Childhood interstitial lung disease

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Introduction

- Children's interstitial lung disease (chILD) encompasses a heterogeneous group of innate, genetic, infectious and inflammatory diseases, quite different from that seen in adulthood
- Prevalence of individual entities is likely <1 per 100000 individuals
- Categorisation is based on a multidisciplinary approach including clinical, radiological, genetic and histological findings

Eur Respir Rev. 2022 Mar 9;31(163)

chILD - Classification

- ILD – more prevalent in infancy
- ILD – not specific to any infancy and childhood

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ILD: more prevalent in infancy	
A1 : diffuse development disorders	• Acinar dysplasia • Alveolocapillary dysplasia with misalignment of pulmonary veins • Congenital alveolar dysplasia
A2: growth abnormalities	• Alveolar simplification • Chronic neonatal lung disease • Bronchopulmonary dysplasia • Chromosomal alterations
A3 : specific entities of undefined etiology	• Pulmonary interstitial glycogenosis • Neuroendocrine hyperplasia of infancy
A4: Surfactant dysfunction mutations and related disorders	• Pulmonary alveolar proteinosis • Chronic pneumonitis of infancy • Desquamative interstitial pneumonia • Nonspecific interstitial pneumonia
Ax : unclear respiratory distress syndrome in the mature neonate	
Ay: unclear respiratory distress syndrome in the almost mature neonate (30–36 weeks)	

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ILD not specific to any infancy and childhood	
B1: ILD related to systemic disease processes	• Storage disease • Langerhans cell histiocytosis • Endogenous lipid pneumonia • Immune-related disorders
B2: ILD of the normal host and due to exposures	• Hypersensitivity pneumonitis • Infection • Aspiration pneumonia • Eosinophilic bronchiolitis
B3: ILD of the immunocompromised host	• Obliterative bronchiolitis/restrictive allograft syndrome
B4: ILD with structural vascular changes	• Pulmonary hypertension • Pulmonary veno-occlusive disease • Pulmonary capillary haemangiomatosis Vasculitis
B5: ILD related to reactive lymphoid lesions	• Follicular bronchitis • Lymphocytic interstitial pneumonia

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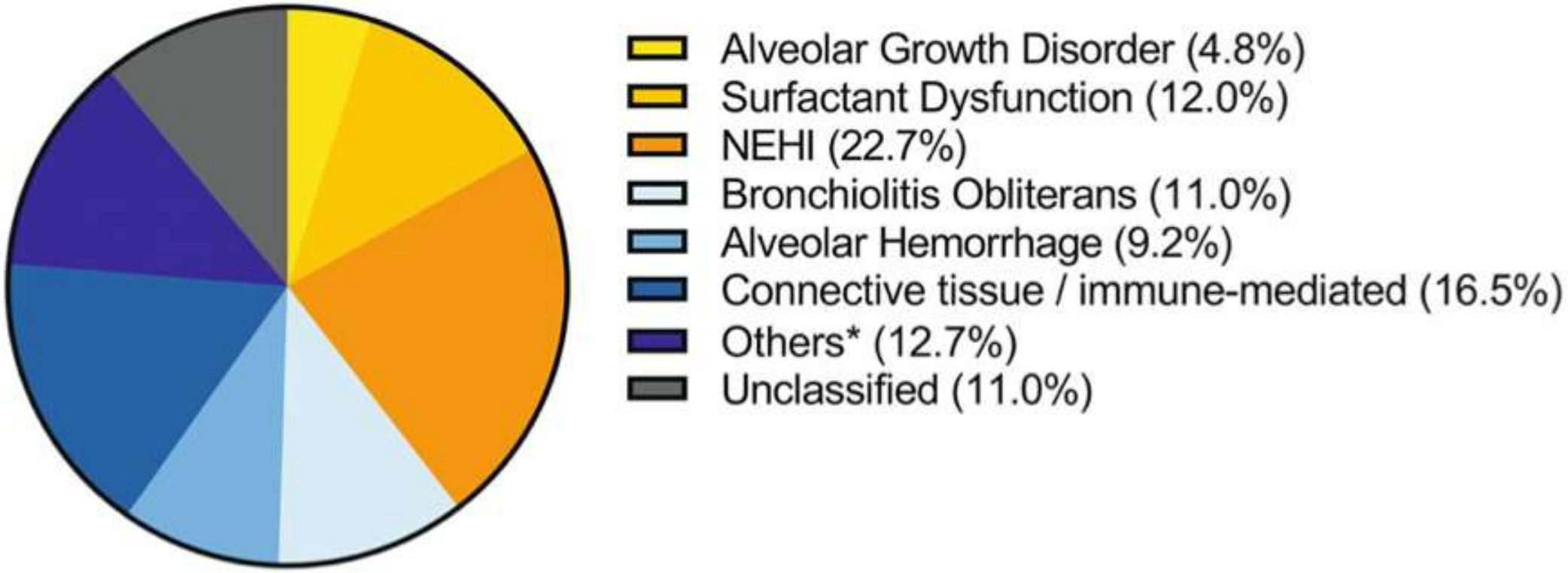
The US national registry for childhood interstitial and diffuse lung disease



*Other category includes groupings with small numbers of cases, including environmental/toxic/drug related, pulmonary interstitial glycogenosis, lung developmental dysplasia, pulmonary alveolar proteinosis

Pediatr Pulmonol. 2023 Jul 4:10.1002

Clinical presentation - chILD

- Progressive respiratory failure in the perinatal period
- a slowly progressive, dyspnoea either at rest or with exercise intolerance in older children
- “chILD syndrome”
- Respiratory symptoms (cough, rapid and/or difficulty breathing, exercise intolerance),
- Respiratory signs (resting tachypnoea, adventitious sounds, retractions, digital clubbing, failure to thrive, respiratory failure)
- Hypoxaemia
- Diffuse abnormalities on chest radiography or high-resolution computed tomography (HRCT)

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Before investigating for a specific chILD diagnosis - exclude

- Cystic fibrosis
- Acquired or congenital immunodeficiency,
- Congenital heart disease
- Bronchopulmonary dysplasia
- Pulmonary infection
- Primary ciliary dyskinesia
- Recurrent aspiration

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A1 : diffuse development disorders

Acinar Dysplasia	Congenital alveolar dysplasia	Alveolocapillary dysplasia with misalignment of pulmonary veins
• Pulmonary maturation arrest resembling the pseudo-glandular or early canalicular phase	Pulmonary maturation arrest - late canalicular or early saccular phase	Refractory respiratory failure with sever Pulmonary hypertension and right heart failure
• Females • Death occurs within hours after birth	No sex predominance Requires – mechanical ventilation/ECMO support	No sex predominance Death occurs with in hours to weeks
• Lungs appear small and has bronchi and occasionally bronchioles embedded in a loose mesenchyme completely lacking acini or alveoli	Lungs – heavy Reduced number of alveolar capillaries and predominant of type 2 pneumocytes	Reduced number of septal capillaries with central intraseptal location
• Genetic alterations including TBX4, FGF10 or FGFR2 in 65% of infants		FOXF1 (forkhead box F1) mutation in 40–90%

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Diffuse growth abnormalities of lung parenchyma (A2)

Diffuse growth abnormalities of lung parenchyma (A2)

- Alveolar growth abnormalities - incomplete or insufficient alveolarisation of prenatal or postnatal origin
- Manifest within first year of life
- Preterm delivery
- Pulmonary hypoplasia, in primary form associated with genetic abnormalities (NKX2-1 (NK2 homeobox 1; TTF1 (thyroid transcription factor 1)) deficiency, FLNA (filamin A) mutation
- Secondary form : impaired lung unfolding triggered by diaphragmatic hernia, oligohydramnios, thoracic skeletal dysplasia

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Specific entities of unknown aetiology (A3)

