

Key points

- › Presentation of ILD is very non-specific.
- › Imaging, especially HRCT, confirms the presence of ILD, but is rarely diagnostic.
- › Invasive diagnosis is almost always needed.
- › Bronchoscopy rarely gives diagnostic information in paediatric ILD.
- › For most paediatric ILD, transbronchial or percutaneous lung biopsy gives insufficient tissue for diagnosis and carries increased risk.
- › Open lung biopsy or VATS is the diagnostic investigation of choice.





Paediatric interstitial lung disease

Educational aims

- ▶ To allow the reader to correctly identify infants and children with interstitial lung disease (ILD).
- ▶ To help the reader to appreciate the wide differential diagnosis, including that of disorders specific to infancy, comprising the surfactant protein disorders.
- ▶ To explain the strengths and weaknesses of the different investigative modalities used in establishing a firm diagnosis.
- ▶ To discuss the limited evidence for the different treatment options currently in use.

Summary

Paediatric interstitial disease is rare, and comprises many disparate diseases. This article aims to provide the reader with an update on how to recognise infants and children who should be considered as possibly having ILD. The diagnostic process, including the roles of HRCT and bronchoscopy, and the different methods of lung biopsy, will be set out. The newly recognised entities, such as neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenosis and the disorders of surfactant protein metabolism, are also described. Finally, the article reviews the evidence that exists to guide treatment of these conditions.

There are major differences in interstitial lung disease (ILD) as it occurs in adults and children [1]. Paediatric ILD occurs in the context of the growth and maturing of the paediatric lung. There are huge differences in the functional behaviour of the immune system in adults as opposed to children, and, although little is known about the biology of the development of the post-natal lung, it is probably safe to assume that the normal profiles of cytokine and growth factor expression are very different in childhood compared with adulthood. Indeed, a recent paper describing an extended kindred with familial ILD, which

turned out to be associated with heterozygosity for a surfactant protein (SP)-C mutation (see below for a more detailed discussion of this phenotype), documented that presentation in adult life was with the histology of usual interstitial pneumonitis (UIP) (a form of ILD virtually unknown in children), whereas what was presumably exactly the same disease in children was diagnosed as cellular non-specific interstitial pneumonitis (NSIP) [2]. Another newly described entity, pulmonary interstitial glycogenosis (PIG), may also represent an unusual developmental response to an unspecified insult [3]. Paediatric ILD is much

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Glossary

CPI:	Chronic pneumonitis of infancy
DIP:	Desquamative interstitial pneumonitis
FB-LIP:	Follicular-bronchiolitis-lymphoid interstitial pneumonia
IPH:	Idiopathic pulmonary haemosiderosis
LCH:	Langerhans cell histiocytosis
NEHI:	Neuroendocrine cell hyperplasia of infancy
NSIP:	Non-specific interstitial pneumonitis
PAP:	Pulmonary alveolar proteinosis
PIG:	Pulmonary interstitial glycogenosis
UIP:	Usual interstitial pneumonitis

rarer and less stereotyped than adult ILD; even less, therefore, is known about treatment in children than in adults. Finally, novel entities are being discovered, either specific to infants and sometimes older children (SP-B deficiency, PIG), or common to adults and children (SP-C deficiency).

Paediatric ILD is certainly a rare diagnosis to make. The spectrum may be defined as encompassing inflammatory interstitial diseases of varying morphology with no underlying cause, as well as more specific diagnoses, which may be associated with, for example, an immunodeficiency. Strictly, the definition of ILD is

pathological: increased or abnormal inflammatory cells within the alveoli and interstitium. The infiltrate may be of varying cell types. In an individual case, this definition can only be made after a lung biopsy, and it is more helpful to start at the clinical end, with presentation.

Classification

Classification is complicated by the rarity of these conditions, and the difficulty in making comparisons across different age groups, due to differences in pulmonary and immune cell maturity. There are a variety of useful ways of dividing off parts of the spectrum of paediatric ILD. One classification is summarised in tables 1–3.

The first group is those with a known cause (table 1). These include the metabolic diseases (for example, lysinuric acid intolerance [4] and Gaucher's disease), and neurocutaneous syndromes, *e.g.* tuberose sclerosis. The surfactant protein deficiencies, discussed in more detail below, belong in this category. Other known specific causes include drugs (particularly chemotherapy for malignant disease), radiation, and graft-versus-host disease after bone marrow transplantation.

The second category is ILD associated with another condition, the cause of which may or may not be known (table 2). These include autoimmune/connective tissue (systemic lupus erythematosus, Wegener's granulomatosis) and ILD in the context of other organ failure.

The final group is ILD with no known cause (table 3). In some cases, investigation reveals a specific histological entity, for example, lymphangiectasia or other diseases of pulmonary lymphatics, sarcoidosis or a pulmonary haemorrhagic syndrome localised to the lung (idiopathic pulmonary haemosiderosis (IPH) or neutrophilic capillaritis).

Lymphoid disorders may present as an ILD. The spectrum of follicular bronchiolitis-lymphoid interstitial pneumonia (FB-LIP) may be the presenting feature of a congenital or acquired immunodeficiency. The cause of the remainder of this group is unknown. Finally, there remains a large group of children with alveolitis of undetermined cause.

