Children's Interstitial Lung Disease ChILD

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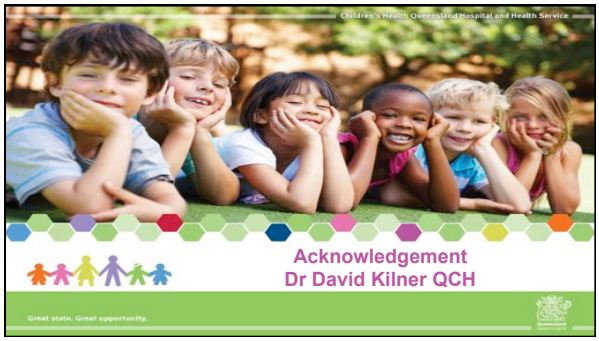
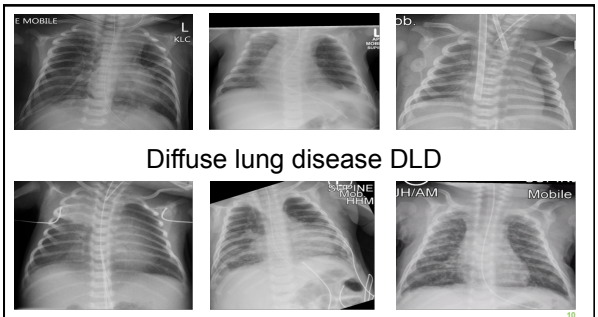


Acknowledgement
Dr David Kilner QCH

Children's Health Queensland Hospital and Health Service
Great state. Great opportunity.

Overview

- Present 6 cases
- Define chILD/diffuse lung disease
- Discuss the evolving classification of DLD in children
- Closer look at specific chILD syndromes occurring in infancy
- Review diagnostic and treatment pathways
- Treatment
- Prognosis



Diffuse lung disease DLD

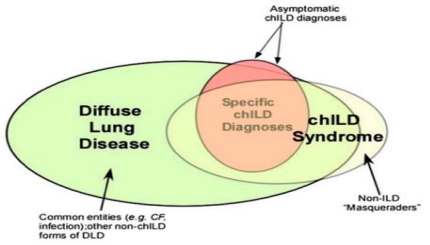
Defining interstitial lung disease in children (chILD)

- Recognition in the early 2000's that adult classification of ILD inadequate
- Not all conditions classified as ILD affect the interstitium
- DLD has become the preferred term
- chILD syndrome definition developed to describe child from the DLD group that needs closer evaluation

chILD syndrome

- The chILD syndrome exists when a child with DLD has had the common causes of DLD excluded as the primary diagnosis and has at least three of the following four criteria:
  - respiratory symptoms (e.g., cough, rapid and/or difficult breathing, or poor exercise intolerance)
  - respiratory signs (e.g., resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure)
  - hypoxaemia
  - diffuse abnormalities on CXR or a CT scan.
- This definition is sensitive for detecting the presence of a chILD disease, but its specificity has not been determined.

Kurland et al. Am J Resp Crit Care Med 2013;188:376–394



Kurland et al. Am J Respir Crit Care Med 2013;188:376–394

I. Disorders of infancy

- **A. Diffuse developmental disorders**
  1. Acinar/Alveolar Dysgenesis/Primary Pulmonary Hypoplasia
  2. Congenital Alveolar Dysplasia
  3. Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins
- **B. Growth abnormalities**
  1. Prenatal conditions: Secondary pulmonary hypoplasia from oligohydramnios, thoracic mass lesion, neuromuscular dysfunction, etc
  2. Post-natal conditions: chronic neonatal lung disease
     - *a) Prematurity related chronic lung disease*
     - *b) Term infants with chronic lung disease*
  3. Structural changes in chromosomal abnormalities
     - *a) Trisomy 21*
     - *b) Others*
  4. Associated with congenital heart disease in chromosomally normal children

Deutsch et al. Am J Respir Crit Care Med 2007;176:1120–1128
Fan et al. AnnalsATS 2015;12:1498-1505