Pulmonary interstitial glycogenosis

- Common manifestation of a cellular, noninflammatory disorder of the lung interstitium
- Associated with alveolar simplification, acinar dysplasia /misalignment of pulmonary veins, pulmonary hypertension or congenital lobular emphysema
- Isolated form – good prognosis with spontaneous resolution with steroids

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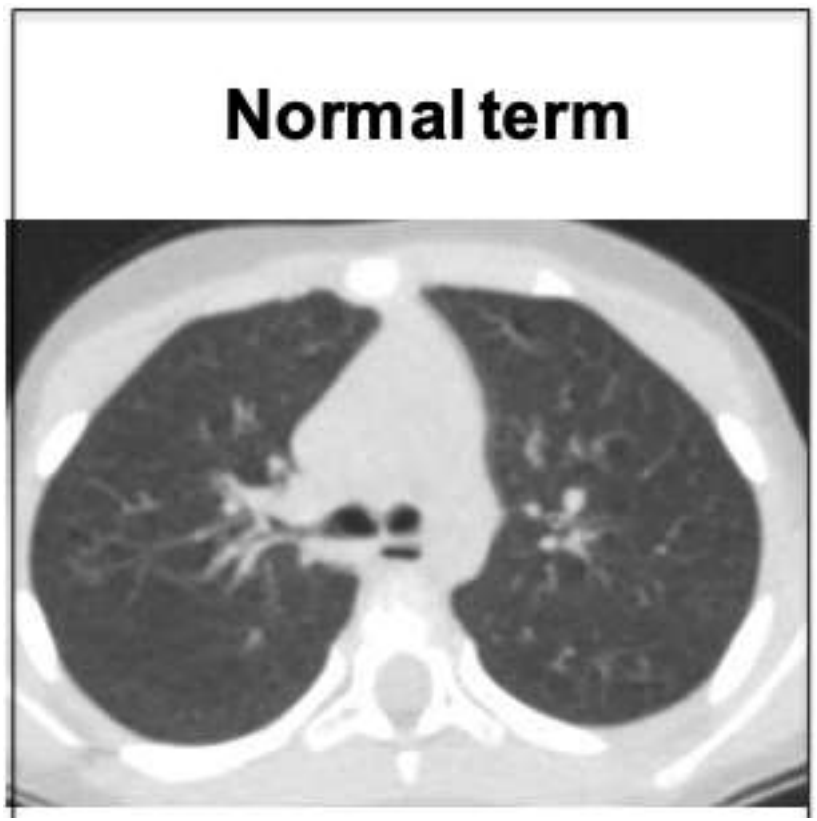

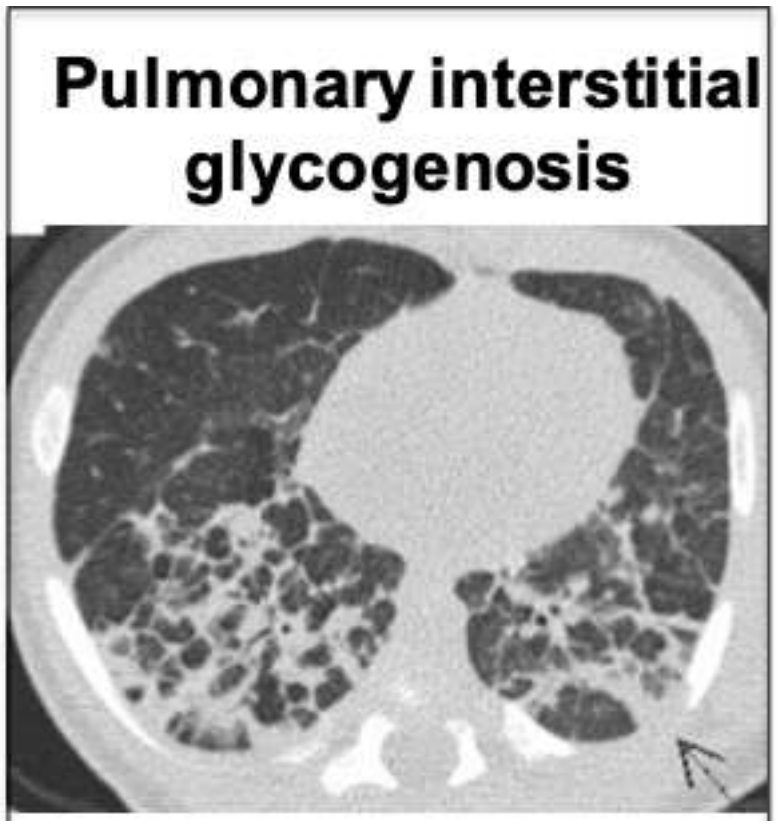

Canakis et al., Am J Respir Crit Care Med 2002
Deutschand Young, 2010

Isolated pulmonary interstitial glycogenosis associated with alveolar growth abnormalities: A long-term follow-up study

TABLE 1 Clinical characteristics, treatment, and follow-up of patients

	Sex	Birth weight (g)	Gestational age (wk; z-score)	Gestational age, wk	Age at presentation[a] first symptoms support treatment duration	Age at diagnosis, mo (y)	Treatment (time, mo)	Age at clinical resolution, y[d]	Follow-up time Weight; z-score Height; z-score
Case 1	Male	2420	34; +0.73	34	1 d Respiratory distress, tachypnea, hypoxemia MV 10 d, O_2 2 m	2 (2002)	Corticosteroids[a] (3) Hydroxychloroquine[b] (24)	2	15 y 56.4 kg; −0.44 163 cm; −0.87
Case 2	Female	3000	39; −0.50	39	1 d Respiratory distress, tachypnea pneumothorax, hypoxemia O_2 2 d	5 (2003)	Corticosteroids[b] (12) Hydroxychloroquine[c] (48)	3	13 y 42.4 kg; −0.76 163.2 cm; +1.05
Case 3	Female	3015	38; +0.09	38	1 d Respiratory distress, tachypnea pneumothorax, hypoxemia, failure to thrive MV 12 d, O_2 11 m	6.5 (2004)	Corticosteroids[b] (12) O_2 (11)	2.5	13 y 49.3 kg; −0.32 163.2; +0.67
Case 4	Female	3410	41; +0.15	41	11 d Respiratory distress, tachypnea, hypoxemia O_2 30 d	3.5 (2005)	Corticosteroids[b] (6)	0.8	12 y 60 kg; +1.88 155 cm; +0.84
Case 5	Male	2860	36; +0.63	36	3 d Respiratory distress, tachypnea, pneumothorax, hypoxemia O_2 14 h	6 (2005)	Hydroxychloroquine[c] (6)	1.3	12 y 33.8 kg; −0.77 145 cm; −0.07
Case 6	Male	2920	38; −0.57	38	3.5 m Respiratory distress, tachypnea, hypoxemia, failure to thrive O_2 29 m	5 (2007)	Corticosteroids[b] (12) Hydroxychloroquine[c] (6) O_2 (29)	3.8	10 y 27 kg; −0.83 136 cm; +0.18
Case 7	Male	3000	39; −0.76	39	1 m Tachypnea	9 (2008)	Corticosteroids[b] (6)	1.5	9 y 25.7 kg; −1.23 131.5 cm; −1.03
Case 8	Female	3790	39; +1.63	39	2.5 m Tachypnea	5 (2010)	Corticosteroids[b] (6)	1.5	7 y 25.3 kg; +0.46 123 cm; +0.72
Case 9	Female	1600	32; −0.12	32	1 d Respiratory distress, hypoxemia HFMV 14 d, O_2 21 m	4 (2012)	Corticosteroids[b] (6) Hydroxychloroquine[c] (6) O_2 (21)	3	5 y 17.1 kg; −0.86 110 cm; −0.66