The current author and co-workers have recently reviewed their biopsy experience in an attempt to revisit the classification of these conditions (table 4) [5]. The histological features of chronic pneumonitis of infancy (CPI) (a condition only relatively recently described (figure 1) [6]),

Table 1 ILD associated with known causes

<i>Infectious or post-infectious disorders</i>
<i>Environmental inhalants (toxic substances, antigenic dusts)</i>
<i>Drug-induced disorders</i>
<i>Neoplastic diseases</i>
<i>Lymphoproliferative disorders</i>
<i>Metabolic disorders</i>
<i>Congenital surfactant protein disorders</i>
<i>Degenerative disorders</i>
<i>Neurocutaneous syndromes with ILD</i>
<i>Radiation-induced ILD</i>

Table 2 ILD associated with other conditions

<i>Collagen vascular disease</i>
<i>Pulmonary vasculitis syndromes</i>
<i>LCH*</i>
<i>ILD with liver disease</i>
<i>ILD with bowel disease</i>
<i>ILD with renal disease</i>
<i>Amyloidosis</i>
<i>Graft-versus-host disease</i>
<i>Acute respiratory distress syndrome (recovering phase)</i>
<i>Hypereosinophilic syndromes</i>
<i>Pulmonary veno-occlusive disease</i>

*: may be localised to the lung in older children.

Table 3 ILD of unknown cause

<i>Sarcoidosis</i>
<i>PAP[†]</i>
<i>Idiopathic interstitial pneumonia group[‡]</i>
<i>Pulmonary haemorrhagic syndromes localised to the lung</i>
<i>Congenital lymphatic disorders[§]</i>
<i>Normal histology[§]</i>

†: distinguish from congenital surfactant protein deficiencies, PAP is more common in adults; ‡: see table 4; §: may be strictly a mimic of ILD rather than considered a true ILD; ¶: the relationship with NEHI (if any) has yet to be established.

desquamative interstitial pneumonitis (DIP) (figure 2) and chronic NSIP (figure 3) are summarised in table 4.

Another helpful way of sub-classifying paediatric ILD is by age; there are a number of conditions, some only relatively recently described, which present in infancy (table 5). Whether some of these seemingly exclusively infant diseases in fact present later on with dissimilar histology is not known. For example, the relationship of neuroendocrine cell hyperplasia of

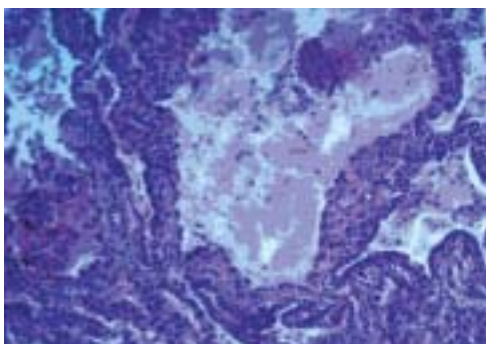


Figure 1
CPI: there is florid type 2 cell hyperplasia and proteinaceous intra-alveolar material.

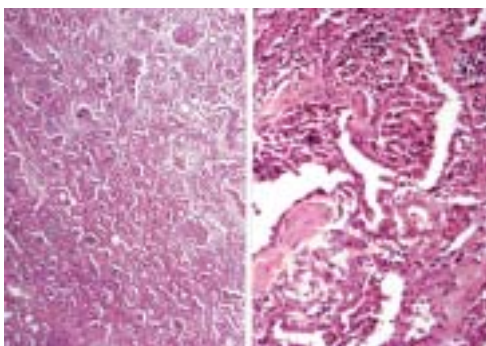


Figure 2
DIP: note the large numbers of intra-alveolar macrophages.

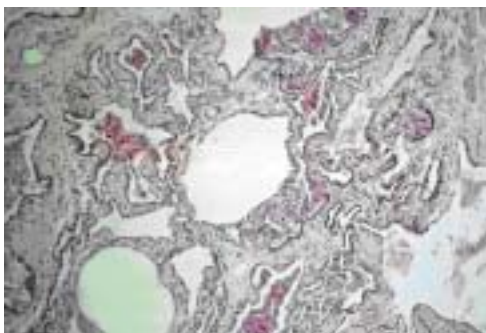


Figure 3
NSIP: there are no particularly distinctive features, and this category has been criticised as a dustbin diagnosis.

Table 4 Histological classification of paediatric ILD

Histological diagnosis	Pathological features
CPI	Florid type-2 cell hyperplasia Mild interstitial inflammation Proteinosis-like intra-alveolar material
DIP	Homogeneous interstitial pneumonitis Dominant alveolar macrophages
NSIP	Homogeneous interstitial pneumonitis No single predominant feature May or may not be fibrosis
FB-LIP spectrum	Lymphoid interstitial infiltrate Lymphoid follicles in bronchiolar walls
PIG	Interstitial glycogen deposition

Table 5 ILD presenting in infancy

NEHI
Familial DIP
CPI
Surfactant deficiency syndromes
Follicular bronchitis/bronchiolitis
PIG
Acute pulmonary haemorrhage of infancy
Idiopathic pulmonary fibrosis of infancy

infancy (NEHI) and adult idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells is unclear [7].