I. Disorders of infancy

- **C. Specific conditions of unknown/poorly understood aetiology**
  1. Pulmonary Interstitial Glycogenosis
  2. Neuroendocrine Cell Hyperplasia of Infancy/persistent tachypnoea of infancy
- **D. Surfactant dysfunction disorders and related abnormalities**
  1. Surfactant dysfunction disorders
     - *a) Surfactant Protein B genetic mutations: pulmonary alveolar proteinosis*
     - *b) Surfactant Protein C genetic mutations: CPI>PAP, DIP, NSIP*
     - *c) ABCA3 genetic mutations: PAP>CPI, DIP, NSIP*
     - *d) NKX2.1 genetic mutations*
     - *e) Congenital GMCSF receptor deficiency: PAP*
     - *f) Others with histology consistent with surfactant dysfunction disorder without a recognized genetic disorder**
  2. Lysinuric protein intolerance: PAP histologic pattern

Deutsch et al. Am J Respir Crit Care Med 2007;176:1120–1128
Fan et al. AnnalsATS 2015;12:1498-1505

II. Disorders of the immunocompetent

- **A. Infections and post-infectious processes**
  1. Chronic airway changes with and without preceding history of viral respiratory infection
  2. Organizing pneumonia (formerly bronchiolitis obliterans/organizing pneumonia)
  3. Specific infections identified
     - *a) Bacterial*
     - *b) Fungal*
     - *c) Mycobacterial*
     - *d) Viral*
- **B. Disorders related to environmental agents**
  1. Hypersensitivity pneumonitis
  2. Toxic inhalation
- **C. Aspiration syndromes**
- **D. Eosinophilic pneumonias**
- **E. Acute interstitial pneumonia/Hamman-Rich syndrome/ Idiopathic diffuse alveolar damage**
- **F. Nonspecific interstitial pneumonia**
- **G. Idiopathic pulmonary hemosiderosis**
- **H. Others**

Deutsch et al. Am J Respir Crit Care Med 2007;176:1120–1128
Fan et al. AnnalsATS 2015;12:1498-1505

III. Disorders related to systemic diseases

- **A. Immune-mediated disorders**
  1. Specific pulmonary manifestations
     - *a) Goodpasture syndrome*
     - *b) Acquired pulmonary alveolar proteinosis/autoantibody to GMCSF*
     - *c) Pulmonary vasculitis syndromes*
  2. Nonspecific pulmonary manifestations
     - *a) Nonspecific interstitial pneumonia*
     - *b) Pulmonary haemorrhage syndromes*
     - *c) Lymphoproliferative disease*
     - *d) Organizing pneumonia*
     - *e) Nonspecific airway changes including lymphocytic bronchiolitis, lymphoid hyperplasia, and mild constrictive changes*
  3. Other manifestations of collagen-vascular disease
- **B. Storage disease**
- **C. Sarcoidosis**
- **D. Langerhans Cell Histiocytosis**
- **E. Malignant infiltrates**
- **F. Others**

Deutsch et al. Am J Respir Crit Care Med 2007;176:1120–1128
Fan et al. AnnalsATS 2015;12:1498-1505

IV. Disorders of the immunocompromised host

- **A. Opportunistic infections**
  1. Pneumocystic jiroveci
  2. Fungal/yeast
  3. Bacterial
  4. Mycobacterial
  5. Viral
  6. Suspected infection
- **B. Disorders related to therapeutic intervention**
  1. Chemotherapeutic drug injury
  2. Radiation injury
  3. Combined
  4. Drug hypersensitivity
- **C. Disorders related to solid organ, lung, and bone marrow transplantation and rejection syndromes**
  1. Rejection
  2. Graft versus host disease
  3. Post-transplant lymphoproliferative disorder
- **D. Diffuse alveolar damage of undetermined aetiology**
- **E. Lymphoid infiltrates related to immune compromise (non-transplanted patients)**
  1. Nonspecific lymphoproliferation
  2. With lymphoid hyperplasia
  3. With poorly formed granulomas
  4. Malignant

Fan et al. AnnalsATS 2015;12:1498-1505

V. Vascular disorders masquerading as ILD

A. Arterial hypertensive vasculopathy
B. Congestive vasculopathy and veno-occlusive disease
C. Lymphatic disorders
   1. Lymphangiectasis
   2. Lymphangiomatosis
D. Pulmonary oedema
E. Thromboembolic disease