Pediatr Pulmonol. 2019 Jun;54(6):837-846

TABLE 2 High-resolution computed tomography at diagnosis and follow-up

	Age	Ground glass pattern	Parenchymal bands	Septal thickening	Architectural distortion	Air trapping	Peripheral triangular opacities
Case 1	2 mo[a]	+++	+	++	+	++	+
	12 y[b]	–	++	+/–	+++	+	+/–
Case 2	4 mo[a]	++	++	++	+++	+++	+
	8 y[b]	–	+++	++	+++	+++	++
Case 3	5 mo[a]	+++	+	+	–	+	–
	6.5 y[b]	++	+	++	+	+	+
Case 4	2.5 mo[a]	+++	–	++	–	+	+
	8 y[b]	–	+/–	–	–	+/–	–
Case 5	4 mo[a]	++	+++	+/-	+++	+	++
	6.5 y[b]	++	++	+/-	++	+++	++
Case 6	3 mo[a]	++	–	+	+	++	–
	4.5 y[b]	+/-	–	+	–	–	–
Case 7	9 mo[a]	++	–	–	–	++	–
	7.5 y[b]	–	–	–	–	–	–
Case 8	5 mo[a]	++	++	+	++	++	+
	6 y[b]	+	+++	++	+++	+++	+++
Case 9	1 mo[a]	++	+	++	++	++	–
	3 y[b]	+	++	+	+	–	–

Pediatr Pulmonol. 2019 Jun;54(6):837-846

Persistent tachypnoea of infancy and neuroendocrine cell hyperplasia of infancy

- First year of life
- Persistent tachypnea and poor weight gain
- Radiology - ground-glass opacities confined to the middle lobe, lingula and para-mediastinal areas
- Histology - Increased numbers of bombesine -immunopositive pulmonary neuroendocrine cells
- Supplemental oxygen
- Nutritional support in some cases
- Spontaneous improvement

European Respiratory Review. 2022 Mar 31;31(163)
Am J Respir Crit Care Med. 2016 Feb 15;193(4):438-47

Long-term evolution of neuroendocrine cell hyperplasia of infancy: the FRENCHI findings

	All cohort	<2 years	2–6 years	7–12 years	13–18 years
Number of patients	54 (100%)	14 (26%)	27 (50%)	10 (18.5%)	3 (5.5%)
Male gender	34/54 (63%)	9 (64.3%)	17 (63%)	7 (70%)	1 (33.3%)
Clinically considered cured	15/54 (27.8%)	2 (14.3%)	8 (29.5%)	4 (40%)	1 (33.3%)
Respiratory exacerbation	35/54 (64.8%)	5 (35.7%)	21 (77.8)	7 (70%)	2 (66.6%)
Asthma diagnosis	20/54 (37%)	1 (7.1%)	12 (44.4%)	4 (40%)	3 (100%)
Sleep disorders	2/54 (3.7%)	0	0	1 (10%)	1 (33.3%)
Failure to thrive	12/23 (52.2%)	2 (14.3%)	7 (25.9%)	3 (30%)	0
Improvement of the CT scan findings	25/44 (56.8%)	4 (28.6%)	14 (51.8%)	6 (60%)	1 (33.3%)
Improvement of lung function tests	11/27 (40.7%)	—	5 (18.5%)	4 (40%)	2 (66.6%)
Oxygen therapy persistence	17/54 (31.5%)	9 (64.3%)	8 (29.5%)	0	0
Long-term azithromycin	23/54 (42.6%)	6 (42.8%)	12 (44.4%)	5 (50%)	0
Inhaled treatments	24/54 (44.4%)	6 (42.8%)	10 (37%)	6 (60%)	2 (66.6%)

European Journal of Pediatrics (2023) 182:949–956

Mutations with surfactant dysfunction (A4)

Surfactant Protein B deficiency

- Term infants
- Respiratory distress syndrome
- Incidence 1 per million
- Autosomal recessive
- CXR – diffuse haziness
- 100% mortality

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ATP-binding cassette member A-3 (*ABCA3*)

- Transmembrane protein on the limiting membrane of lamellar bodies
- Facilitates transport of lipids essential for surfactant production
- Recessive; 1 in 4,000 to 1 in 20,000

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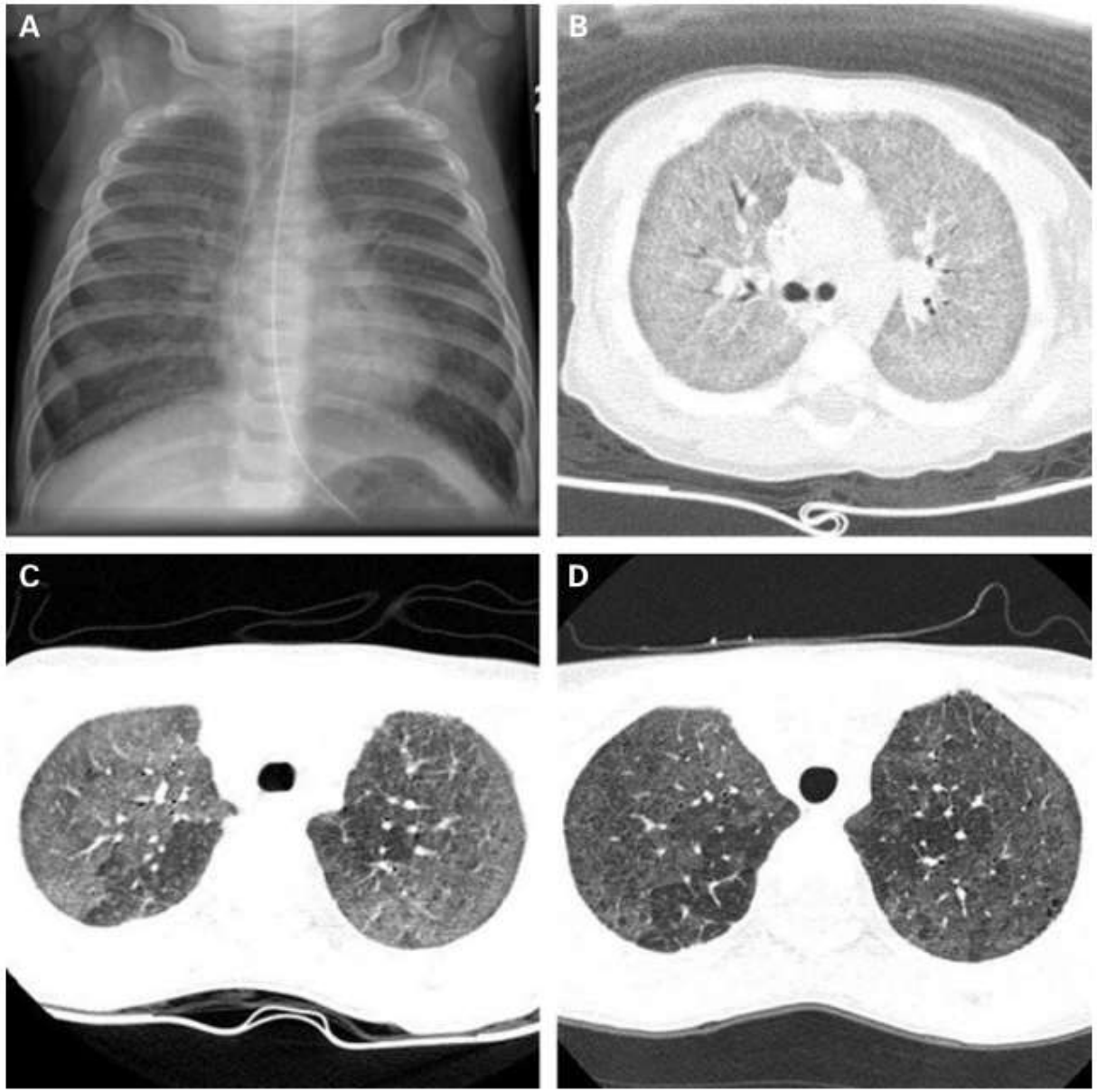