How to identify children with ILD

Clinical features

Children with ILD may present at any age. The peak time of presentation is the newborn period [8]. They have a very non-specific presentation (table 6) [9], usually with cough, tachypnoea and respiratory distress of at least 1 month in duration. Specific features that should be sought include: the presence of ILD in other family members [8]; any relationship to feeding or swallowing; possible inhalant triggers in the environment; or features suggestive of a multisystem disease, in particular affecting the skin, joints, eyes or kidneys. There may be failure to thrive. Cyanosis is a feature of advanced disease. There are many more common causes of these symptoms, and, usually, other diagnoses such as asthma will have been considered.

Physical examination may reveal the following: digital clubbing (which is often overlooked and will not be identified unless specifically sought); signs of respiratory distress, such as tachypnoea and recession; and sometimes

crackles on auscultation. A full examination of other systems, and testing the urine for blood and protein, is mandatory. A high index of suspicion is needed (table 7).

Pulmonary function tests

In children old enough to perform lung function tests, restrictive physiology is usual (reduction in both forced expired volume in one second (FEV₁) and forced vital capacity (FVC), with a normal or elevated FEV₁/FVC ratio). Carbon monoxide transfer is usually reduced, but may be elevated if there has been a recent pulmonary haemorrhage due to IPH [10] or another pulmonary bleeding disorder. Exercise testing may reveal desaturation, pointing to ILD, but generally is probably better for assessing severity, and following disease progression or response to treatment, rather than making a diagnosis. However, many cases of paediatric ILD occur in an age group in which lung function testing is difficult outside a research context. There is little published about infant and pre-school lung function testing in paediatric ILD, and, given the very different and diverse pathologies in this age group, it would be a mistake to assume that the findings would be as in older children. Indeed, there is some evidence that the physiology of ILD may be obstructive rather than restrictive in infants. This is a field where more research is needed.

Imaging

The chest radiograph is usually very non-specific and non-diagnostic [11]. There may be ground-glass shadowing with prominent air

bronchograms, or coarse nodular or reticular-nodular shadowing; in advanced cases, honeycombing is seen. However, some children with ILD may have normal chest radiography. In general, the chest radiograph has poor sensitivity and specificity, and correlates poorly with symptoms, histology or response to treatment. In most cases, the definitive recognition that the tachypnoeic child has an ILD will be from the high-resolution computed tomographic (HRCT) scan. On occasion, a primary airway disease, such as reflux and aspiration, or bronchiectasis, may be seen, prompting completely different lines of investigation. Alternatively, a child with an apparently normal chest radiograph may in fact be shown to have extensive ground-glass shadowing or other changes suggestive of ILD (figure 4).

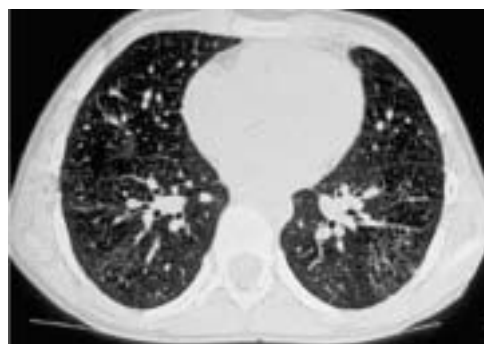


Figure 4
HRCT showing peripheral distribution of reticular nodular shadowing. The chest radiograph was normal. Open lung biopsy showed burnt out DIP.

There are three other reasons for performing HRCT in this context. First, in very few cases, HRCT may be diagnostic. This is much less common than in adult ILD, but specific patterns, such as IPH, Langerhans cell histiocytosis (LCH; figure 5), pulmonary microlithiasis or pulmonary alveolar

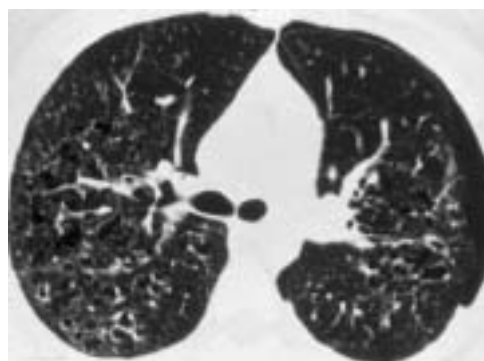


Figure 5
HRCT shows nodules and cavities, and a shallow left pneumothorax. The appearances are diagnostic of LCH.

Table 6 Presenting symptoms of ILD in children

Chronic cough >1 month
Tachypnoea and respiratory distress >1 month
Failure to thrive
Cyanosis (if the disease has been missed early or is rapidly progressive)

Table 7 When to suspect ILD in a child

Positive family history of ILD
Unexplained digital clubbing
Crackles on auscultation, except if there is evidence of acute infection
Family history of unexplained neonatal deaths
Respiratory distress in the context of multisystem disease (especially skin, joints, eyes or kidneys)
Abnormal urinary sediment with unexplained respiratory distress
Unexplained respiratory distress when there is exposure to potential inhalant triggers, e.g. pigeons

proteinosis (PAP) may be identified, obviating the need for further tests [12]. The second reason is to determine the site of a biopsy of the lung, which will probably be required in most cases. Finally, HRCT appearances should be correlated with the ultimate diagnosis, in the hope that, in the future, more accurate interpretation of HRCT will obviate the need for lung biopsy.

