



## British Paediatric Orphan Lung Diseases (BPOLD)

### Name of Disease:

Interstitial lung disease in children (chILD). This comprises a huge number of diseases, which have recently been reviewed in detail, see [<Link to AB chapter>](#)

### Clinician:

Professor Andrew Bush MD FRCP FRCPC  
Professor of Paediatric Respiriology at Imperial College and Consultant Paediatric Chest Physician at Royal Brompton Hospital, London, UK

### Clinical details:

#### Definition

#### Clinical Presentations

This is very non-specific. Unsurprisingly, in young children in the biggest series in the literature [Am J Respir Crit Care Med. 2007; 176: 1120-8] there was a high incidence of prematurity and neonatal onset of symptoms (28% preterm, 38% intubated at birth, 57% needing oxygen). 58% were male, and 34% had a family history of lung disease. 30% were biopsied by 3 months of age 52% by 6 months, and 72% in the first year of life. Presenting features (descending order of frequency, more than one permitted per child) were hypoxaemia, tachypnoea, retractions, gastro-oesophageal reflux, pulmonary hypertension, failure to thrive, crackles, cough and wheeze (surprisingly, approximately 20%). 25% had no abnormal auscultatory findings. The network has defined 'chILD syndrome' [Am J Respir Crit Care Med 2005; 172: 940-1] to try to refine referrals for more detailed work up for ILD. This requires at least three of the following criteria in the absence of any other aetiology as the primary cause: (1) symptoms of impaired respiratory function, (2) hypoxemia, (3) diffuse infiltrates, (4) presence of adventitious sounds (crackles), and (5) abnormal lung function. It should be noted that although this is a good guide to the presence of ILD, it cannot replace clinical judgement, and over-reliance on the index may lead to false negatives and positives. There is less information to guide diagnostic awareness in older children. chILD can be a great mimic, and the possibility should at least be considered in any puzzling respiratory problem in childhood.

[Evidence gap: there is a need for standardised protocols to gather clinical data](#)

#### Causes

#### Diagnosis and investigations

**Stepwise approach to investigation:** This is summarised in Table 1. Not all tests are required on all children, and an individualised program is essential.

#### **Table 1: Staged work up of ILD in Childhood**

1. Confirm presence of chILD – HRCT (rarely gives a specific diagnosis)
2. Assess and score severity
  - Symptoms
  - Overnight saturation study
  - Echocardiogram
  - (Pulmonary function tests at least in the older child)
3. Determine aetiology
  - Blood tests
  - Consider bronchoscopy
  - Lung biopsy (usually VATS or mini-thoracotomy rather than transbronchial or transthoracic needle biopsy)
4. Look for aspiration as a co-morbidity
  - pH probe for reflux
  - Assessment of swallow
  - Consider need to exclude H-type fistula and laryngeal cleft

**Role of HRCT** Firstly to confirm that the child does have chILD with HRCT. HRCT may also allow specific diagnoses to be made, which include hypersensitivity pneumonitis, adult-type Langerhans' cell histiocytosis, pulmonary hemorrhage, idiopathic alveolar microlithiasis [AJR 2000; 174: 549-554; AJR 2008; 191: 914-20]. and NEHI [Pediatr Radiol. 2006; 36: 1328]. For most chILD patients, CT is not diagnostic.

➤ Evidence gap: there is a need for standardised HRCT protocols to allow between centre comparisons, and reporting by a panel of expert radiologists

**Assessment of Disease Severity** A five point severity score has been proposed based on symptoms, level of arterial saturation, and the presence or otherwise of pulmonary hypertension (Table 2) [Pediatr Pulmonol 2004; 38: 369-78].

**Table 2:** Illness severity score used in chILD

SCORE	SYMPTOMS	HYPOXAEMIA <90% ON SLEEP OR EXERCISE	HYPOXAEMIA <90% REST	PULMONARY HYPERTENSION
1	No	No	No	No
2	Yes	No	No	No
3	Yes	Yes	No	No
4	Yes	Yes	Yes	No
5	Yes	Yes	Yes	Yes

**Echocardiography** This test is used to non-invasively measure pulmonary artery pressure and exclude cardiac mimics of chILD.

