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REVIEW ARTICLE

CLINICAL APPROACH FOR CHILDHOOD INTERSTITIAL LUNG DISEASE (chILD)
"JOURNEY TO SOLVE THE MYSTERY"

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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 establish a protocol for establishing a firm diagnosis of chILD.
- To discuss the limited evidence for the different treatment options currently in use.

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

The adopted protocol of chILD syndrome in this review is the concept proposed by chILD cooperative group of the US NIH- sponsored Rare Lung Disease Consortium. This recently formed consortium of centers, perhaps in collaboration with centers worldwide, facilitated the use of standardized diagnostic criteria and developed a network for clinical trials of chILD.

www.childfoundation.info/chILD

What is chILD Syndrome?

Interstitial Lung Disease (ILD) in children is a diffuse lung pathology that affects both the alveoli and the

surrounding pulmonary interstitium with all its contents (i.e. Pneumonitis).[1]

Most children who present with symptoms and signs of chILD will have a relatively easily identified aetiology, the commonest being either post-infectious disease or that related to aspiration. Once a cause for ILD like presentations has been identified, these children are no longer classified as having chILD syndrome. For example; if the cause of chILD syndrome is aspiration, the final diagnosis is usually "Aspiration Pneumonitis" rather than chILD secondary to aspiration.

Thus, chILD syndrome would be nominated for children who presented with pneumonitis and no cause has been identified yet.[2]

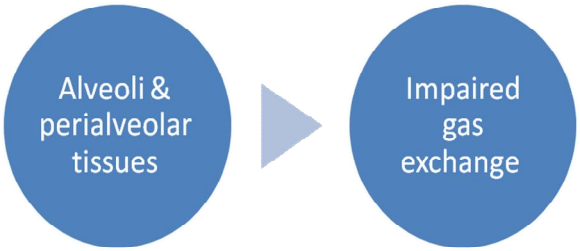
Inability to understand this concept has been always a part of the confusion in the literature!

Pathophysiology of chILD Syndrome

Childhood ILD is not a disease but a group of disorders (see causes) which share a common pathophysiologic features, namely, structural remodeling of the distal airspaces. This remodeling has been believed to be the sequela of persistent inflammation; however, more recently, the paradigm has shifted away from inflammation to one of tissue injury with aberrant wound healing resulting in collagenous fibrosis.[1]

Wound healing and fibrosis are complex pathophysiologic processes that involve numerous cell types and cellular processes, such as adhesion; migration; proliferation; apoptosis; and a vast array of soluble mediators, extracellular matrix (ECM) molecules, and signaling intermediates.[2]

However; the most serious pathogenesis in those children would always be the affection of the alveolar level which manifests with significant impaired gas exchange manifestations, in chILD, these processes occur in an organ that is still developing, further complicating the pathophysiology.[3]



The interstitium of the lung is the connective tissue between the alveoli, between alveolar epithelium and capillary endothelium, and around the blood vessels and airways, and which provides the fibrous structure to the lung. Thus, chILD may be presented with the classic restrictive lung disease seen in adult ILD. Nevertheless, obstructive lung disease is also common in children and may be the predominant abnormality.[2,3]

Fibrotic remodeling is responsible for most of the morbidity and mortality associated with ILD. Remodeling - of distal airspaces- results in hypoxemia. Persistent hypoxemia results in pulmonary hypertension and vascular remodeling, leading to corpulmonale.[4] The increased work of breathing associated with reduced compliance results in increased energy expenditure, which, combined with the effects of inflammatory mediators, can result in cachexia. Portions of the lung may be replaced by fibrotic septae between dilated airspaces, the so-called honeycomb changes of endstage interstitial disease.[5] Although the events described above are necessary for repair of the injured lung, excessive activation or failure of resolution of any of these pathways can result in disabling fibrosis.[6]

What are the differences between childhood ILD and adulthood ILD?