The differential diagnosis

The differential diagnosis of ILD encompasses most of paediatric pulmonology. In practice, there are a few groups of conditions that are particularly important [12–14]. Unsuspected immunodeficiency (for example HIV, hypogammaglobulinaemia) with any secondary opportunistic infection (and, in particular, *Pneumocystis carinii* pneumonia) may present as ILD. An immune work-up is part of the diagnostic testing for ILD, and may need to include immunoglobulins and subclasses, response to vaccine antibodies, lymphocyte subsets, and lymphocyte function tests. If the index of suspicion is high, then referral for more detailed evaluation to a paediatric immunologist is mandatory.

Another group of conditions which needs to be considered is aspiration, usually due to gastro-oesophageal reflux, incoordinate swallowing, H-type fistula or laryngeal cleft. Included in this category is chemical pneumonitis due to aspiration of oil contained in nosedrops or other medication. Any cause of bronchiectasis or chronic bronchial sepsis may cause respiratory distress and non-specific chest radiograph shadowing; however, HRCT should indicate this diagnosis.

Pulmonary oedema also enters the differential diagnosis. Usually, the cause is cardiac, for example left-to-right shunting due to an arterial duct or ventricular septal defect. Non-cardiogenic pulmonary oedema usually presents acutely and is not often a diagnostic consideration in chronic ILD.

Finally, pulmonary vascular diseases may mimic ILD [15]. These include pulmonary embolism [16] (which may be thrombo-embolic or non-thrombotic due to tumour, intravenous drug abuse, schistosomal ovuli, etc.), pulmonary veno-occlusive disease and pulmonary capillary haemangiomas. This last diagnosis is very rare.

An echocardiogram should be an early investigation. It may reveal an unexpected cardiac lesion that has precipitated pulmonary oedema,

or enable a non-invasive estimate of pulmonary artery pressure; this is useful, since pulmonary hypertension may complicate paediatric ILD. If ILD is a serious diagnostic possibility, further investigations are needed, regardless of the chest radiography appearances. The next investigation is HRCT, which should precede the performance of an extensive panel of blood tests.

Non-invasive diagnosis

Having reached the point of determining, by means of history, physical examination and HRCT, that the diagnosis is ILD, a systematic sequence of investigation should be commenced. The least invasive is serology. It is better to perform a few targeted investigations, rather than a huge battery of tests in every case, and delay definitive diagnosis while waiting for the results.

A full immunological work-up may disclose an unsuspected immunodeficiency, pointing either to a lymphoid lung disorder (FB-LIP spectrum) or an opportunistic infection, which may be diagnosed best by bronchoscopy and bronchoalveolar lavage (BAL). If opportunistic infection is suspected, HIV testing is mandatory. An auto-antibody profile, which should include anti-neutrophil cytoplasmic antibody, may lead to a diagnosis of Wegener's granulomatosis or other connective tissue disease, and obviate the need for a lung biopsy. The presence of renal disease would suggest Goodpasture's syndrome, or Wegener's or another vasculitis, which may be confirmed by serological testing. A positive angiotensin converting enzyme would suggest a diagnosis of sarcoidosis. Positive precipitins to, for example, pigeon antigen, would suggest an allergic alveolitis if there is a compatible history, allowing treatment to be instigated without further investigation. Having described these possibilities, it has been found that a positive serological diagnosis is rare in paediatric ILD [17].

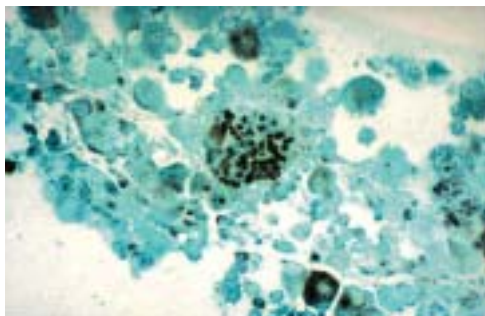
Role of bronchoscopy

Fibreoptic bronchoscopy (FOB) allows inspection and biopsy of the airways (almost invariably not informative in ILD), BAL and transbronchial biopsy (TBB). However, the procedure requires a general anaesthetic or such heavy sedation as almost to amount to general anaesthesia. It should only be performed if there is a real likelihood of a definitive diagnosis being reached. BAL

is very good for the diagnosis of opportunistic infections in an immunocompromised host (figure 6), in particular if the child has not received prior antibiotic therapy.

Figure 6

BAL from a child thought to have ILD. Silver stain shows *Pneumocystis carinii* in a child who ultimately proved to have an immunodeficiency.



