	0.234[a]
Patent ductus arteriosus	14 (41.2)	9 (39.1)	2 (28.6)	0.934[a]
Surgical closure	4 (28.6)	0	1 (50)	0.455[a]
Necrotizing enterocolitis ≥ grade 2	1 (3)	2 (8.7)	0	0.694[a]
Intraventricular hemorrhage ≥ grade 3	1 (33.3)	1 (100)	1 (50)	0.999[a]
Periventricular leukomalacia	3 (9.4)	1 (4.5)	0	0.765[a]
Retinopathy of prematurity ≥ grade 2	2 (50)	1 (100)	0	0.999[a]
Sepsis	19 (55.9)	9 (39.1)	4 (57.1)	0.459[a]
Pneumonia	3 (9.4)	2 (9.1)	3 (42.9)	0.087[a]

[a]Fisher's exact test; [b]Kruskal-Wallis test.

Table 3 (continued). Pleural effusion characteristics and demographic/clinical data according to type.

	Chylothorax (n = 34)	Transudate (n = 23)	Exudate (n = 7)	P
Previous thoracic surgery, n (%)	25 (73.5)	9 (39.1)	4 (57.1)	**0.031**[a]
Day of diagnosis after surgery, median (min-max)	6 (1-63)	4 (1-9)	3 (1-6)	0.189[b]
Duration of pleural effusion (days), median (min-max)	11 (1-108)	8 (2-32)	15 (1-30)	0.661[b]
Treatment, n (%)				
Spontaneous resolution	3 (8.8)	4 (17.4)	0	0.503[a]
Thoracocentesis	10 (29.4)	4 (17.4)	2 (28.6)	0.586[a]
Chest tube	24 (70.6)	8 (34.8)	4 (57.1)	**0.026**[a]
Duration (days), median (min-max)	10 (1-54)	13 (2-32)	8 (1-30)	0.774[b]
Octreotide	12 (35.3)	0	0	**0.001**[a]
Medium-chain triglycerides	16 (47.1)	0	0	**< 0.001**[a]
Albumin infusion	6 (17.6)	8 (34.8)	1 (14.3)	0.308[a]
Diuretics	14 (41.2)	15 (65.2)	1 (14.3)	**0.041**[a]
Thoracic duct ligation	2 (5.9)	0	0	0.602[a]
Mechanical ventilation, n (%)	31 (91.2)	20 (87)	7 (100)	0.844[a]
Mechanical ventilation (days), median (min-max)	19 (1-96)	11 (2-89)	16 (7-57)	0.206[b]
Oxygen therapy, n (%)	31 (91.2)	23 (100)	7 (100)	0.484[a]
Oxygen therapy (days), median (min-max)	17 (1-167)	13 (1-156)	16 (10-69)	0.241[b]
Start of enteral feeding (days), median (min-max)	30 (14-106)	11 (8-49)	13 (13-13)	0.077[b]
Parenteral feeding, n (%)	29 (85.3)	21 (91.3)	7 (100)	0.616[a]
Parenteral feeding (days), median (min-max)	20 (1-119)	16 (2-88)	15 (12-63)	0.235[b]
NICU stay (days), median (min-max)	38 (1-167)	21 (3-135)	41 (12-167)	0.064[b]
Deceased, n (%)	11 (32.4)	8 (34.8)	3 (42.9)	0.930[a]

[a]Fisher's exact test; [b]Kruskal-Wallis test.

Table 4. Characteristics and demographic/clinical data of chylous pleural effusions (n = 34).