There are major differences in interstitial lung disease (ILD) as it occurs in adults and children.[2] Pediatric ILD occurs in the context of the growth and maturing of the pediatric lung. There are huge differences in the functional behavior 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 o cytokine and growth factor expression are very different in childhood compared with adulthood.[4]

Indeed, a paper by Thomas et al, 2002 which describes 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).[5]

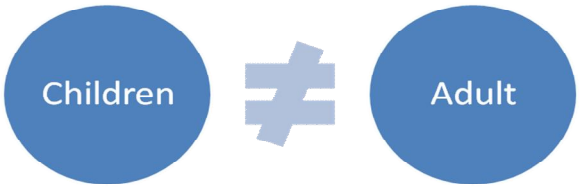
Another newly described entity, pulmonary interstitial glycogenosis (PIG), may also represent an unusual developmental response to an unspecified insult.[6] Pediatric ILD is much rarer and less stereotyped than adult ILD; even less, therefore, is known about treatment in children than in adults.[2]

Summary of differences between adulthood ILD and child

1. Children's ILD occurs at developing lung (Different immune system responses, cytokines and growth

factors milieu).

2. Different histological presentations by the same etiology (e.g. UIP the histological pattern associated with idiopathic pulmonary fibrosis, the commonest ILD in adults, is rarely if ever seen in children).
3. Specific forms of ILD, such as NEHI and PIG are only seen in children.
4. Rarer and less stereotyped
5. More difficult to manage



How to identify children with ILD?

The spectrum of chILD 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.[7] 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.[5]

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 (look box of clinical features),[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 multi-system disease, in particular affecting the skin, joints, eyes or kidneys.[2]

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.[7]

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.[9]

The common clinical features of child[3]

Persistent 3 of the following 4 ≥1 month:

1- Symptoms of impaired respiratory functions (cough, breathlessness, exercise intolerance).

2- Evidence of impaired gas exchange (hypoxia or hypercapnia either at rest or induced by exercise).

3- Diffuse/Patchy radiological chest abnormality on CXR or CT scan.

4- Adventitious sounds on auscultation (crepitations or wheeze).

Staging of chILD

No widely used staging system is available for chILD, which is appropriate because the spectrum of possible final diagnoses is large. In adults, a scoring system is available for IPF, based on clinical, radiographic, and pathologic findings (i.e, CRP scoring system).[8]

Fan et al, devised a simple scoring system for chILD. A score of 5 indicates the worst outcome, with a 38% survival rate at 60 months. A score of 2, 3, or 4 indicates a survival rate of 76%. Data from Cox proportional hazards modeling suggested a 140% increase in risk of death with each unit increase in score.[10]

The Fan scoring system is as follows (1998).

Fan staging of child[10]

1- Asymptomatic.

2- Symptomatic with normal SaO2.

3- Symptomatic with nocturnal or exercise-induced ↓SaO2.

4- Desaturation (↓SaO2) at rest.

5- Evidence of pulmonary hypertension.

Causes of chILD

The differential diagnosis of childhood ILD encompasses most of pediatric pulmonology. Nevertheless, the commonest causes in children would always be post infectious or aspiration syndromes (included in this category is chemical pneumonitis due to aspiration of oil contained in nose drops or other medication).[10-12]

Major causes of chILD

- Infectious.

- Aspiration (gastrooesophageal reflux disorder – GORD-, incoordinate swallowing, H-type fistula or laryngeal cleft).
- Environmental (hypersensitivity pneumonitis).
- Drug-induced.
- Neoplastic diseases (&LCH= Langerhans cell histocytosis).
- Lymphoproliferative disorders (including HIV).
- Metabolic disorders (for example, lysinuric acid intolerance and Gaucher's disease).
- Surfactant disorders.
- Neurocutaneous syndromes.
- Idiopathic pulmonary hemosidrosis.
- Collagen vascular disease (including; Pulmonary vasculitis syndromes).
- Radiation-induced.
- Amyloidosis.
- Graft-versus-host disease.
- ARDS (recovering phase).
- Hypereosinophilic syndromes.
- Pulmonary veno-occlusive disease.
- Sarcoidosis.
- With chronic liver, kidney, bowel diseases.

There is a possibility that causes of ILD in children depend on the age of the child. Here are the most important age related etiologies of chILD.[11]

Causes in children under 2 years	Causes in older children
1. Aspiration lung disease.	1. Aspiration lung disease.
2. Idiopathic pulmonary hemosiderosis.	2. Infectious or post infectious; organisms as for the under twos, plus Chlamydophila pnwumoniae and Legionella pneumophilia.
3. Surfactant dysfunction mutations (SPB and SPC and ABCA3).	3. Hypersensitivity pneumonitis.
4. Infectious or post infectious; usually related to either viral infection (adenovirus, CMV, EBV or influenza) or atypical bacterial infections (Chlamydia trachomatis, Mycoplasma pneumiae).	4. Sarcoidosis.
	5. Lymphocytic interstitial pneumonitis with HIV infection.
	6. Idiopathic pulmonary hemosidersosis and Goodpasture's syndrome.
	7. Connective tissue disease and vasculitis; systemic lupus, juvenile arthritis, Wegner's granulomatosis, Churg Strauss syndrome, Dermatomyositis, Polyarteritis nodosa and mixed connective tissue disease.
	8. Surfactant dysfunction mutations (SPC and ABCA3 mutations can present later in childhood; SPB invariably presents in early infancy).
	9. Pulmonary alveolar proteinosis (PAP).