A – X ray AP view at 1 month
B – Ct chest at 1 month
C – CT chest at 5 yrs
D – CT chest at 9 yrs

Thorax. 2008 Apr;63(4):366-73

Surfactant Protein C deficiency

- 50% cases are autosomal dominant with variable penetrance
- 50% sporadic disease caused by a de novo single mutation
- Autosomal recessive pattern – respiratory distress syndrome at 3 – 6 months of age
- Large phenotypic heterogeneity, both in disease onset (infants to adults) and progression
- Autosomal dominant manifests as pulmonary fibrosis in children and adults

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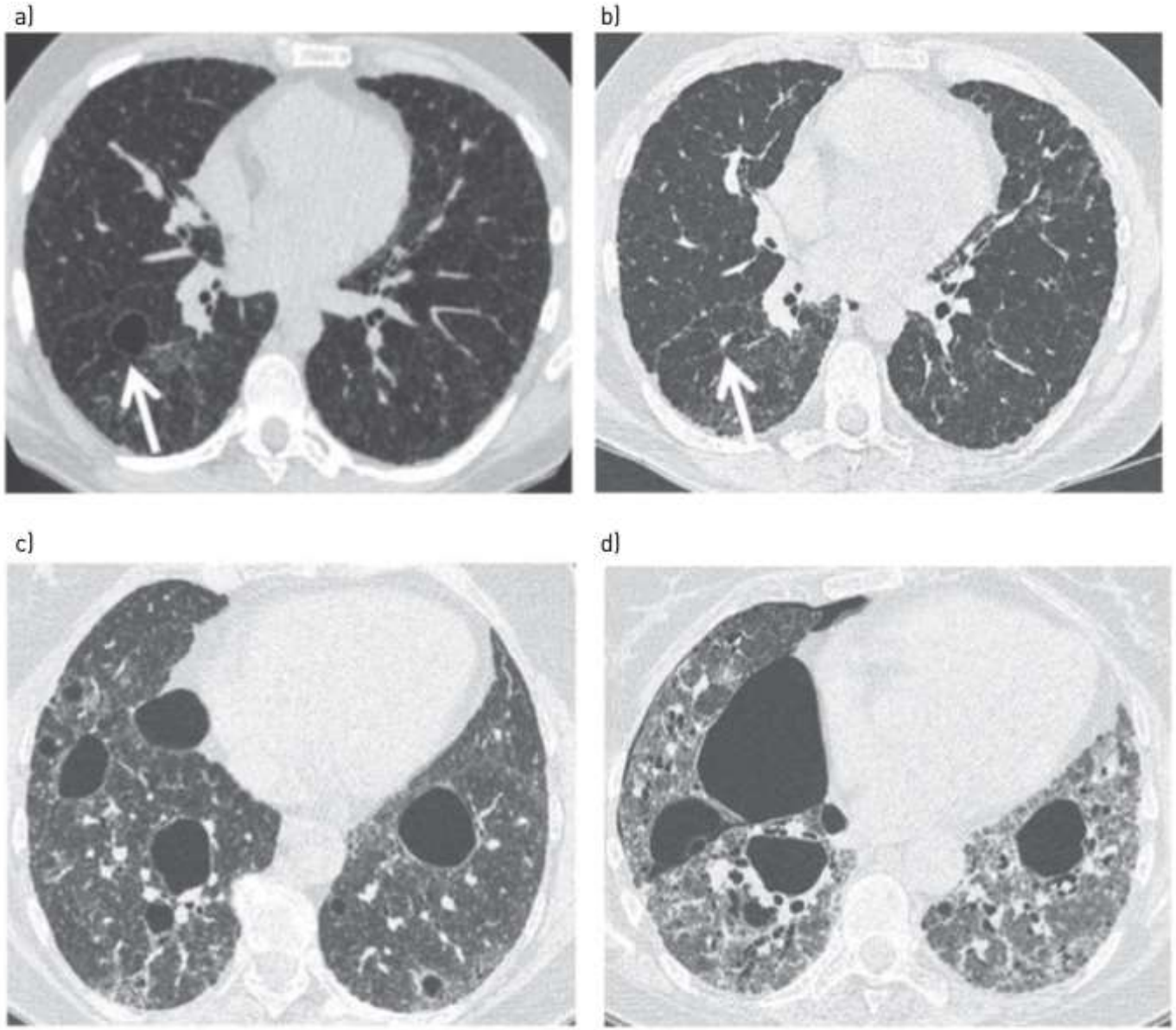

Thorax. 2008 Apr;63(4):366-73

Pulmonary alveolar proteinosis

- Intra-alveolar accumulation of surfactant, triggered by a disturbance of surfactant homeostasis with increased protein expression, reduced protein degradation or both
- Perinatal period - genetic alterations of SFTPB, SFTPC, ABCA3 or TTF1
- Older children - CSF2RA (GM-CSF receptor α), CSF2RB (GM-CSF receptor β) or OAS1 (2’-5’-oligoadenylate synthetase 1) mutations, haematological neoplasia, infections (cytomegalovirus, respiratory syncytial virus), GM-CSF autoantibodies and inhalation of inorganic dust

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ILD related to systemic disease processes (B1)

Storage diseases

- Neiman pick disease –Lysosomal disorder due to deficiency of alpha sphingomyelinase
- Accumulation of lipid laden macrophages, so called Niemann–Pick cells (NP cells) in various organs such as the liver, the spleen, the bone marrow, the central nervous system and also the lung
- Retrospective study of 13 patients with Neiman picks disease type B
- HRCT findings - smooth interlobular septal thickening (n = 13), ground-glass opacities (n = 13) intralobular lines (n = 12; 92.3%),a crazy- paving pattern (n = 5),and areas of air trapping (n = 1)

J Bras Pneumol. 2017 Nov Dec;43(6):451-455

Storage disease

- Ground-glass opacities focal in 10 patients (76.9%) and diffuse in 3 (23.1%)
- Pulmonary involvement bilateral in all of the 13 cases studied, predominantly affecting the lower lobes

J Bras Pneumol. 2017 Nov Dec;43(6):451-455

Neiman pick disease

Patients no.—gender	Type	Age at diagnosis	Respiratory symptoms at diagnosis	Organs involved at diagnosis	Duration of follow up (years)	Respiratory evolution
1—girl	A	2 months	Bronchiolitis	Lung, liver, spleen, CNS	3	Chronic respiratory insufficiency
2—girl	B	6 months	Bronchiolitis	Lung, liver, spleen	7	Stable COPD
3—boy	B	5 years	None	Lung, liver, spleen	4	Stable COPD
4—girl	B	1.5 years	Recurrent bronchitis	Lung, liver	21	Stable COPD
5—girl	B	4 years	Asthma	Lung, liver, spleen	10	Stable COPD
6—girl	B	9 years	None	Lung	1	Chronic cough
7—girl	B	11 months	Asthma	Lung, spleen	1.5	Chronic respiratory insufficiency
8—boy	B	19 months	Isolated dyspnea	Lung, liver, spleen	3	Stable COPD
9—boy	B	5 years	Asthma	Lung, liver, spleen	10	Stable COPD
10—boy	B	1.5 years	None	Liver, spleen	8	Chronic respiratory insufficiency
11—girl	B	3.5 years	Isolated dyspnea	Lung, liver, spleen	7	Chronic respiratory insufficiency
12—girl	C	5 months	Bronchiolitis with respiratory failure	Lung, liver, spleen, CNS	3	Death of respiratory failure
13—boy	C	4 months	Recurrent bronchitis	Lung, spleen, CNS	3	Chronic respiratory insufficiency