Close attention should be paid to recent guidelines on bronchoscopy [18] and BAL [19]. In the context of ILD in the otherwise normal host, the diagnostic yield is poor [20]. However, BAL is diagnostic in a few specific conditions, which include IPH (figure 7), LCH, PAP and lipoid pneumonia due to aspiration of oily medications [21–24]. However, there is so little paediatric BAL experience in ILD, and such a paucity of normal ranges, that, in general, BAL is not useful in other ILD.

Figure 7

BAL from a child with ILD. The Prussian Blue stain shows haemosiderin-laden macrophages, establishing the diagnosis of pulmonary haemorrhage. Note that diagnosing IPH requires the exclusion of secondary causes of pulmonary haemorrhage.



TBB is of immense value in the context of possible lung rejection after transplant [25], where, in fact, it is the small airways rather than the alveoli that are the major target. In children with ILD, it is only useful for conditions with very specific histological features (e.g. alveolar microlithiasis) [26]. The samples are too small for diagnosis of most paediatric ILD. There are also safety issues; pneumothorax requiring a chest drain is not uncommon and bleeding may be difficult to control on rare occasions. Furthermore, TBB is possible in very young children only through a rigid bronchoscope or by a modification of the 2.2-mm bronchoscope. In this method [27], the bronchoscope is threaded through a feeding tube, which is positioned in a segmental orifice under direct vision. The endoscope is removed, leaving the tube *in situ*, and biopsy forceps are

then passed down it to perform a TBB. Such samples are also likely to be too small to be diagnostic in most cases of paediatric ILD.

Invasive diagnosis

It will be obvious from the above that the majority of paediatric ILD will require a biopsy for diagnosis (figure 8), and this should not be delayed unless there is a realistic prospect that lesser procedures will obviate the need for this invasive procedure. In particular, it is wrong to submit the child to a series of anaesthetics, e.g. for HRCT and then FOB, before going on to a biopsy. When a biopsy is performed, the destination of the tissue should also be planned; some should be stored for future use at -70°C . Standard histology, immunohistochemistry, electron microscopy and culture of the biopsy for mycobacteria and fungi in particular should always be performed. The limitations of TBB in ILD have been discussed above; the other choices are percutaneous CT-guided biopsy, open lung biopsy (OLB) through a mini-thoracotomy incision and video-assisted thoracic surgery (VATS) [28–32].



Figure 8

HRCT scan showing patchy ground-glass shadowing. The appearances are non-specific. Open lung biopsy led to a diagnosis of DIP.

Percutaneous biopsy has been used in some centres [31, 32], but is not the optimal technique [33, 34]: the child requires a full general anaesthetic; the pieces of tissue, although obtained under CT control, are not taken under direct vision; and, because the procedure is blind and uncontrolled, there is an unacceptable incidence of bleeding and pneumothorax. Biopsy of the lung under direct vision is safe, well tolerated and should be regarded as the gold standard. Whether it is performed through a mini-thoracotomy or as a VATS procedure will depend on the size of the child and the experience of the surgeon.

The current author has recently reviewed his own experience of OLB through a mini-thoracotomy [30]. The chest drain is usually removed in the operating theatre and the child is left with an insignificant lateral scar. Complications are few and the procedure is well tolerated. Large samples can be obtained and a diagnosis is usually possible.

The alternative to performing a biopsy is an empirical trial of oral steroids. However, this is not optimal, as many ILDs are known not to respond and this therapy is not without hazard. Some conditions that may present as ILD may actually be made worse by corticosteroids, for example unsuspected opportunistic infection in a host initially thought to be immunocompetent. Furthermore, if OLB is subsequently undertaken after a failed trial of steroids, wound healing may be compromised.

Spectrum in Europe

The most comprehensive review of the spectrum of paediatric ILD was the report of the ERS Task Force [8]. They reviewed 185 cases, which are summarised in table 8. They confirmed the predominance of cases in young children (aged <2 years), and that nearly 10% of cases have affected siblings. A surprising finding was seven cases of UIP, which is said to be almost unheard of in children. All were confirmed by lung biopsy, and it would have been interesting to have these cases reviewed independently. The Task Force provides a most comprehensive description of what is the current state of the art in Europe, and should serve to stimulate further work in this complex field.

Recent advances

Surfactant protein abnormalities/PAP spectrum

It has become apparent that the histological appearances of PAP, in which alveoli are filled with granular, eosinophilic material, which stains with periodic-acid Schiff, with preservation of lung architecture, can be produced by three clinically distinct conditions [35]: congenital, comprising mutations in the genes encoding SP-B or C, or the β_C chain of the granulocyte-macrophage colony stimulating factor (GM-CSF) receptor (see below and [36]); secondary, in conditions associated with functional impairment of the macrophage (such as haematological cancers, some infections [37–40]); and later onset, probably an auto-immune disease, with auto-antibodies targeting GM-CSF [41, 42]. The role of GM-CSF in surfactant

Table 8 Spectrum of ILD in Europe

Diagnostic entity	All patients	Patients <2 years
<i>Pulmonary haemosiderosis</i>	14	5
<i>PAP</i>	14	7
<i>Hypersensitivity pneumonitis</i>	24	0
<i>LCH</i>	3	3
<i>Sarcoidosis</i>	29	1
<i>Pulmonary lymphangiomyomatosis</i>	1	0
<i>Lymphocyte infiltrative disorder</i>	1	0
<i>Auto-immune-related ILD</i>	3	0
<i>DIP</i>	13	11
<i>UIP</i>	7	2
<i>LIP</i>	1	0
<i>Idiopathic pulmonary fibrosis</i>	46	12
<i>Interstitial pneumonitis</i>	21	15