The differential diagnosis

There are many relatively common conditions that can present with symptoms and signs similar to those of chILD and these must be excluded as part of the initial assessment.[13] These conditions are shown in the box.

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 pediatric immunologist is mandatory.[15]

Any cause of bronchiectasis or chronic bronchial sepsis may cause respiratory distress and non-specific chest radiograph shadowing; however, HRCT should indicate this diagnosis.[1]

Pulmonary edema 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.[7] Non-cardiogenic pulmonary oedema usually presents acutely and is not often a diagnostic consideration in chronic ILD.[13]

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 haemangiomatosis. 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 pediatric ILD.[7]

Conditions that may mimic chILD (DD to rule out):

- Cystic fibrosis.
- Asthma.
- Cardiac (heart) disease.
- Primary ciliary dyskinesia.
- Scoliosis and chest wall abnormalities.
- Neuro-muscular disease / Neurocutaneous diseases.
- Immune deficiency.
- TB.
- Developmental abnormalities (Bronchpulmonary dysplasia (BPD) - Alveolar capillary dysplasia- Pulmonary hypoplasia).

How to diagnose a case of chILD?

First: History

Specific history that may assist the diagnosis includes the following:[3,16]

1- Age at onset of symptoms.

2- Rate of progression of symptoms.

3- Gestation (events during pregnancy).

4- History of choking or regurgitation or heartburn may be consistent with aspiration. Developmental delay makes this more likely. An H-type tracheo-oesophageal fistula may give symptoms that are worse at mealtimes.

5- Family history of:

   a) Consanguinity.

   b) Neonatal deaths.

   c) Lung diseases requiring oxygen therapy (about 10% of children with ILD will have an affected relative).

6- Previous episodes of lung infection may suggest infectious cause or immunodeficiency.

7- Exposure to organic dusts, in particular exposure to birds, suggests hypersensitivity pneumonitis.

8- Involvement of other systems, e.g. skin, joints, eyes, suggests connective tissue disease or sarcoidosis.

9- Hemoptysis suggests pulmonary hemosiderosis.

10- Abnormal bowel habit suggests cystic fibrosis (CF).

11- A history of wheeze is common in chILD and may have led to an erroneous diagnosis of asthma.

Second: Clinical examination

Examination findings in children with ILD include:[17]

- Tachypnea
- Chest wall recession
- Inspiratory crepitations
- Wheezes
- Clubbing
- Desaturation

Third: Investigations

Is there one test to diagnose chILD?

Investigation should be directed at excluding other forms of lung disease and to determining the cause, nature and severity of the chILD.

The adopted protocol of investigation according to chILD foundation[1,3,18] passes through 3 serial rounds of investigation as follows.

First round investigations:

1- Imaging (CXR / High resolution CT chest).

2- Lung functions (including DLCO if old enough).

3- SaO2 (at rest and exercise).

4- Blood tests.

   - CBC and film.
   - ESR.
   - Immunoglubins.
   - Serology: for adenovirus, EBV, CMV, Influenza.
   - CMV PCR.
   - HIV ELISA or PCR.
   - Autoantibody panel (anti-nuclear, anti-basement membrane, antineutrophil cytoplasmic antibodies).
   - RAST test if suspected organic dust.
   - Angiotensin converting enzyme (elevated in sarcoidosis).

5- Air way secretions for C&S / PCR – viral / bacterial / fungal.

6- Sweat chloride test.

7- pH study / Contrast swallow.

8- ECG and ECHO.

9- Ciliary Brush Biopsy.

10- Urine for CMV PCR.

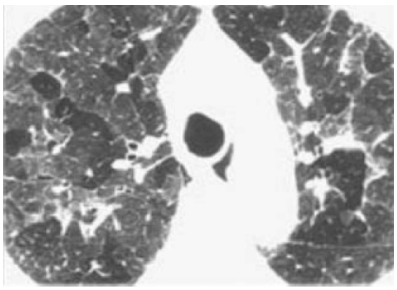
Imaging

Childhood's ILD is a serious diagnostic possibility as further investigations are needed, regardless of the chest radiography appearances.