Pediatric Pulmonology 42:1207–1214 (2007)

Gaucher disease

- Prospective study – 13 patients (median age – 15yr)

Case No.	Sex/Age (*yr*)	Clinical Features	CXR Findings	HRCT Findings
1	M/1	Hepatosplenomegaly Fatal respiratory insufficiency	Diffuse interstitial and alveolar density	NP
2	M/5	Hepatosplenomegaly Recurrent respiratory infections	Bronchial thickening	Localized interstitial interlobular thickening Focal air trapping
3	F/2.5	Hepatosplenomegaly Recurrent respiratory infections	Diffuse Reticulonodular infiltrate	NP
4	M/15	Hepatosplenomegaly Partial splenectomy Scoliosis	Diffuse Reticulonodular infiltrate	Diffuse interstitial intralobular thickening; Interstitial nodules

Am J Respir Crit Care Med. 1998 Mar;157(3 Pt 1):985-9

ILD associated with exposure in the normal host (B2)

ILD – exposure to abnormal host

Hypersensitivity Pneumonitis	Obliterative bronchiolitis
• Children and adolescents	Adeno virus Mycoplasma infection Chronic aspiration
• Children less documented cases	
• Chemical lung disease by inorganic antigens less frequent than in adults	Chronic obstructive physiology
• Diagnosis – clinical history , radiology and transbronchial lung biopsy if required	CT – areas of mosaic attenuation

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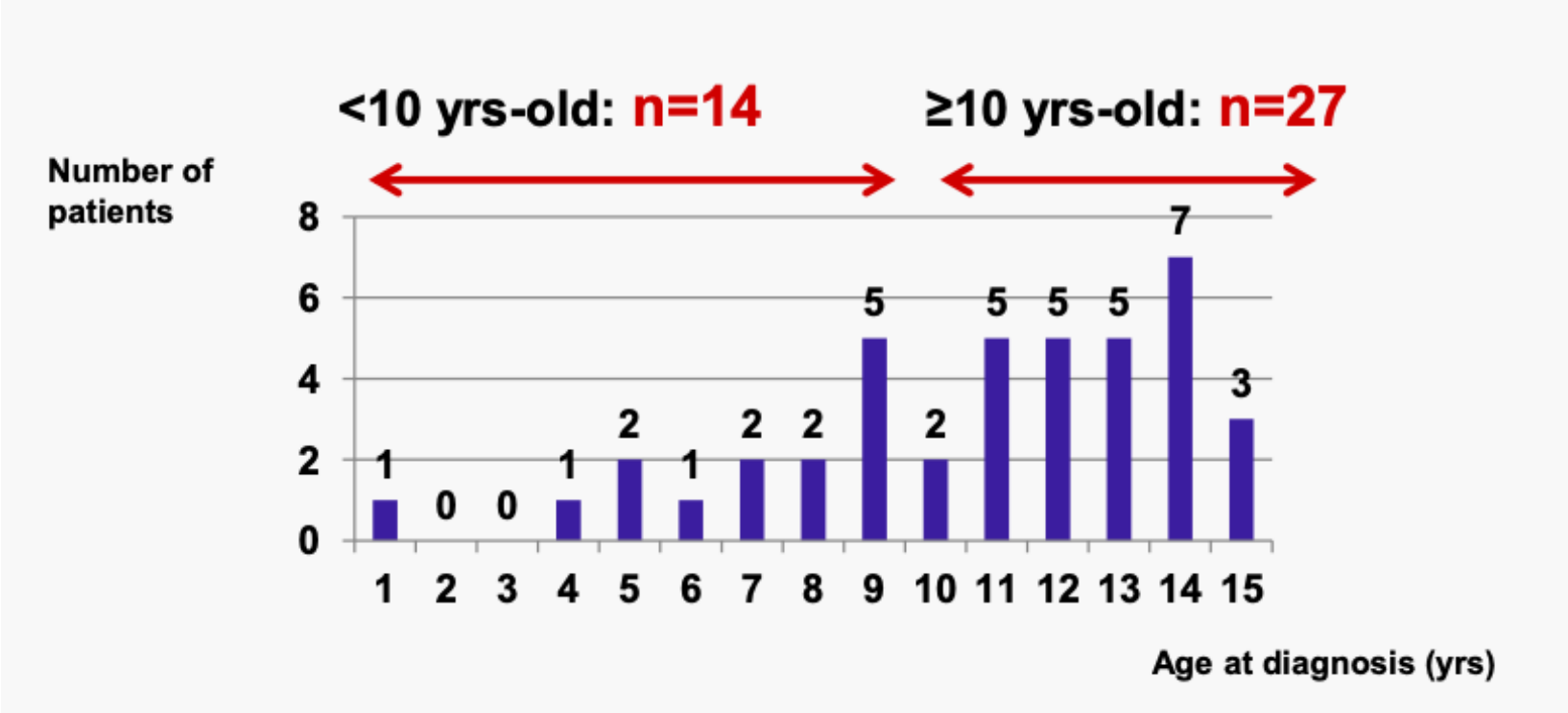
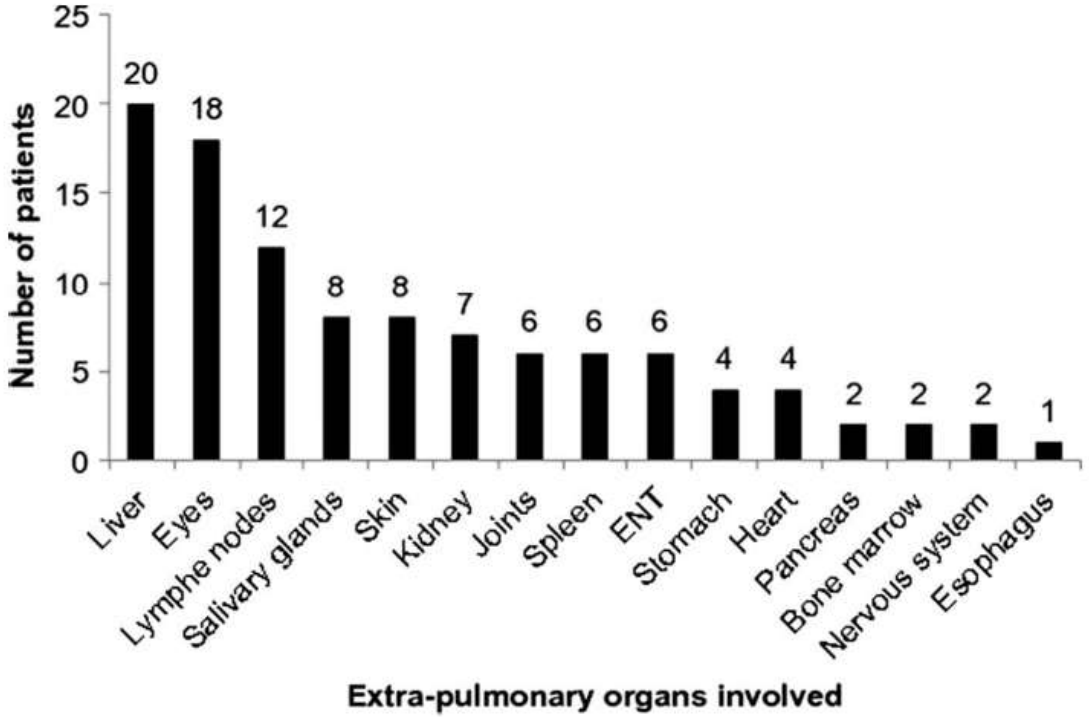
Sarcoidosis

- Study participants - 41 cases in National Reference Center for Rare Lung Diseases
- Median age at diagnosis: 11.8 yrs old