	Congenital (n = 7)	Acquired (n = 27)	P
Gender, n (%)			
Male	5 (71.4)	19 (70.4)	0.956[a]
Female	2 (28.6)	8 (29.6)	
Gestational age at birth (weeks), median (min-max)	36 (30-37)	38 (25-40)	0.177[b]
Birth weight (g), median (min-max)	3,120 (1,530-4,270)	2,410 (705-3,865)	0.357[b]
Small for gestational age, n (%)	0	4 (14.8)	0.559[a]
Parity, n (%)			
Single	7 (100)	23 (85.2)	0.559[a]
Multiple	0	4 (14.8)	
Prenatal diagnosis, n (%)	6 (85.7)	0	0.999[a]
Gestational age at diagnosis (weeks), mean (± SD)	29.2 (± 4.3)	-	-
***In utero* intervention, n (%)**	3 (42.9)	0	**0.006**[a]
Delivery, n (%)			
Vaginal	1 (14.3)	11 (40.7)	0.378[a]
C-section	6 (85.7)	16 (59.3)	
Apgar score, n (%)			
1st minute < 7	5 (71.4)	9 (33.3)	0.097[a]
5th minute < 7	5 (71.4)	3 (11.1)	**0.004**[a]
Endotracheal intubation at birth, n (%)	4 (66.7)	13 (54.2)	0.672[a]
Thoracocentesis in delivery room, n (%)	2 (28.6)	0	**0.037**[a]

[a]Fisher's exact test; [b]Mann-Whitney U test; [c]Chi-square test.

Table 4 (continued). Characteristics and demographic/clinical data of chylous pleural effusions (n = 34).

	Congenital (n = 7)	Acquired (n = 27)	P
Laterality, n (%)			
Unilateral	0	18 (66.7)	**0.002**[a]
Right	0	7 (38.9)	0.999[a]
Left	0	11 (61.1)	
Bilateral	7 (100)	9 (33.3)	**0.002**[a]
Volume, n (%)			
Small	2 (28.6)	5 (18.5)	0.841[a]
Moderate	4 (57.1)	17 (63)	
Large	1 (14.3)	5 (18.5)	
Respiratory distress, n (%)	5 (71.4)	21 (77.8)	0.999[a]
Other associated effusions, n (%)	5 (71.4)	4 (14.8)	**0.014**[a]
Ascites	5 (100)	4 (100)	**0.007**[a]
Pericardial	3 (60)	1 (25)	**0.021**[a]
Subcutaneous edema	5 (100)	3 (75)	**0.004**[a]
Associated congenital malformation, n (%)			
Heart disease	0	13 (48.1)	
Diaphragmatic hernia	0	6 (22.2)	**< 0.0001**[a]
Esophageal atresia	0	6 (22.2)	
Others	0	1 (3.7)	
Chromosomal anomalies, n (%)	0	3 (14.3)	0.999[a]
Dysmorphic syndrome, n (%)	0	2 (7.4)	0.999[a]
Neonatal morbidity, n (%)			
Hyaline membrane disease	1 (16.7)	6 (22.2)	0.999[a]
Bronchopulmonary dysplasia	0	3 (11.1)	0.589[a]
Patent ductus arteriosus	1 (14.3)	13 (48.1)	0.198[a]
Surgical closure	0	4 (30.8)	0.999[a]
Necrotizing enterocolitis ≥ grade 2	0	1 (3.7)	0.999[a]
Intraventricular hemorrhage ≥ grade 3	0	1 (50)	0.999[a]
Periventricular leukomalacia	0	3 (11.5)	0.607[a]
Retinopathy of prematurity ≥ grade 2	0	2 (50)	0.999[a]
Sepsis	2 (28.6)	17 (63)	0.199[a]
Pneumonia	0	3 (11.5)	0.607[a]
Previous thoracic surgery, n (%)	0	25 (92.6)	**< 0.0001**[a]
Day of diagnosis after surgery, median (min-max)	0	6 (1-63)	0.999[a]
Duration of pleural effusion (days), median (min-max)	9 (1-30)	13 (1-108)	0.379[b]
Treatment, n (%)			
Spontaneous resolution	1 (14.3)	2 (7.4)	0.999[a]
Thoracocentesis	5 (71.4)	5 (18.5)	**0.014**[a]
Chest tube	3 (42.9)	21 (77.8)	0.157[a]
Duration (days), median (min-max)	5 (2-11)	10 (1-54)	0.234[b]
Octreotide	2 (28.6)	10 (37)	0.999[a]
Duration (days), median (min-max)	3 (2-4)	21 (1-40)	0.121[b]
Medium-chain triglycerides	4 (57.1)	12 (44.4)	0.681[a]
Albumin infusion	2 (28.6)	4 (14.8)	0.580[a]
Diuretics	0	14 (51.9)	**0.026**[a]
Thoracic duct ligation	0	2 (7.4)	0.999[a]
Mechanical ventilation, n (%)	5 (71.4)	26 (96.3)	**0.039**[c]
Mechanical ventilation (days), median (min-max)	7 (1-19)	21 (4-96)	**0.013**[b]
Oxygen therapy, n (%)	5 (71.4)	26 (96.3)	**0.039**[c]
Oxygen therapy (days), median (min-max)	7 (1-33)	19 (1-167)	0.071[b]
Start of enteral feeding (days), median (min-max)	0	30 (14-106)	0.999[b]
Parenteral feeding, n (%)	3 (42.9)	26 (96.3)	**0.003**[a]
Parenteral feeding (days), median (min-max)	12 (11-38)	21 (1-119)	0.315[b]
NICU stay (days), median (min-max)	9 (1-48)	42 (6-167)	**0.004**[b]
Deceased, n (%)	3 (42.9)	8 (29.6)	0.656[a]