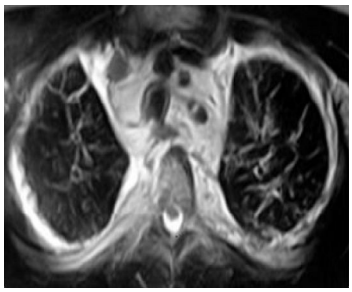
The next investigation is HRCT, which should precede the performance of an extensive panel of blood tests.[8]

Imagaing is an important part of diagnosing ILD. CXR appearance may be normal even with active disease. More usually there is a combination of increased reticular or reticulonodular markings and generalized hazy shadowing (ground glass appearance).[18] HRCT scans will nearly always be abnormal with reticular markings and ground glass changes (e.g. are they the normal or abnormal parts of the lung) careful controlled ventilation inspiratory and expiratory scans are needed. It will usually be necessary to sedate or anaesthetize children less than 4 years of age. Poor quality image will only confuse the clinical picture. It may be possible to combine sedation or anesthesia used for CT scan with a subsequent BAL (do not do the BAL first; the subsequent CT scan will cause some alarm!). The CT may also show architectural distortion and traction bronchiectasis. Increased interstitial markings can give a honeycomb appearance to the lung.[19]

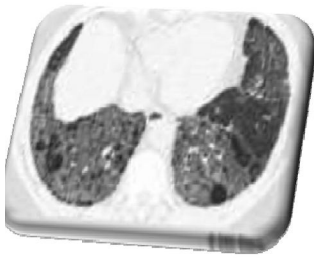
The chest radiograph is usually very non-specific and non-diagnostic.[2,20] There may be groundglass shadowing with prominent air bronchograms, or coarse nodular or reticularnodular shadowing; in advanced cases, honeycombing is seen. However, some children with ILD may have normal chest radiography. 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.[21]



Subacute hypersensitivity Pneumonitis



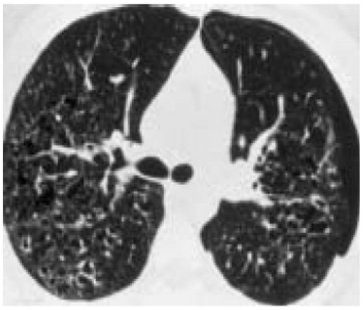
Chronic hypersensitivity pneumonitis



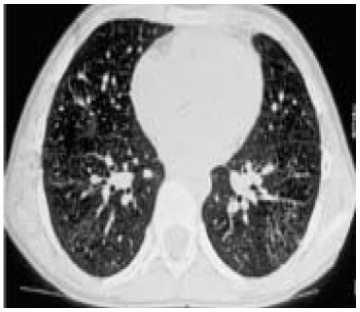
Aspiration Pneumonitis

On occasion, a primary airway disease, such as reflux and aspiration, or bronchiectasis, may be seen, prompting completely different lines of investigation.[22-24]

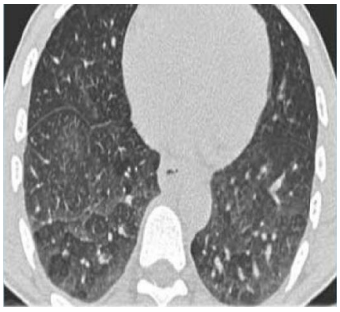
Alternatively, a child with an apparently normal chest radiograph may in fact be shown to have extensive ground-glass shadowing or other changes suggestive of ILD.[25] There are three other reasons for performing HRCT in this context. First, in very few cases, HRCT may be diagnostic. This is much less common than in adult ILD, but specific patterns, such as IPH, Langerhans cell histiocytosis , pulmonary microlithiasis or pulmonary alveolar proteinosis (PAP) may be identified, obviating the need for further tests.[26] 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.[27,28]



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



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



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

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 (FEV_1) and forced vital capacity (FVC), with a normal or elevated FEV_1/FVC ratio). Carbon monoxide transfer is usually reduced, but may be elevated if there has been a recent pulmonary haemorrhage due to IPH[3,7] 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 pediatric ILD occur in an age group in which lung function testing is difficult outside a research context.[2,29,30]

There is little published about infant and pre-school lung function testing in pediatric 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.[31,32]

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.