Data taken from [8].

biology was highlighted when the GM-CSF knockout mouse was found to have a PAP-like illness with normal surfactant synthesis, with recovery after GM-CSF replacement [43, 44]. Subsequently, auto-antibodies against GM-CSF were found in late-onset PAP [41, 42]. It would appear that GM-CSF regulates surfactant homeostasis via CD36 peroxisome proliferator-activated receptor (PPAR)- γ [45]. GM-CSF therapy in PAP restores PPAR- γ levels to normal.

A detailed review of surfactant protein physiology is beyond the scope of this paper. In brief, SP-A and -D are, with mannose-binding lectin, part of the collectin system of innate pulmonary defences. The surface tension properties of surfactant derive from SP-B and -C, and it is mutations in these genes which are associated with PAP and also other forms of ILD.

SP-B deficiency

Defects in the gene encoding SP-B were found to be associated with the congenital form of PAP. The SP-B gene is located on chromosome 2, and consists of 11 exons and 9.5 kb. The gene product is a prepro-SP-B, ~40 kDa, which is processed at both amino and carboxyterminal ends to produce mature SP-B (8 kDa).

A number of mutations have been described, the commonest being a frameshift mutation in exon 4 (1549C→GAA, 121ins2), but also 122delC [46], 457delC [47] and other mutations listed in [48]. The mutation frequency in the population is probably 1 per 1–3,000 individuals [49].

The underlying metabolic defect has been characterised in detail [50]. The mutated gene is

transcribed normally, but an unstable mRNA is produced. Typically, it presents as relentlessly progressive respiratory failure in a term baby, with radiographs showing ground-glass shadowing or established fibrosis.

Diagnosis is established by absence of SP-B staining of tracheal aspirates or lung biopsy. Reliance on tracheal aspirate alone may be misleading; transient absence of SP-B from aspirate, but not lung biopsy, was described in an infant with a mutation in one SP-B gene, but with the second gene copy normal [51]. Diagnostic confusion may also be caused because SP-C is also misprocessed, but this is a secondary phenomenon [52].

The only known therapy is lung transplantation, which has been performed successfully in a few infants [53], despite the development of antibodies against SP-B after transplantation.

A recent report has broadened the spectrum of SP-B deficiency to a cause of ILD in older children. Two infants with respiratory failure, one surviving untransplanted for several years, were found to have immunostaining consistent with SP-B deficiency [54]. Both children were homozygous for an exon 5 splice site mutation, which resulted in a frameshift and a premature termination codon in exon 7. However, Western blot determined the presence of reduced amounts of mature SP-B and an abnormal SP-B proprotein, presumed to be a result of skipping exon 7, and resulting in a milder phenotype than the classical disease.



SP-C deficiency

Defects in SP-C have been found to be associated with adult and paediatric ILD. The first case was in a female diagnosed with DIP at age 1 year, who was treated with corticosteroids until age 15 years. Her infant also had NSIP. The maternal grandfather had died of a life-long undiagnosed respiratory disorder. The same abnormality has been described in other kindreds with ILD [55, 56].

It is likely that inherited surfactant protein problems are more common than expected. NOGEE *et al.* [57] determined the presence of SP-C mutations in infants, and found a mutation in 11 out of 34 patients evaluated. It is likely that the mutations may be of sporadic or autosomal dominant inheritance. Mutation analysis of SP-B and -C genes should increasingly be considered as part of the work up of ILD of unknown cause, particularly if familial.

Other surfactant problems

It is likely that further inherited surfactant protein problems will be described, given the complex post-translational processing of these molecules. Two infants with respiratory failure were found to have greatly reduced SP-B without aberrant SP-C [58]. There were no normal lamellar bodies. However, the SP-B and -C genes were sequenced and found to be normal. The reasons for the abnormal surfactant accumulations within pneumocytes are unclear, but could include a primary secretory defect, a defect in surfactant phospholipids, or an abnormal interaction between the phospholipids and surfactant proteins.

A recent study in 21 infants with severe neonatal surfactant deficiency of unknown cause, with normal SP-B and -C gene sequences, revealed mutations in 16 infants in the ATP-binding cassette transporter A3 (ABCA3). Lung ultrastructure showed markedly abnormal lamellar bodies. ABCA3 is localised to lamellar bodies, suggesting an important role in surfactant metabolism [59]. It is likely that mutations in many other genes encoding for proteins that are important in surfactant metabolism will be implicated in ILD.

PIG

The first description of this condition was in seven infants who presented with tachypnoea, hypoxaemia and diffuse infiltrates with hyperinflation [3]. Lung biopsy showed interstitial expansion by spindle cells containing periodic-acid Schiff-positive, diastase labile material consistent with

glycogen. Five were treated with pulse corticosteroids and one with additional hydroxychloroquine; six out of seven did well. CANAKIS *et al.* [3] proposed that this was an abnormality in lung cytodifferentiation involving interstitial mesenchymal cells, because abundant glycogen is not normally found in pulmonary interstitial cells.