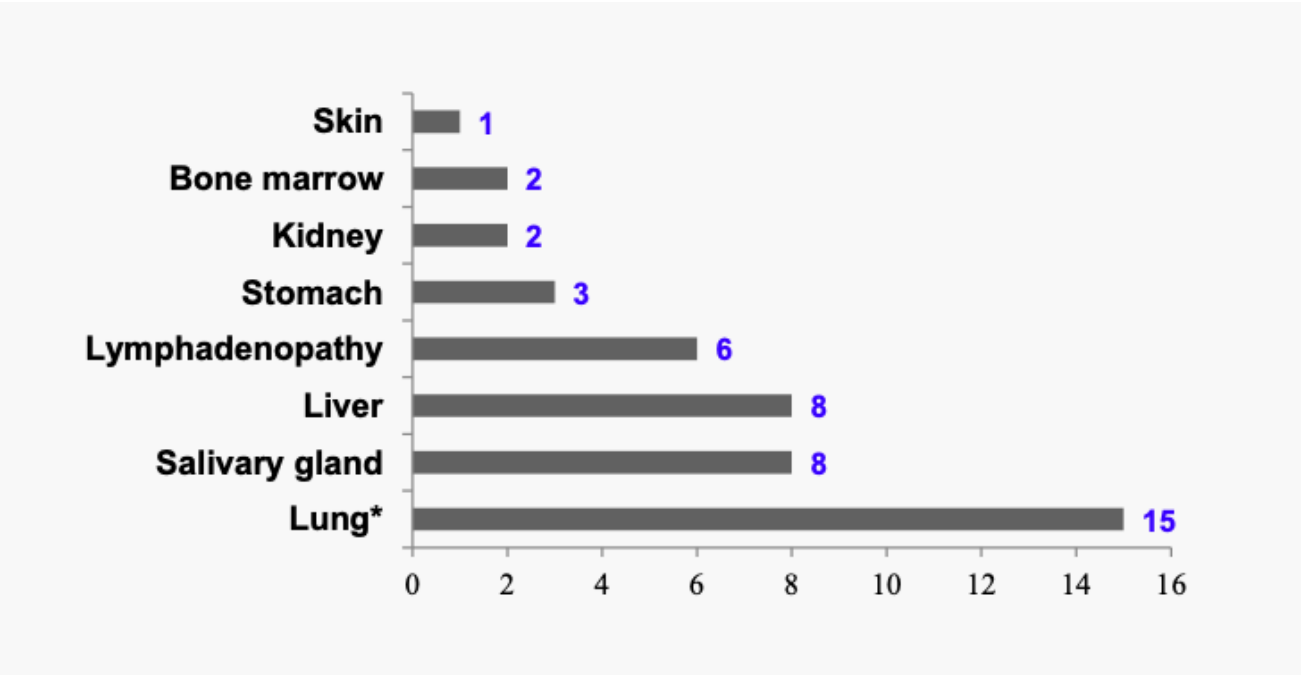


Nathan N, et al. Thorax 2015;70:537–542

Sarcoidosis



Sites of contributing biopsies



Nathan N, et al. Thorax 2015;70:537–542

Sarcoidosis

At 18 months followup

Age group and no. of patients	< 10 yrs (n= 14)	>10yrs (n=24)
Recovery	7 (50%)	7 (29%)
Stabilisation	3 (21%)	3 (13%)
Relapses	4 (29%)	14 (58%)

Nathan N, et al. Thorax 2015;70:537–542

Idiopathic pulmonary hemosiderosis

- 25 cases: National Reference Center for Rare Lung Diseases
- Median age at diagnosis: 4.3 yrs old
- Restrictive pattern (in 40%)
- Decreased DLCO (in 35%)
- CT chest - Bilateral abnormalities in most cases, with: Ground-glass opacities,sub pleural cysts and micronodules, thickened interlobular septa

Taytard J et al. Orphanet J Rare Dis 2013

Idiopathic pulmonary hemosiderosis

- Etiological hypotheses:
- Environmental, genetic, allergic, auto-immune
- Autoimmune assessment at diagnosis in the study population
-

	Positive (n)
Celiac disease Ig	4
Cow's milk allergy	3
ANCA	6
Anti nuclear antibodies	5
Anti smooth muscle antibodies	3
Rheumatoid factor	2
Anti ds DNA antibodies	1
Anti glomerular basal membrane	0

Taytard J et al. Orphanet J Rare Dis 2013

ILD – connective tissue disease

- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Juvenile Dermatomyositis (JDM)
- Juvenile Onset Systemic Sclerosis (Juvenile Scleroderma)
- Mixed Connective Tissue Disease (MCTD)

Indian J Pediatr(October 2015) 82(10):956–961

ILD of the immunocompromised host (B3)

Errors of immunity - acquired (AEI) or inborn (IEI)

- Remodelling - distal airways in the form of obliterative bronchiolitis may occur either post-infection or result from alloimmune reactions in stem cell or lung transplanted patients
- CVID, ILD is observed in 10–60% of patients
- Granulomatous-lymphocytic interstitial lung disease (GLILD) - combination of noncaseating granulomas and lymphoid proliferations, has been introduced as a characteristic pattern in these patients
- Enteropathy, coeliac disease, pernicious and haemolytic anaemia, thyroiditis, hepatitis, and arthritis
-

Front Immunol 2020; 11: 1950

Eur Respir Rev 2018; 27: 180019

Histopathology – Inborn error of immunity

- Noncaseating preferably intra-alveolar compact granulomas sometimes accompanied by plasma cells
- Lymphoid hyperplasia consisting of peribronchial lymphoid infiltrates with or without germinal centres, diffuse forms of lymphoid hyperplasia, nodular lymphoid hyperplasia, lymphocytic interstitial pneumonia or NSIP patterns
- Organising pneumonia pattern with and without accompanying granulomas
- Bronchiectasis associated with the presence of granulomas
- Interstitial fibrosis

Hum Pathol 2015; 46: 1306–1314

ILD with structural vascular changes (B4)

ILD with structural vascular changes (B4)

- Pulmonary veno occlusive disease
- Pulmonary capillary hemangiomatosis
- Mutations of EIF2AK4 (eukaryotic translation initiation factor 2α kinase 4) have been linked to disease genesis in sporadic and familial
- Pulmonary artery Hypertension – familial and sporadic