**Pulmonary function testing** This is not part of the score, but should be performed in older children with ILD, who will often have restrictive physiology, with low lung volumes, reduced FEV<sub>1</sub> and FVC, with a normal or increased FEV<sub>1</sub>/FVC ratio. These can also be in monitoring therapy. An elevated DL<sub>CO</sub> in the setting of chILD suggests pulmonary haemorrhage or pulmonary venous hypertension; a low DL<sub>CO</sub> is very non-specific. There is little experience of infant and pre-school pulmonary function in chILD, and any such tests should be interpreted with caution.

➤ [Evidence gap: we need more data on the role of infant and pre-school lung function testing](#)

### **Determination of Aetiology**

Investigations, and their timing, depend on the clinical picture and the level of sickness of the child. Ideally testing should precede blind trials of treatment, but in some cases delay may be inappropriate. In most, the first step will be the performance of a panel of blood tests to try to determine the cause non-invasively. Possible tests are summarised in Table 2. Great Ormond Street Hospital genetic laboratories will perform surfactant protein genes studies [<Link to the two PDFs>](#). Depending on the degree of clinical urgency, it may be appropriate to await the results before any further testing; a positive Surfactant gene result may obviate the need for any further investigation.

➤ [Evidence gap: we need standardised protocols for blood work in chILD](#)

**The role of bronchoscopy** This is only indicated if it is probable that the results will preclude the need for a lung biopsy. If opportunistic infection is thought likely, then FOB and BAL is the next choice investigation [Eur Respir J 1995; 8: 1725-1730]. Pulmonary haemorrhage can be confirmed by the presence of haemosiderin laden macrophages in BAL [Arch Pathol Lab Med. 2006; 130: 1684-6], but this does not distinguish between primary and secondary causes, nor allow the diagnosis of pulmonary capillaritis, which may require different treatment (below). Other chILD diagnoses that may be made on BAL include Niemann-Pick disease [Neurol Sci. 2005; 26: 171-3], Langerhans' cell histiocytosis [J Pediatr. 1996; 129: 913-5], and pulmonary alveolar proteinosis [Diagn Cytopathol. 2001; 24: 389-95]. There is insufficient paediatric experience to recommend BAL cytology as a means of definitive diagnosis of other chILDs. Transbronchial biopsy has only a limited role in chILD. The samples obtained are very small, and, unless the suspected ILD has very specific and focal features, which are uniformly distributed within the lung, such as pulmonary alveolar microlithiasis or metastatic thyroid cancer, the samples are usually not diagnostic. Furthermore, there is significant morbidity (bleeding, pneumothorax).

➤ [Evidence gap: we need more data so we can start to diagnose chILD on BAL cytology](#)

**The timing and role of lung biopsy** Some advocate a blind trial of oral corticosteroids, and only biopsy children who do not respond. We disagree, but acknowledge there is insufficient evidence.

- With modern surgical techniques, the morbidity of a lung biopsy is small.
- Many chILDs are not steroid responsive; if occult undiagnosed infection is present, steroids may actually be harmful.
- The morbidity of high dose systemic corticosteroids may be considerable, including complications of surgery if biopsy is undertaken after a high dose steroid trial.
- There are specific treatments for particular chILDs, so a precise diagnosis is essential.
- Some chILDs have a genetic basis, and if a specific diagnosis is not made, the family may miss out on crucial information.

Hence we recommend lung biopsy is performed if the diagnosis is in doubt, before a blind trial of treatment unless the child is too sick.

**Techniques of lung biopsy** Surgical biopsy is the method of choice. Ideally this should be preceded by a BAL, best performed with a flexible bronchoscope to get a good wedge position before lavage. The choice of biopsy technique (mini-thoracotomy or VATS) depends on local surgical expertise; increasingly VATS is the method of choice. Absolutely crucial is close collaboration between surgeon and pathology laboratory. Biopsies should be taken from areas of differing severity, avoiding the tips of the middle lobe and lingula. The biopsy should ideally be a wedge at least 10mm depth and 20mm along the pleural axis, unless precluded by the size of the patient (i.e. a neonate). The samples should be handled according to standard protocols [Pediatr Dev Pathol. 2006; 9: 173-80], and placed in a container with no fixative for rapid transport to the pathologist who will divide up the specimens. Samples should be taken for electron and ideally a small portion is snap frozen. The

remainder should undergo gentle inflation with formalin, prior to fixation overnight. Care should be made not to over-inflate at the specimen, as this may artefactually cause widening of the interlobular septa and mimic lymphangiectasia.