NEHI

Another ILD that has so far only been recognised in infants is NEHI [60]. Infants present with respiratory distress, and hyperinflation and ground-glass opacities are found on HRCT. Lung biopsies look essentially normal, unless they are stained for bombesin, which demonstrates hyperplasia of the neuroendocrine cells and bodies. Bombesin staining should be part of the evaluation of clinical ILD with an apparently normal lung biopsy, as there is a relationship between NEHI and cases of paediatric ILD in infancy with normal histology.

Treatment

Conventional treatment

Obviously if an underlying cause, such as extrinsic allergic alveolitis, is identified, then this should be dealt with as far as possible. If there is no underlying cause amenable to action, then the first question to be asked is whether treatment is needed at all. Some children with ILD, even after having gone on to oxygen, go into spontaneous remission after months or even years. In one case, a young female who had two first cousins who had died of what was described as Hamman Rich syndrome (acute rapidly progressive pulmonary fibrosis), confirmed at autopsy, was diagnosed shortly after birth as having the same condition. She remained oxygen dependent for 7 years, but spontaneously improved and, at age 30 years, is well on no treatment and has normal lung function.

In most cases, treatment will probably be considered. In theory, the aims of treatment are to reduce inflammation and to reduce fibrosis. These laudable goals are limited by the fact that the therapeutic armamentarium is limited. The mainstay of anti-inflammatory treatment is prednisolone, supplemented with cyclophosphamide for some vasculitides. Antifibrotic agents are scarce, although hydroxychloroquine may act in this way. An alternative might be colchicine, at least in theory, but there is little experience in paediatric ILD with this medication. There are no large, randomised, controlled trials

that can be used to guide treatment. Some anecdotal evidence exists that suggests that prednisolone and hydroxychloroquine are the treatments of choice for "chronic pneumonitis" of unknown cause [61]. If they fail, any further therapy is anecdotal, and azathioprine, cyclophosphamide (low-dose or pulsed) and cyclosporin are among the therapies that have been used.

There is no consensus as to how much and for how long steroids are to be given to patients. In an ill child, the author would use pulsed methyl prednisolone 500 mg per m² daily for 5–7 days, followed by prednisolone 2 mg per kg per day, combined with hydroxychloroquine 6–10 mg per kg per day. The dilemma is always to determine when the child has ceased to be steroid responsive, and time is needed for improvement. One method is to repeat the pulses of steroids for 3 days each month, desisting if there is no further improvement.

There are other therapies for specific ILDs for which no satisfactory trials have been carried out. IPH probably responds best to hydroxychloroquine [62], which may have to be combined with oral corticosteroids; the current best practice is to continue for 2–3 years after the last relapse and confirm remission with a repeat BAL. Unlike with chloroquine, which is known to have retinal toxicity, ocular complications of hydroxychloroquine are so rare that UK guidelines at least do not mandate a formal ophthalmological review. However, most paediatricians will think it wise to involve ophthalmic services, not least also to detect and treat early the ocular complications of ILD, for example anterior uveitis in sarcoidosis.

PAP may be treated with large-volume lavage, although the response is usually disappointing compared with that seen in adult PAP. In the future, therapy with GM-CSF may offer promise in some forms of the disease [63]. Isolated pulmonary LCH, which may be seen rarely in teenagers, may regress spontaneously if tobacco-smoke exposure is stopped, otherwise steroids, cotrimoxazole or cytotoxics, such as etoposide, should be used (these are the treatments employed for multisystem LCH with pulmonary involvement [64]). Wegener's granulomatosis is treated with prednisolone and cyclophosphamide. The specific treatments of the various congenital and acquired immunodeficiencies that may present as FB-LIP is beyond the scope of this article.

Finally, on occasion, a surprising infection may be found to have mimicked ILD, such as



unsuspected *Pneumocystis carinii* pneumonia. Such infections obviously require treatment with appropriate chemotherapy. These different therapeutic options for admittedly rare diseases that may present as ILD are a powerful argument against a blind trial of prednisolone without a biopsy in all cases.

Monitoring therapy is a matter for debate. Invasive testing with repeated BAL is not routine, with the exception of BAL to check if IPH has remitted. Likewise, the radiation involved in serial HRCT scans makes this investigation unappealing. Usually, one relies on general features, such as growth pattern, resting respiratory rate and oxygen requirement, supplemented by lung function tests and exercise testing in those old enough to perform these investigations.

The final resort in children progressing relentlessly to respiratory failure is lung transplantation. This may be an option even in small infants, and has been employed successfully in cases of SP-B deficiency. The dilemma in other conditions is that the child is often taking high doses of oral steroids, and these need to be weaned down prior to acceptance for transplantation. This carries the risk of deterioration in the underlying lung condition.