Genes involved in familial PAH

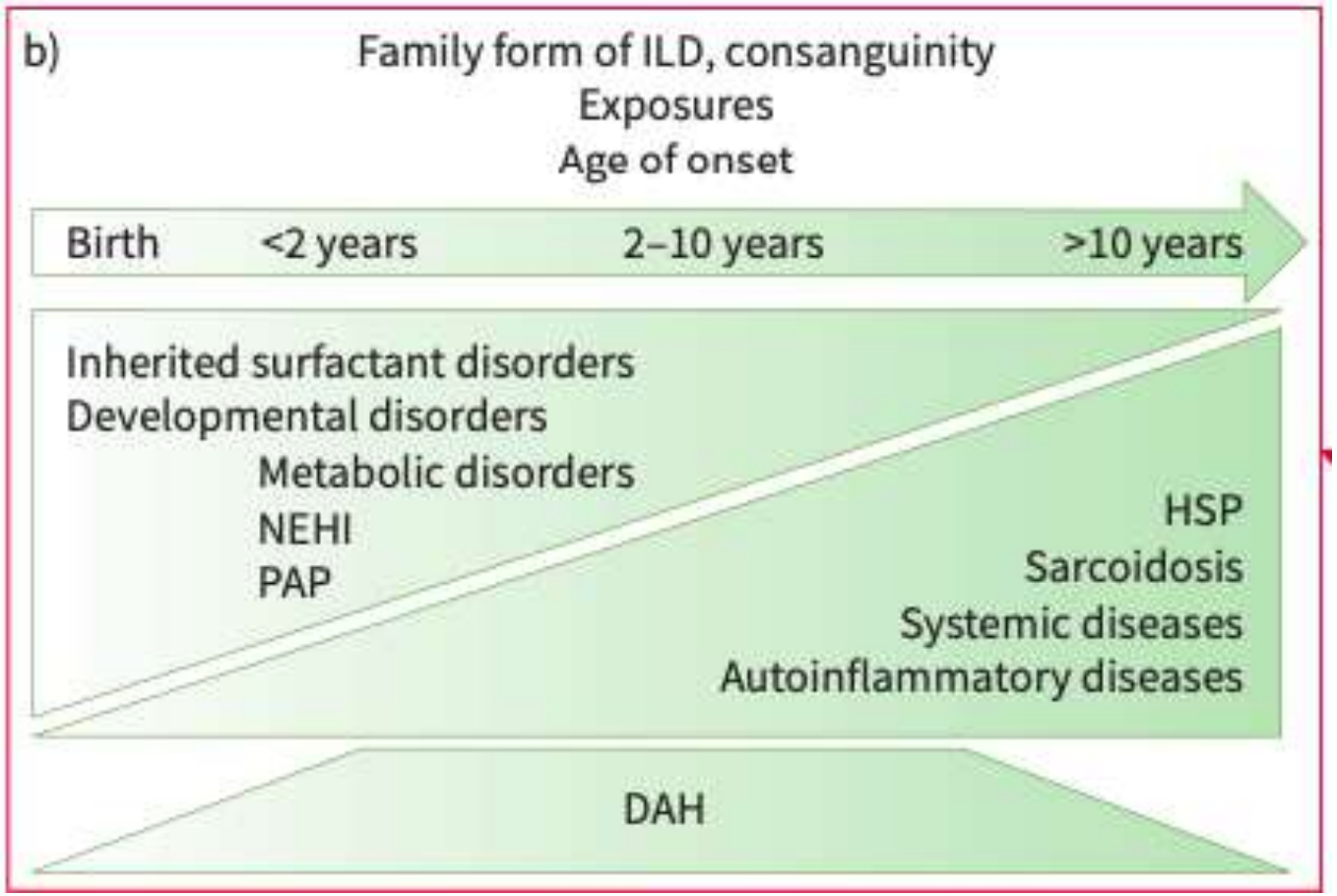
- ALK1 (activin A receptor like type kinase)
- BMPR2 (bone morphogenetic protein receptor type 2)
- TBX4 (T-box transcription factor)
- KCNK3 (potassium two pore domain channel subfamily k member)
- SMAD9 (SMAD family member 9)

Diagnostic workup of childhood interstitial lung disease

Diagnosis requires:

- Respiratory symptoms,
- Clinical signs of respiratory insufficiency,
- Hypoxaemia or low pulsed oxygen saturation a
- Diffuse parenchymal lung disease on chest radiography or thoracic computed tomography (CT) scan

- Medical history, family screening and careful clinical examination
- Consanguinity increase the risk of rare recessive homozygous disease (ABCA3, MARS/other ARS genes and SFTPB)
- Habits and living conditions can orientate one to chILD related to lung toxicity (e.g. drugs, medications and radiation) or hypersensitivity pneumonitis and other exposure-related diseases (e.g. birds, hay, mould and air conditioners)



Eur Respir Rev 2023; 32: 220188

TABLE 2 Biological investigations in childhood interstitial lung disease

Investigation	Indicates
Haematology	
Complete blood count	
Reticulocytes	Anaemia and/or diffuse alveolar haemorrhage
Haemostasis	Anaemia and/or diffuse alveolar haemorrhage
Biochemistry	
Serum electrolytes, creatinine	
Liver enzymes	Hepatomegaly and/or pulmonary alveolar proteinosis
Thyroxine, thyroid-stimulating hormone	Surfactant disorder (*NKX2-1*)
Serum protein electrophoresis, sedimentation rate	Autoinflammatory/inflammatory disorder
Angiotensin converting enzyme	Sarcoidosis
Iron, ferritin	Anaemia and/or diffuse alveolar haemorrhage and inflammatory syndrome
Calcium, ionised calcium, phosphorous	Sarcoidosis
Lactate dehydrogenase	Alveolar lung injury
Proteinuria	Autoinflammatory/inflammatory disorder
Calciuria	Sarcoidosis
Ammonaemia	
Chromatography of blood and urine amino acids	Metabolic disorder, *e.g.* lysinuric proteinuria
Chromatography of urinary organic acids	
Serologies	
Epstein–Barr virus serology and viral load	
Cytomegalovirus serology and viral load	If subacute, neonatal or immune deficiency
HIV-1/HIV-2 serology and viral load	*Pneumocystis jirovecii*, immune deficiency
Mycoplasma pneumoniae serology and nasopharyngeal PCR	Subacute
Chlamydia pneumoniae serology and nasopharyngeal PCR	Subacute
Chlamydia trachomatis serology and nasopharyngeal PCR	Subacute in newborns
Ureaplasma urealyticum serology and nasopharyngeal PCR	
IgG precipitins	Hypersensitivity pneumonitis, farmer's lung, bird fancier's lung

Eur Respir Rev 2023; 32: 220188

Immunology	
Post-vaccinal serologies	Immune deficiency
IgG, IgA, IgM and IgG subclasses	Immune deficiency, autoinflammatory/ inflammatory disorder
C3, C4, CH50	
Lymphocyte count/differential	
Circulating immune complexes	
Antinuclear antibodies	
ANCAc (PR3), ANCAp (MPO)	
Rheumatoid factor	
Anti-CCP	
Anti-cardiolipin	
Scleroderma, polymyositis and myositis antibodies (KU, PM-Scl75, TIF1γ, MDA-5, PM-Scl100, Ml2, KJ; anti-synthetase (PL7, PL12, OJ, centromere, SRP, JO1), smooth muscle, glomerular basement membrane)	Muscular, oesophageal and/or cutaneous involvement
GM-CSF auto-antibodies	Pulmonary alveolar proteinosis

Genetic tests

- Genetic cause is currently identified in ∼20% of patients with child
- Genetic analysis is recommended for all paediatric patients with chronic ILD, whether sporadic or familial with no identified cause
- Specialised genetics centres, and the detection of a genetic anomaly must always be explained to the patient and their family during genetic counselling consultation

TABLE 3 Main genes and proteins currently implicated in childhood interstitial lung disease (chILD) groups, their mode of transmission and the associated phenotypes

Gene (protein)	Inheritance pattern	Phenotypes
Inherited surfactant disorders		
SFTPA1, *SFTPA2*	AD	Very rarely chILD, adult ILD and adenocarcinoma of the lung
SFTPB	AR	Neonatal respiratory distress ± PH
SFTPC	AD	Neonatal respiratory distress; ILD in infants or children, adults
ABCA3	AR	Neonatal respiratory distress ± PH; ILD in infants or children, adults
NKX2-1	AD	Brain–lung–thyroid syndrome
PAP		
MARS	AR	PAP; hepatomegaly with cholestasis, anaemia, neurological impairment
CSF2RA, *CSF2RB*	GR and AR	PAP (infants, children, adults)
GATA2	AR	Secondary PAP; immune deficiency with myelodysplasia
Autoinflammatory disorders		
TMEM173	AD	Early chILD with autoimmune and inflammatory disease ± joint and skin involvement
COPA	AD	Early chILD or DAH with autoimmune and inflammatory disease ± joint and kidney involvement
ZNFX1		chILD with severe viral infections, neurological symptoms, thrombotic microangiopathy
OAS1	AD	PAP with immunodeficiency and autoinflammation
Other chILD		
FLNA	GA and GD	chILD with emphysema; cardiac abnormalities, neurological impairment; girls>boys
NHLRC2	AR	FINCA
Diffuse abnormalities of lung development		
FOXF1	AD	chILD with PH; alveolar capillary dysplasia ± misalignment of pulmonary veins
TBX4, *FGFR2*	AD and AR	chILD with PH; acinar dysplasia
EIF2AK4	AR	chILD with PH; pulmonary haemangiomatosis; veno-occlusive disease