VI. Unclassified

A. End-stage disease
B. Non-diagnostic
C. Inadequate tissue
D. Insufficient information

Deutsch et al. Am J Respir Crit Care Med 2007;176:1120–1128
Fan et al. AnnalsATS 2015;12:1498-1505

Diffuse Lung Disease in Young Children
Application of a Novel Classification Scheme

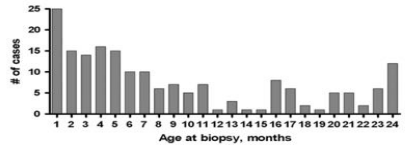
Deutsch et al. Am J Respir Crit Care Med 2007;176:1120–1128

Diffuse Lung Disease in Biopsied Children 2 to 18 Years of Age
Application of the chILD Classification Scheme

Fan et al. AnnalsATS 2015;12:1498-1505

Deterding. AnnalsATS 2015;12:1451-1457

Diffuse Lung Disease in Young Children
Application of a Novel Classification Scheme



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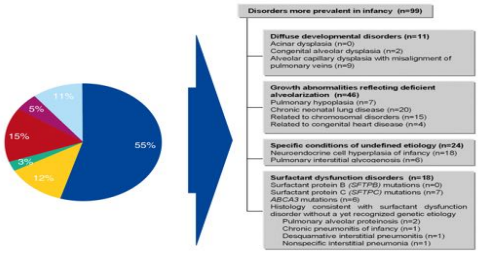


Deterding. AnnalsATS 2015;12:1451-1457
Deutsch et al. Am J Respir Crit Care Med 2007;176:1120–1128

Disorders more prevalent in infancy – Diffuse developmental disorders

- Alveolar capillary dysplasia with misalignment of the pulmonary veins – most common
- Due to mutation in the FOXF1 gene
- Term infant (90%), PPHN with onset of cyanosis and respiratory failure within 48 hours of birth
- Later on in presentation – severe PHT refractory to therapy, high mortality
- Minimal or no parenchymal disease
- Extrapulmonary findings in 50-80% - GUT (PUJ obstruction with hydronephrosis), GIT (malrotation, TOF, anal atresia), CVS (HLHS, PDA, ASD)
- CXR – diffuse haziness, GGO, normal
- Confirm diagnosis on histology, ante/post mortem

Bishop et al. AJRCCM 2011;184:172-179

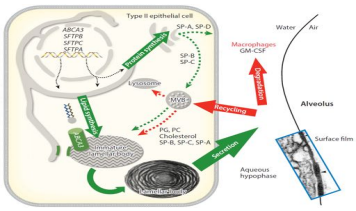
Surfactant dysfunction disorders Presentation

Box 1 When to consider investigation for surfactant protein dysfunction syndromes (SPDS)

- Term neonates (>36 weeks gestation) with respiratory distress that is unexplained, rapidly progressive or not responding to conventional treatments.
- Infants and children with chronic respiratory symptoms or failure to thrive, with a positive family history of SPDS, unexplained respiratory symptoms earlier in life or parental consanguinity.
- Children with chronic interstitial lung disease or lung function testing demonstrating a restrictive lung disease without a clear aetiology.
- Children with high-resolution CT scan showing diffuse disease affecting the entire lung.
- Children with histopathological findings of alveolar proteinosis or abnormal or absent lamellar bodies on electron microscopy.

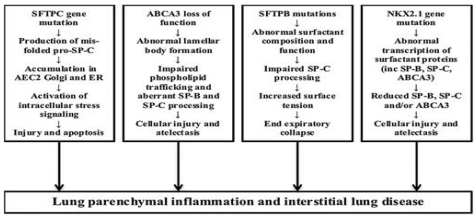
Gupta and Zheng. Arch Dis Child 2017;102:84–90

Surfactant dysfunction disorders
Surfactant physiology



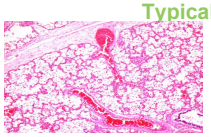
Whitsett et al. Annu Rev Pathol Mech Dis 2015;10:371-393