Treatment of sarcoidosis with infliximab

Infliximab is a chimeric immunoglobulin G monoclonal antibody against tumour necrosis factor (TNF)- α , which has been dramatically successful in Crohn's disease and rheumatoid arthritis [65, 66], including juvenile forms of this disease. Alveolar macrophages from sarcoidosis patients with active sarcoid secrete large amounts of TNF- α [67, 68], so there is at least a logical basis for this treatment [69–71]. It is often combined with once weekly methotrexate 10 mg per m² to reduce antibody formation against infliximab.

There are only a few case reports of its use in sarcoidosis, and a randomised trial is awaited. However, it would seem reasonable to consider this as an option in refractory sarcoidosis in children.

Prognosis

It should be said that histological changes and response to treatment are not closely related in ILD, and in each individual case prognosis is unpredictable. There may also be genetic issues to be considered. The early onset of ILD frequently prompts the family to seek genetic counselling about whether future children will be affected. If a specific genetic entity with known Mendelian inheritance patterns has been identified, the answer is straightforward. In the absence of known inheritance patterns, such evidence available would suggest that a 10% recurrence risk could reasonably be quoted [8, 72].

Summary and conclusion

There is a wide spectrum of conditions which present as or mimic paediatric ILD. A CT scan should be used to confirm the presence of ILD and guide the site of a biopsy. Occasionally, the CT appearances are definitive, obviating the need for further investigation. Most children will, however, need a tissue diagnosis, and OLB is the method of choice. Repeated anaesthetics for non-definitive investigations must be avoided. Early lung biopsy under direct vision is advisable unless it is highly likely that a less invasive test will be diagnostic; the preferred technique will vary between institutions. Treatment options are largely based on anecdote, but there are specific therapies available for particular paediatric ILD.

Educational questions

1. In the diagnosis of paediatric ILD, are the following true or false?:
 - a) The chest radiograph is rarely diagnostic of a specific entity.
 - b) CT scanning is diagnostic of CPI.
 - c) Serological tests are often positive.
 - d) BAL is mandatory before considering lung biopsy.
 - e) Transbronchial biopsy is the best method of obtaining tissue for histology.
2. The following ILD can present in late childhood, true or false?:
 - a) NEHI.
 - b) Surfactant protein deficiency.
 - c) CPI.
 - d) DIP.
 - e) LCH.
3. The following treatments may be appropriate, true or false?:
 - a) Methylprednisolone for DIP.
 - b) Hydroxychloroquine for IPH.
 - c) Infliximab for PIG.
 - d) Methotrexate for SP-B deficiency.
 - e) Cyclosporin A for ABCA3 deficiency.
4. The following systemic disease are associated with paediatric ILD, true or false?:
 - a) Lysinuric acid deficiency.
 - b) Sickle cell anaemia.
 - c) Gaucher's disease.
 - d) Phenylketonuria.
 - e) Sarcoidosis.
5. Which of the following histological associations with underlying diagnoses are correct?:
 - a) SP-C deficiency causes UIP in children.
 - b) NEHI is a cause of increased airway bombesin immunoreactivity.
 - c) PIG is associated with lung and liver glycogen deposition.
 - d) SP-C deficiency causes a PAP-like picture.
 - e) Type 2 cell hyperplasia is a feature of CPI.

Suggested further reading

Fan LL, Deterding RR, Langston C. *Paediatric interstitial lung disease revisited. Pediatr Pulmonol* 2004; 38: 369–378.

A detailed review article, written by investigators with unrivalled clinical experience. An overview of all the common conditions encompassed by interstitial lung disease in children.

Clement A, Allen J, Corrin B, et al. *Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J* 2004; 24: 686–697.

Definitive review of the current state of the art in Europe, in terms of diagnostic work-up, diagnoses encountered and treatment options.

Grutters JC, du Bois RM. *Genetics of fibrosing lung diseases. Eur Respir J* 2005; 25: 915–927.

Very wide ranging review of the genetics of interstitial lung disease. It includes rarities such as Hermansky-Pudlak syndrome and much about basic mechanisms that will need to be tested in paediatric ILD.

Brody AS. *Imaging considerations: interstitial lung disease in children. Radiol Clin North Am* 2005; 43: 391–403.

Detailed review of the imaging techniques and results by one of the foremost exponents in the field of paediatric radiology.

Hartl D, Griese M. *Interstitial lung disease in children – genetic background and associated phenotypes. Respir Res* 2005; 6: 32.

Detailed and well-referenced advanced overview of paediatric ILD.

Fauroux B, Clement A. *Paediatric sarcoidosis. Paediatr Respir Rev* 2005; 2: 128–133.

Comprehensive overview of the management of this rare, but taxing condition in childhood. A 'must-read' for anyone with a patient with this condition.

Suggested answers

1. a) True
b) False
c) False
d) False
e) False
2. a) False
b) True
c) False
d) True
e) True
3. a) True
b) True
c) False
d) False
e) False
4. a) True
b) False
c) True
d) False
e) True
5. a) False (UIP in adults, NSIP in children)
b) True
c) False (no extrapulmonary increase in glycogen)
d) True
e) True

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Useful weblinks

www.pILDFamilyNetwork.org

This is the website of the newly launched Foundation for orphan lung diseases in the USA, set up by the parents of affected children.

www.bpold.co.uk

The website of the British orphan lung disease study.