Other non-invasive investigations

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.[2]

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).[33] If opportunistic infection is suspected, HIV testing is mandatory. An auto-antibody profile, which should include antineutrophil cytoplasmic antibody, may lead to a diagnosis of Wegener's granulomatosis or other connective tissue disease, and obviate the need for a lung biopsy.[31] The presence of renal disease would suggest Goodpasture's syndrome, or Wegener's or another vasculitis, which may be confirmed by serological testing.[32]

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 pediatric ILD.[33]

Second round investigations:

1- High resolution controlled ventilation inspiratory and expiratory CT scan.

2- Bronchoscopy and BAL for cytology (LCH, iron laden macrophages, PAP) and cultures.

3- Prone Oesophagram for H type fistula.

4- Videofluroscopy for aspiration evidence.

5- Cardiac Catheter (check pulmonary venous drainage and pulmonary arterial pressure).

6- Detailed lymphocytes subsets and lymphocyte

function tests.

7- Tuberculin test and TB –Elispot IGRA test.

Role of bronchoscopy

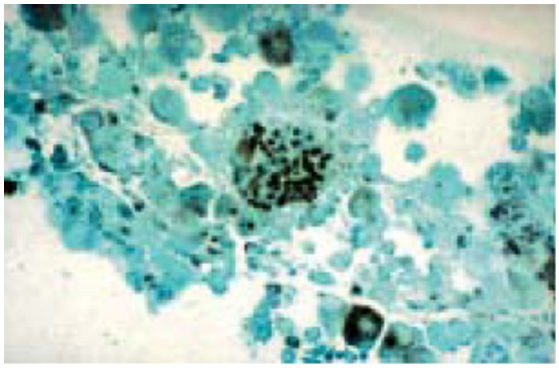
Fibreoptic bronchoscopy (FOB) allows inspection and biopsy of the airways (almost invariably not informative in ILD), BAL and transbronchial biopsy (TBB). However, the procedure requires a general anaesthetic or such heavy sedation as almost to amount to general anaesthesia[1,33] It should only be performed 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, in particular if the child has not received prior antibiotic therapy.[34]

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, LCH, PAP and lipoid pneumonia due to aspiration of oily medications.[21–24]

However, there is so little pediatric BAL experience in ILD, and such a paucity of normal ranges, that, in general, BAL is not useful in other ILD.

TBB is of immense value in the context of possible lung rejection after transplant,[35] 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).[36]

The samples are too small for diagnosis of most paediatric ILD. There are also safety issues; pneumo-thorax 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,[37] 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.[38]



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

BAL from a child with ILD. The Prussion 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.

Third round investigations:

1- Lung biopsy (Transbronchial, percutaneous, thoracoscopic, open lung).

CT guided from affected patch and unaffected patch, for:

- o Special stains (e.g. Bompesin or PAS).
- o Immunoblotting for sufactant proteins at lung biopsy.
- o Electron microscopy study of biopsy.

2. DNA for mutations in SPB, SPC and ABCA3 (only available at specialist centers).

Invasive diagnosis (Lung biopsy)

It will be obvious from the above that the majority of pediatric ILD will require a biopsy for diagnosis, 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 anesthetics, e.g. for HRCT and then FOB, before going on to a biopsy.[39]

Tips for Lung biopsy in chILD[3]

- Almost all children with ILD will require a lung biopsy as part of definitive investigation.
- The biopsy may be diagnostic, e.g. showing evidence of vasculitis or interstitial fibrosis, but this is not always the case.
- Although lung biopsy can be performed using transbronchial and percutanous approaches the amount of tissue obtained may be too small to make an accurate histological diagnosis. Thoracoscopic or open lung biopsy is preferred by most centers.
- The site for biopsy should be guided by the CT scan. In general, the right middle lobe and the lingular (which are the surgeon's favorites) should be avoided as they are often spared in patchy disease. Ideally 2 sites should be biopsied; one site thought to be affected and one site thought to be normal.
- Since ILD is often patchy a negative biopsy does not exclude the diagnosis.