Surfactant dysfunction disorders
Pathophysiology

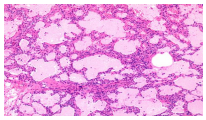


Gupta and Zheng. Arch Dis Child 2017;102:84–90

Surfactant dysfunction disorders
Typical biopsy findings



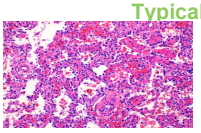
Normal lung
- Terminal bronchiole (bottom right), alveolar ducts and alveoli within a lung lobule bounded by an inter-lobular septum
- Artery accompanying the bronchiole, vein lies separately in the inter-lobular septum
- Thin alveolar septae

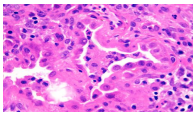


PAP occurring in surfactant protein B deficiency
- Interstitial thickening, with large amounts of granular, proteinaceous debris within alveolar spaces
- Little type II pneumocyte hyperplasia evident

Armes et al. J Clin Pathol 2015;68:100–110

Surfactant dysfunction disorders
Typical biopsy findings



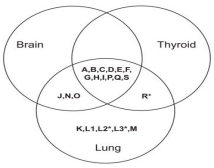


Chronic pneumonitis of infancy with known surfactant protein C deficiency

- Diffuse interstitial thickening and type II pneumocyte hyperplasia without significant alveolar proteinosis or desquamative pneumonia
- Higher power, type II pneumocyte hyperplasia present with thickened interstitium containing scattered chronic inflammatory cells

Armes et al. J Clin Pathol 2015;68:100–110

NKX2.1 (TTF) mutation



Hamvas et al. Chest 2013;144:794-804

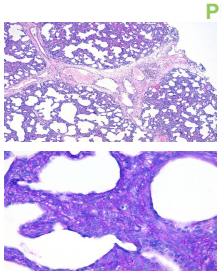
- 16 heterozygous missense, nonsense, frameshift mutations
- 5 whole gene deletions
- 76% neonatal RDS presentation
- 19% chILD, 1 adult with pulmonary fibrosis
- Brain involvement included
  - Chorea
  - Ataxia
  - Psychomotor delay
  - Hypotonia
- Hypothyroidism
- 57% had full BLT syndrome
- Heterogenous pulmonary histology as well as alveolar simplification

Specific conditions of unknown/poorly understood aetiology
Pulmonary interstitial glycogenosis

- Neonatal distress in late pre-term/term infants
- Often have co-morbid CNLD, pulmonary hypertension +/- CHD (62%) – ASD, VSD, PDA, HLHS, TOF, coarct aorta, PVS, MS
- HRCT – GGO – diffuse to scattered, cystic lucencies, septal thickening
- Diffuse in younger infants, often patchy in older infants
- Disorder related to lung development, abnormal cells identified as lipofibroblasts found in the alveolar wall of rats, may be involved with septation in humans

Weinman et al. Pediatric Radiology 2018;48:1066–1072
Liptzin et al. Pediatric Pulmonology 2018;1-8
Deutsch and Young. AJRCCM 2016;193:694-696

PIG histology



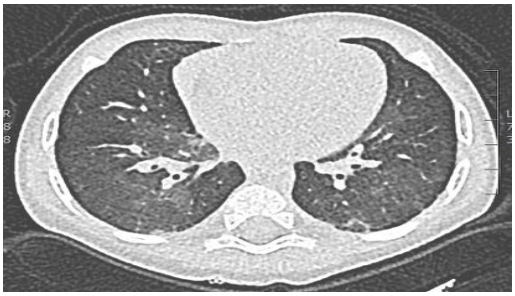
- Diffuse enlargement and simplification of alveolar spaces
- Interstitium thickened with oedema of the interlobular septum, with distension of the veins and lymphatics
- Thick alveolar septae due to oval and spindle cells with cytoplasmic glycogen demonstrated by periodic acid Schiff
- No inflammatory cell infiltrate

Armes et al. J Clin Pathol 2015;68:100–110 32

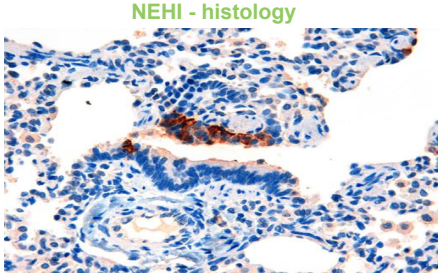
Specific conditions of unknown/poorly understood aetiology
NEHI