[a]Fisher's exact test; [b]Mann-Whitney U test; [c]Chi-square test.

were treated with octreotide; 5 of them died. The comparative analysis of clinical outcomes in both congenital and acquired chylous effusions showed no statistical differences between the group of alive newborns who received octreotide and the group who did not.

In this series, 27 (32.9%) newborns died (9 in the group of congenital effusions and 18 in the group of acquired effusions). The causes of death were related to the underlying disease and not to the pleural effusion. The analysis of predictive factors for death showed only one predictive variable: blood albumin level. Higher blood levels of albumin are protective (OR 0.912; 95% CI 0.85-0.98) – **Tab. 5**; a blood albumin level ≤ 12.1 g/L had a sensitivity of 81.5% for mortality.

Table 5. Predictive factor for death (n = 27).

	Deceased	OR[a]	95% CI
Blood albumin level (g/L), median (min-max)	27 (8-40)	**0.912**	**0.85-0.98**

95% CI: 95% confidence interval, OR: odds ratio; [a]Logistic regression.

Discussion

The 82 cases of neonatal pleural effusions identified in our study are representative of 18 years of retrospective investigation, which is longer than any other series described. Our estimated effusions' incidence, 110 per 10,000 admissions, is according to the literature (from 5.5 to 220 per 10,000 admissions) [3, 26]. In our study there were no significant differences between gender, although pleural effusions occurred more commonly in males as described in previous reports [2].

Etiology and management

As described in **Tab. 2**, acquired effusions were more common than congenital ones, comprising about three-quarters of the cases. Regarding congenital effusions, fetal hydrops was the most frequent etiology and transudate was the most frequent type. Concerning acquired effusions, postoperative after intrathoracic surgery was the most common etiology and chylothorax was the most common type.

Comparing the three types of effusion presented in **Tab. 3**, the preponderance of acquired effusions is observed in all of them. Apgar scores appeared to be lower immediately after birth, with slight recovery at 5th minute, and none of the exudates had low scores; this is probably related to the morbidity caused by congenital effusions at birth. Associated effusions in other cavities, namely ascites and subcutaneous edema, were especially found in transudates, probably dependent on the cases of fetal hydrops. About associated malformations, transudates were particularly found in diaphragmatic hernias, possibly because of physiological disturbances of fluid regulation following surgical repair of the hernia sac. On the other hand, chylothoraces were more commonly associated to CHD, probably because of postoperative effusions. In fact, postoperative effusions were mainly chylous.

There were also differences on treatment modalities between types: although thoracocentesis was equally performed, chest tube drainage was particularly used in chylothoraces while diuretic therapy was a frequent option for transudates. As expected, octreotide, medium-chain triglycerides (MCT) and thoracic duct ligation were only used in chylothoraces.

Chylous effusions

Chylothorax is a rare cause of respiratory distress in the newborn and the most common form of pleural effusion in the neonatal period [27]. In fact, chylothorax was the most common type of effusion (41.5%) in this study. It is defined by the accumulation of chyle in the pleural space [6] and some authors distinguish three subtypes according to its cause: congenital, traumatic and nontraumatic [4, 6, 27].