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, immuno-histochemistry, electron microscopy and culture of the biopsy for mycobacteria and fungi in particular should always be performed.[40]

The limitations of TBB in ILD have been discussed above; the other choices are percutaneous CTguided biopsy, open lung biopsy (OLB) through a mini-thoracotomy incision and video-assisted thoracic surgery (VATS).[34]

Percutaneous biopsy has been used in some centres,[41] but is not the optimal technique:[42] 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.[43]

The current author has recently reviewed his own experience of OLB through a mini-thoracotomy.[44] 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.[2] Large samples can be obtained and a diagnosis is usually possible.[44]

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.[7]

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.[45]

Histologic Classification of chILD[3]

DIP: Desquamative interstitial pneumonitis

CIP: Chronic pneumonitisof infancy

NSIP: Non-specific interstitial pneumonitis

FB/LIP: Follicular bronchiolitis /lymphoid Interstitial Pneumonia

BO/OP: Organizing pneumonia (old BOOP)

PIG: Pulmonary interstitial glycogenosis

NEHI: Neuroendocrine cell hyperplasia of infancy

This is where some confusion can arise. The histological classification is often not the diagnosis; rather than it is the pattern of disease that the pathologist describes on the lung biopsy. For example, desquamative interstitial pneumonitis (DIP), chronic interstitial pneumonitis (CIP) and nonspecific interstitial pneumonitis of infancy (NSIP) can all be seen in children with surfactant dysfunction mutations (SPB, SPC and ABCA3 genes).[2,3]

Histological classification depends on the following[46]

- Presence and severity of any interstitial fibrosis.
- Presence of alveolar thickening.
- Degree of desquamation of material into the alveolar spaces and the presence of inflammatory cells (lymphocytes, neutrophils, plasma cells or macrophages).
- Presence or increase in specific cell types (such as pulmonary neuroendocrine cells and interstitial spindle cells).

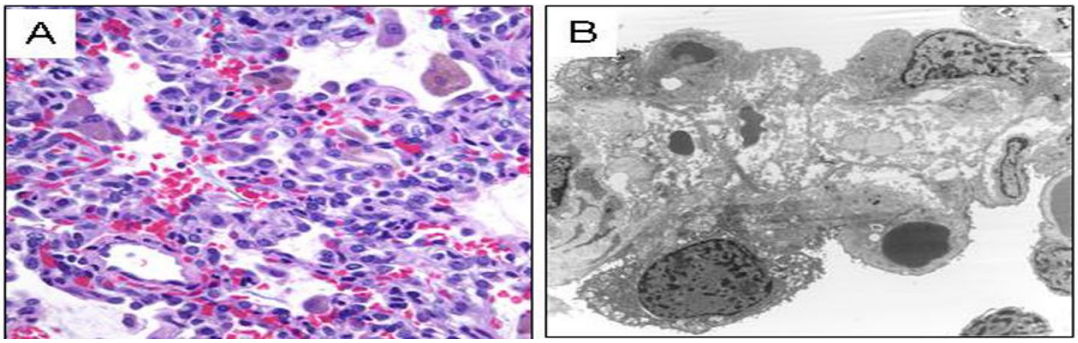
In children, ILD may manifest one of the following histological patterns:

1- Pulmonary Interstitial Glycogenosis (PIG)

The first description of this condition was in seven infants who presented with tachypnoea, hypoxaemia and diffuse infiltrates with hyperinflation either at birth or within 4 weeks of life.[40]

Lung biopsy showed interstitial expansion by immature spindle cells containing periodic-acid Schiff positive, diastase labile material consistent with glycogen. The condition is thought to represent dysmaturity of the interstitial cells with expectation of improvement with time with near normal lung functions by 6 years of age.[3]

Five were treated with pulse corticosteroids and one with additional hydroxychloroquine; six out of seven did well. CANAKIS et al.[40] proposed that this was an abnormality in lung cyto-differentiation involving interstitial mesenchymal cells, because abundant glycogen is not normally found in pulmonary interstitial cells.



Pulmonary interstitial glycogenosis (PIG).

(A) Lung histopathology from a 5-week-old infant shows diffuse interstitial widening and cellularity with bland-appearing vacuolated foamy cells that contain glycogen (periodic acid-Schiff [PAS] stain). These cells seen in PIG are strongly immunoreactive with vimentin (not shown). Pigmented alveolar macrophages were an additional finding in this infant with history of meconium aspiration.

(B) Electron microscopy demonstrates that these mesenchymal cells contain abundant monoparticulate glycogen.