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CT scan: in chILD diagnosis

TABLE 1 Childhood interstitial lung disease diagnostic assessment based on computed tomography scan pattern

Elementary lesions	Distribution	Suspected diagnoses
GGO	Dense, diffuse	Inherited surfactant disorders
GGO, peripheral traction cysts	Diffuse	Inherited surfactant disorders
GGO, peripheral and/or parenchymal traction cysts, traction bronchiectasis, reticulations		Inherited surfactant disorders (older age); autoinflammatory disorders
Diffuse (sometimes ill-defined centrilobular) nodules, diffuse GGO ± alveolar consolidation	Patchy	Diffuse alveolar haemorrhage
GGO, cysts, honeycombing and reticulations	Peripheral	Connective tissue diseases, systemic and autoimmune diseases
GGO	Paramediastinal, paracardial, middle lobe, lingula (usual); others (aberrant)	Persistent tachypnoea of infancy/ neuroendocrine cell hyperplasia of infancy
GGO and air trapping	Centrilobular	Hypersensitivity pneumonitis
Reversed halo sign		Organising pneumonia
Crazy paving	More intense in lower lobes	Pulmonary alveolar proteinosis
Micronodules, hilar lymphadenopathies	Lymphatic distribution	Sarcoidosis
Centrilobular nodules	Diffuse	Hypersensitivity pneumonitis

GGO: ground-glass opacities.

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Bronchoalveolar lavage

- Combination with radiology including hypersensitivity pneumonitis, pulmonary alveolar proteinosis, pulmonary haemorrhage and several infectious conditions such as Pneumocystis jirovecii infection

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Macrophagy	Cytology and staining	Main likely diagnoses
Bloody	Perls: haemosiderin-laden macrophages >30% or Golde score >50	DAH
Milky	Foamy macrophages, debris, extracellular PAS staining	PAP
Normal	Foamy macrophages, positive fat stain	Metabolic diseases, aspiration syndrome
	Lymphocytes >10%	Systemic diseases, autoinflammatory and autoimmune diseases, HSP (CD8>CD4), sarcoidosis (CD4>CD8)
	Neutrophils >5%	Infections

Pulmonary function test

- 6 min walk test
- Spirometry with DLCO

Cardiac ultrasound

- Search for pulmonary hypertension
- left-sided heart pathology (to eliminate a differential diagnosis)
- Search for cardiac involvement in the context of a general illness (search for pericarditis and associated heart malformation)

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Lung biopsy

- Lung biopsy is usually done as a surgical thoracoscopic or an open procedure depending on the centre's expertise and the child's age
- Indications for lung biopsy are currently declining with the progress of genetic diagnostics.
- Previously considered as the gold standard for chILD diagnosis, it now last line of investigation

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Undefined chILD?

- While these multiple investigations are still pending, chILD with no identified cause may be labelled as a “working diagnosis of undefined ILD”.
- However, when performed, a significant proportion of chILDs (up to 12%) still remain unclassified. only those should be labelled as “undefined chILD”.

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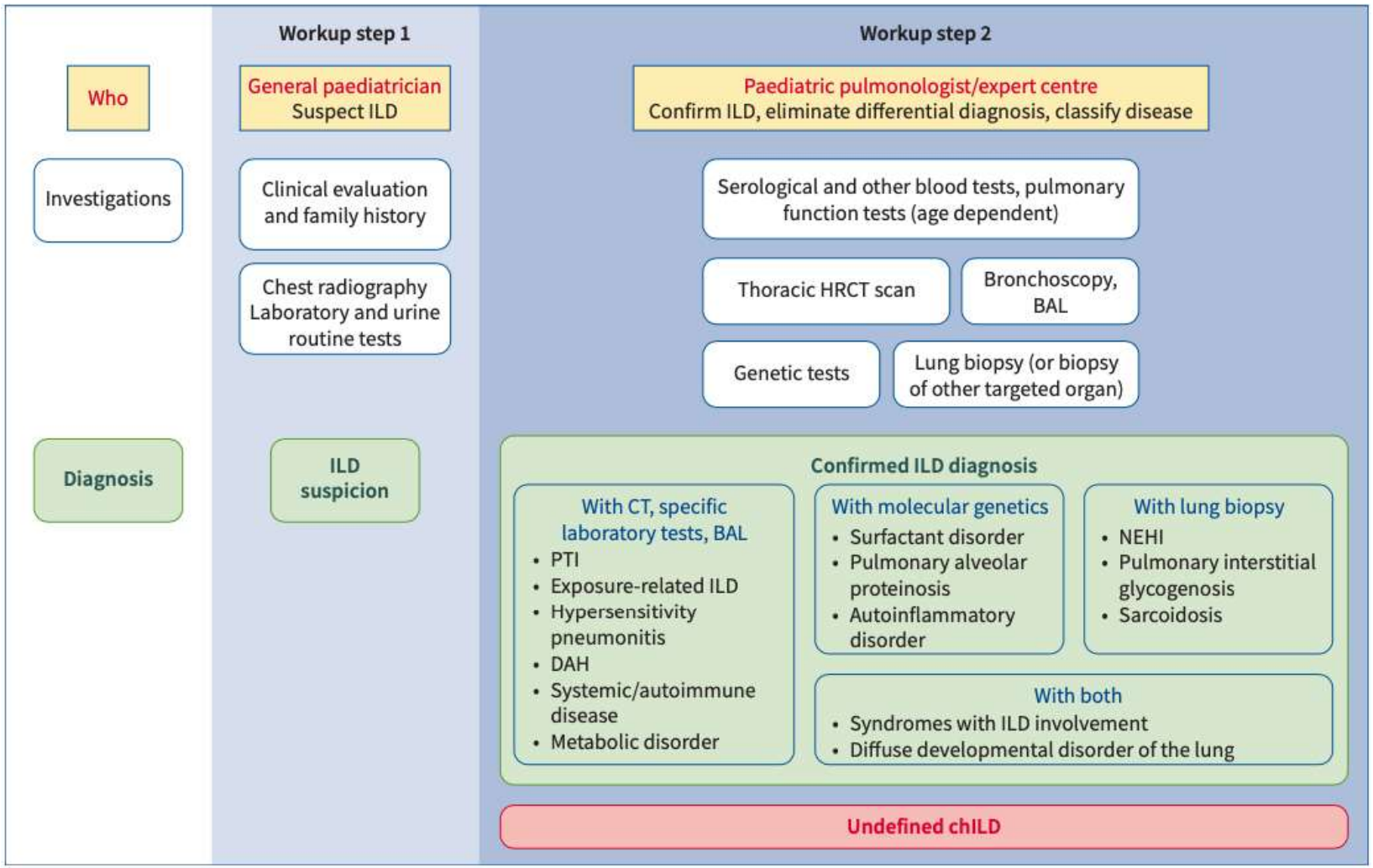

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Take home message

- chILDs - rare and heterogeneous diseases with significant morbidity and mortality
- The number of different chILD aetiologies is high and the diagnostic process requires a stepwise approach
- When facing a chILD suspicion - question about the family and medical history and to initiate investigations (routine laboratory tests and chest radiography) before referring the patient rapidly to a specialised centre

Take home message

- Specific investigations, including CT chest, laboratory tests, BAL, PFTs, genetic testing and eventually lung biopsy, are run in expert centres and their results are discussed during multidisciplinary team meetings
- This diagnostic workup, when complete, allows identification of a chILD aetiology in most cases
- The remaining patients meet the definition of “undefined chILD”
- As medical progress is rapid, this diagnosis must be regularly reassessed