Congenital chylothorax

The etiology of congenital chylothorax is not well understood, but it is thought to occur secondary to trauma to the thoracic duct during delivery or a congenital malformation of the lymphatic vessels [28].

All congenital chylothoraces in our study were bilateral, with lower Apgar scores at 5th minute and occasional need for immediate thoracocentesis in the delivery room, confirming that these were high-risk and unstable neonates with associated morbidities, namely fetal hydrops. In fact, in our series congenital chylothorax was associated with hydrops in 71.4% of the cases, as already reported in other publications [3]. Congenital chylothorax has also been associated with genetic diseases such as Noonan, Down's and Turner syndromes, and primary congenital pulmonary lymphangiectasis [29] but this association was not found in our series.

The management of this effusion starts from the antenatal period [28]. In our series, 42.9% of these infants had some *in utero* intervention (2 pleuro-amniotic shuntings and 1 pleural drainage during amniocentesis); the therapeutic benefit of antenatal drainage relates to resolution of fetal hydrops and prevention of pulmonary hypoplasia and intrauterine fetal death [29]. In our study, thoracocentesis was the preferred strategy in postnatal management. Octreotide was used in 2 cases and both of them died because of other morbidities, so the role of octreotide therapy cannot be considered for comparison in these patients. The published reports about octreotide efficacy in congenital effusions have showed mixed success: Shah et al. observed good results [9] while Horvers et al. found no clear and consistent effect [30]. Both series highlight the need of a randomized controlled trial for further investigation.

Acquired chylothorax

Traumatic chylothorax in the neonate is in most cases iatrogenic after intrathoracic surgery [27]. It may also occur following the use of ECMO catheters or insertion of chest tubes too far for the treatment of pneumothorax [2]. In our study, the majority of acquired chylothoraces were indeed postoperative (92.6%); we also report 1 case of complication after pneumothorax drainage (3.7%). The non-traumatic form is extremely rare in the neonatal period and it is caused by an obstruction of the thoracic duct by intrathoracic tumors, inflammatory diseases or mediastinal lymphangiomatosis [27]. In our series, we report 1 case of compression by a cervical teratoma (3.7%).

In this study, acquired chylothoraces were mainly unilateral, left-sided and of moderate volume. Postoperative effusions were particularly relevant, as reported in other series [3, 10]. This association was stronger for CHD interventions once 52.0% of the postoperative chylothoraces occurred following cardiac surgery, as supported by published data [31]. Chylothoraces after surgery on diaphragmatic hernias and esophageal atresias have been described [32, 33] but in this study they were less common (24.0% each).

Regarding treatment, these patients had increasing needs for diuretic regimens, parenteral feeding and oxygen therapy; they also required longer periods of mechanical ventilation and a longer stay in the NICU when compared to congenital chylothoraces. Two neonates required surgical management with thoracic duct ligation due to failure of medical therapy; no complications were registered.

Octreotide has been used in postoperative chylothoraces with promising results [34]. Although a published series presented poor outcomes [32] and despite the significant heterogeneity of case reports, a recent review concluded that octreotide is relatively safe, and may reduce complications in these patients; a randomized trial is again proposed [34]. In this series, octreotide was used in 10 patients and no significant effects were observed.

Fetal hydrops

In this study, the majority of congenital pleural effusions (78.9%) occurred as nonimmune fetal hydrops (NIFH). In fact, NIFH is an important documented cause of congenital pleural effusion [3]. In our study, cardiovascular disorders and lymph vessel dysplasia (congenital chylothorax) were the two major causes of NIFH and they were equally relevant, each one accounting for one-third of the hydrops cases. These etiologies are consistent with previous reports, although their relative frequency varies in the literature. Bellini et al. described cardiovascular diseases as the predominant cause (21.7%) [14], while Takci et al. reported lymphatic dysplasia as the most common diagnosis (23.5%) [35].

Despite the advances in diagnosis and management, NIHF still presents a high mortality rate (40-50%) [36]. In our series, the mortality rate in hydropic neonates was 53.3%. Huang et al. found that hydrops resulting from lymphatic dysplasias had a more favorable outcome [36]; that association was not found in our sample.