- Present at birth or early infancy with tachypnoea, retractions, crackles, hypoxia and FTT
- Obstructive pattern on iLFT
- Ground-glass opacification - most common finding, involved the right middle lobe and lingula more frequently
- Air trapping with a mosaic pattern second most common finding
- Most resolve within 1-2 years

O'Connor et al. AnnalsATS 2015;12:1730-1732
Calheiros et al. J Bras Pneumol 2013;39:569-578
Lukkarinen et al. Arch Dis Child 2013;98:141–144 33



NEHI - histology



An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy

Geoffrey Kurland, Robin R. Deterding, James S. Hagood, Lisa R. Young, Alan S. Brody, Robert G. Castile, Sharon Dell, Leland L. Fan, Aaron Hamvas, Bettina C. Hilman, Claire Langston, Lawrence M. Nogee, and Gregory J. Redding; on behalf of the American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network

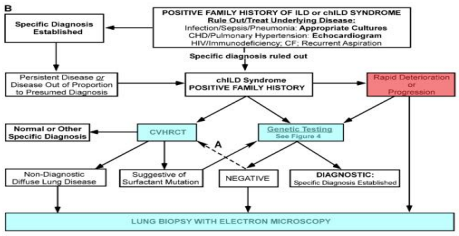
Kurland et al. Am J Respir Crit Care Med 2013;188:376–394

European protocols for the diagnosis and initial treatment of interstitial lung disease in children

Andrew Bush,[1] Steve Cunningham,[2] Jacques de Blic,[3,4] Angelo Barbato,[5] Annick Clement,[6] Ralph Epaud,[7] Meike Hengst,[8] Nural Kiper,[9] Andrew G Nicholson,[10] Martin Wetzke,[11] Deborah Snijders,[5] Nicolaus Schwerk,[12] Matthias Griese,[13] on behalf of the chILD-EU collaboration

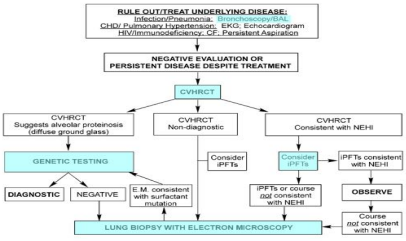
Bush et al. Thorax 2015;70:1078–1084

Neonatal respiratory distress syndrome



Kurland et al. Am J Respir Crit Care Med 2013;188:376–394 37

General diagnostic approach – persistent/chronic symptoms in a child over 1 month



Kurland et al. Am J Respir Crit Care Med 2013;188:376–394

Investigation – Bronchoscopy with BAL

- Exclude infection – fluid sent for bacterial, fungal, mycobacterial culture, viral PCR
- Cell differential – may detect eosinophils
- PAP – milky return
- Stain for lipid/haemosiderin laden macrophages, raised CD4/CD8 ratio in sarcoidosis, CD1a-positive cells in LCH
- Requires a general anaesthetic, as does HRCT, so often done under the same GA

Bush et al. Thorax 2015;70:1078–1084
Kurland et al. Am J Respir Crit Care Med 2013;188:376–394

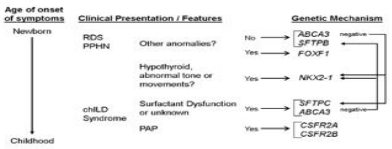
Investigation - HRCT

- Diagnostic in NEHI
- May avoid need for biopsy
- Direct surgeons to optimal site for biopsy
- Requires general anaesthetic in children less than 4-5 years of age
- Performed in centres aware of appropriate radiation dosing used for HRCT in children
- Controlled ventilation HRCT – reduces motion artefact, posterior atelectasis and allows for expiratory views – assess air-trapping

Bush et al. Thorax 2015;70:1078–1084
Kurland et al. Am J Respir Crit Care Med 2013;188:376–394

Investigations - Genetic Testing

- Obviate need for invasive lung biopsy, prognostic information,
- May inform families of appropriate expectations of therapy and goals
- Genetic counselling for future pregnancies