- Evidence gap: we need more data on lung biopsies taken in a standardised manner, reviewed by a panel of interested pathologists, in order to plan treatment and better understand the prevalence of chILD variants
- Evidence gap: we need a database of chILD, with standardised protocols and data collection, including independent review of clinical, radiological and pathological data, interacting with other International databases, so we can begin to do focussed randomised controlled trials

## Course

The clinical course is extremely variable from complete resolution without treatment, to resolution or remission on treatment to progression and early death.

## Treatment

There are no randomised, double blind, placebo controlled trials in chILD.

### Non-specific Therapies

**Oxygen** If the child is hypoxaemic, then oxygen therapy is given. If the child is otherwise well and thriving, no further treatment may be indicated, for example in NEHL.

**Lung transplantation** There are a chILD patients who have been successfully transplanted, more commonly older children.

### Treatment to be considered if a specific diagnosis has not been made

**Corticosteroid therapy** This may be given orally or as intravenous pulses. The dose and timing are empirical. usually methyl prednisolone 500 mgm/m<sup>2</sup> daily for three successive days, followed by single monthly pulses at the same dose for six months. Ideally, oral prednisolone is avoided between pulses. If oral prednisolone is used, a reasonable starting dose is 2 mg/kg/day, tapering according to response. There are anecdotal reports of the use of inhaled corticosteroids as maintenance.

**Hydroxychloroquine** This anti-malarial agent has a number of immunological effects which are possibly beneficial in chILD. Many add it to steroids in chILD, as an aid to steroid tapering.

**Other cytotoxic agents** There are isolated case reports and small case series advocating azathioprine, methotrexate, cyclosporin and plasmapheresis when steroids have failed.

### Treatment of specific conditions

**Hypersensitivity pneumonitis** Although prednisolone is an important treatment, identifying and removing the allergen is of fundamental importance if a good outcome is to be obtained.

**Wegener's granulomatosis and neutrophilic pulmonary capillaritis** Pulsed cyclophosphamide treatment should be considered. For refractory cases, there has been interest in using anti-B-cell strategies, employing the anti-CD20 monoclonal rituximab.

**Anti-TNF strategies for sarcoidosis and other conditions** The soluble TNF- $\alpha$  receptor Etanercept has been used on an anecdotal basis for refractory paediatric sarcoidosis in combination with methotrexate. Other causes of interstitial lung disease which have been successfully treated with etanercept include polyarteritis nodosa, and other rare vasculitic diseases. If etanercept fails, the anti-TNF- $\alpha$  monoclonal antibody, infliximab may be worth trying.

**Pulmonary alveolar proteinosis** Treatment depends on the underlying cause, but large volume lavage and inhaled or subcutaneous GM-CSF have been used successfully. Rituximab has been trialled in refractory cases.

**Langerhans' cell histiocytosis** Cytotoxic therapy supervised by an oncologist is the treatment of choice. Passive and active tobacco smoking must be discouraged.

- Evidence gap: There is no evidence. We must foster international collaborations so we can accumulate groups of chILD patients who can then enter randomised controlled trials.
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#### Useful references:

1. Langston C, Dishop MK. Diffuse lung disease in infancy: a proposed classification applied to 259 diagnostic biopsies. *Pediatr Dev Pathol.* 2009 Nov-Dec;12(6):421-37.

#### Bush Child ERM Chapter

#### Web links:

<http://www.childfoundation.us/> is the website of the North American Parent support group, the Childrens Interstitial Lung Disease Foundation

[www.childlungfoundation.org](http://www.childlungfoundation.org) is the website of the (newly constituted) UK equivalent of the North American group

<http://www.cafamily.org.uk/> Contact a Family is a more general organisation, but is also a useful resource for anyone with a child with a rare disease

<http://www.lunguk.org/> is the home page of the British Lung Foundation, very active in promoting research in all lung diseases

<http://www.childlungfoundation.org/> the website for UK parents and children with a forum and fundraising links.