Leakage of total parenteral nutrition

Extravasation of parenteral fluid as a complication of central venous catheter use is rare and may be caused by vessel perforation, passage into the lymphatic duct, erosion of the vein or hyperosmotic endothelial damage [10]. It should be considered in any neonate who develops a pleural effusion while receiving a central venous infusion. An important differential in these cases is chylothorax due to thoracic duct injury during central line insertion [37]; biochemical analysis of the fluid allows the diagnostic distinction [5].

In our study, leakage of TPN constituted a relevant etiology, being the second most common cause of acquired effusions. All these neonates had percutaneously inserted central venous catheters (PICC), with no umbilical catheterization documented (10 catheters in the superior vena cava and 3 catheters in the left internal jugular vein). The position of the tips of the PICC lines when the effusion was established was not assessed in any of the cases since the catheter was promptly removed. Therefore, we cannot confirm if there was migration/misplacement of the central line tip or vessel perforation. TPN effusions were mostly unilateral (61.5%), which is consistent with previous findings [3]. The resolution of the effusion was fastest in these cases because there was prompt removal of the triggering agent (catheter) and discontinuation of TPN infusion.

According to Revel-Vilk and Ergaz, another important complication of central catheterization in newborns is venous thrombosis [38]; still, in our series none of the cases presented with catheter-related thrombosis in association with the effusion. Likewise, other complications reported in the literature, such as pericardial effusion with or without cardiac tamponade, ascites, catheter removal difficulties, phlebitis or infection [39], were not found in our study.

Pneumonia

Pneumonia can complicate with the spreading of bacterial infection within the thoracic cavity, resulting in pleural effusions, usually empyemas. *S. aureus*, *St. pneumoniae* and *St. pyogenes* are the most common causes [13]; other agents, like *B. fragilis* and *A. calcoaceticus*, have also been reported [3, 26]. Out of the 3 empyemas diagnosed in our series, 1 case was secondary to meconium aspiration syndrome and the other 2 were caused by *Acinetobacter spp.* and *E. aerogenes*.

Hemothorax

Hemothorax most commonly occurs after chest trauma; it is also an occasional manifestation of blood dyscrasias, intrathoracic neoplasms, thrombolytic therapy, and iatrogenic erosion of vessels by surgical procedures [13]. The 3 cases of hemothorax found in our series had a fatal outcome. Still, no prognostic conclusions can be assessed given the limited number of cases.

Iatrogenic causes

In our study, iatrogenic causes of pleural effusion (intrathoracic surgeries and central venous catheter complications) represent an important percentage of cases. This fact must be acknowledged by all professionals in neonatology so they can be aware of these potential preventable causes related to specific neonatal procedures (surgeries and catheters placement).

Prognosis

The mortality rate was relevant (32.9%) but none of the deaths was directly related to the effusion. There are reports of patients dying because of pulmonary hypoplasia related to congenital effusions [3] but this association was not found in our sample. In this study, the major causes of mortality were multiorganic failure, sepsis and extensive hemorrhagic disorders.

From all the variables studied, only blood albumin levels were predictive of prognosis: lower levels were associated to death in both chylous and non-chylous effusions. According to this, we speculated that hypoalbuminemia may reflect worst clinical condition of the patient. Although hypoalbuminemia was already described as a common complication of congenital chylothoraces [29], no information on its prognostic significance in neonatal effusions is reported in the literature. Further investigation on this matter should be encouraged in order to assess if blood albumin levels could become an analytic marker of prognosis in these patients.

This study has two limitations: one is the fact that it is a retrospective study and the second is that it represents the experience of only one NICU.

Conclusion

Pleural effusions are rare in the neonate and can be associated with several clinical conditions. Acquired effusions are more common than the congenital forms, which present as fetal hydrops in most of the cases. Traumatic chylothorax after intrathoracic surgery is the major cause of acquired effusions. Prompt diagnosis and adequate management are crucial. Blood albumin levels appear to be predictive of prognosis but further investigation on this matter should be encouraged. Clinical outcome is generally good, except in hydropic neonates.

Declaration of interest

The Authors declare that there is no conflict of interest. Funding: none.

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