Kurland et al. Am J Respir Crit Care Med 2013;188:376–394

ORIGINAL ARTICLE

Genotype–Phenotype Correlations for Infants and Children with ABCA3 Deficiency

Jennifer A. Wambach[1,2], Alicia M. Casey[2], Martha P. Fishman[2], Daniel J. Wegner[1], Susan E. Wert[3], F. Sessions Cole[1], Aaron Hamvas[1,2], and Lawrence M. Nogee[2]

[1]Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri; [2]Department of Pediatrics, Division of Neonatology, Perinatal and Pulmonary Biology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; [3]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and [4]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland

Null mutation - frameshift and nonsense mutations – no functional protein
Other mutation - missense, predicted splice site mutations, insertion/deletions

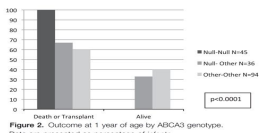


Figure 2. Outcome at 1 year of age by ABCA3 genotype. Data are presented as percentage of infants.

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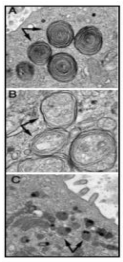
Investigation - biopsy

- May be diagnostic, ***often not***
- Exclude other diagnoses - infection
- Prognosticate – PIG/NEHI
- VATS preferred, lower morbidity
- May be used to guide withdrawal of care or early referral to transplant, e.g., ACDMPV
- Important to send for EM ABCA3



Gower et al. NeoReviews 2008;9:e458-466

Management

- Supportive care
  - Respiratory support – oxygen via nasal prongs, ventilation – invasive/ non-invasive
  - Nutritional support – consider gastrostomy if required long-term and NGT fed
  - Routine vaccinations, flu vaccine, Synagis
  - Early treatment of respiratory exacerbations
  - Symptom care in those with progressive respiratory failure

Bush et al. Thorax 2015;70:1078–1084

Management

- Pharmacotherapy
  - Steroids (not NEHI)
    - Intravenous methylprednisolone (10-30 mg/kg for 3 days), pulse monthly for 6 months; assess response within 7 days in ventilated, 28 days if not
    - Oral prednisolone 1mg/kg daily in between pulses in children who are ventilated
    - Oral prednisolone - alternative to methylprednisolone in children who are not ventilated
  - Hydroxychloroquine 10 mg/kg daily (6.5 mg/kg if less than 6); assess response in 3-4 weeks in children ventilated, 3 months in children who are not ventilated
  - Azithromycin 10 mg/kg 3 times a week; assess response within 3 months
  - PPHN mgmt

Bush et al. Thorax 2015;70:1078–1084

Management of children with interstitial lung diseases: the difficult issue of acute exacerbations

Annick Clement[1], Jacques de Blic[2], Ralph Epaud[3], Laurie Galeron[1], Nadia Nathan[1], Alice Hadchouel[2], Angelo Barbato[4], Deborah Snijders[4], Nural Kiper[5], Steve Cunningham[6], Matthias Griese[7], Andrew Bush[8] and Nicolaus Schwerk[7] on behalf of the chILD-EU collaboration

Final list of acute exacerbation criteria

1. Increase in respiratory rate ⩾20% from baseline
2. Increase or development in/of dyspnoea
3. Newly developing or increased abnormalities on chest imaging
4. Onset/increase of/in oxygen demand to attain the individual baseline saturation [at rest and/or during exercise]
5. Need for an additional level of ventilatory support (in addition to oxygen)
6. Decrease in spirometry in children able to perform the tests [⩾10% from baseline for vital capacity]
7. Reduced exercise tolerance in children able to perform the test#

Clement et al. Eur Respir J 2016;48:1559–1563

Summary

- DLD in children is an assortment of rare disorders, together affect a significant number of children
- Very likely to present to regional centres initially
- Maintain a high index of suspicion
  - neonatal RDS/PPHN in term infants
  - unexplained DLD, particularly if radiologic changes are persistent
  - children presenting with clinical and radiological findings out of keeping with the usual causes of DLD
- Affected children are probably best managed in a centre experienced in the management of chILD, early contact with tertiary centre