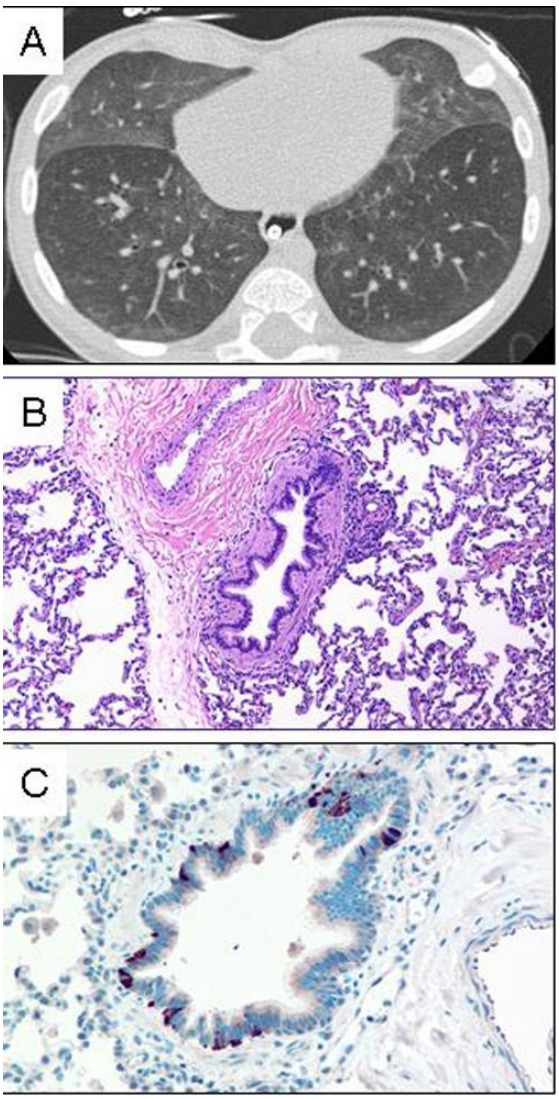
2- Neuroendocrine cell hyperplasia of infancy (NEHI)

Another ILD that has so far only been recognized in infants is NEHI.[31] Infants in first year of life present with respiratory distress, impressive respiratory crepitation 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 pulmonary neuroendocrine cells (PNECs).

PNECs are granulated epithelial cells found in normal airway epithelium and occasionally as small cluster within the lung parenchyma as neuroepithial bodies (NEB).[47] They are thought to be oxygen sensing cells that secrete several bioactive products (bombesin like peptide, serotonin and calcitonin) capable of brocho-constriction, vasoactivity and epithelial differentiation. They are abundant in fetal life and may play a role in pulmonary development.[2]

So, 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 pediatric ILD in infancy with normal histology.[1]

The diagnosis is a useful one to make because these children have a good prognosis. They do not respond to steroids or hydroxychoroquine, although a trial of steroids will nearly always be given. There is a platue period where the clinical condition remains unchanged, followed by slow improvement, without significant relapses. Most children require daytime oxygen for several months and night time oxygen for 2-3 years. In older children lung function may be normal or may show mild obstruction.[48]



Neuroendocrine cell hyperplasia of infancy (NEHI).

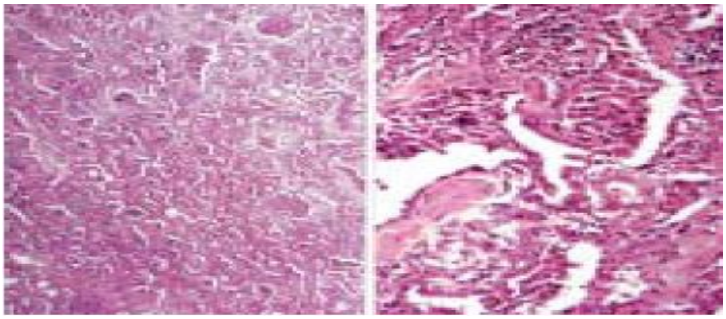
(A) Chest high-resolution CT (HRCT) scanning (at total lung capacity) in a 6-month-old infant with tachypnea, hypoxemia, and failure to thrive. Sharply defined areas of ground glass opacity are seen most prominent in the right middle lobe and lingual. Diffuse air-trapping was seen on expiratory images (not shown). No additional abnormalities were identified.

(B) Hematoxylin and eosin staining of the lung biopsy reveals near-normal lung architecture.

(C) Bombesin immunostaining reveals increased numbers of neuroendocrine cells.

3- Desquamative interstitial pneumonitis (DIP)

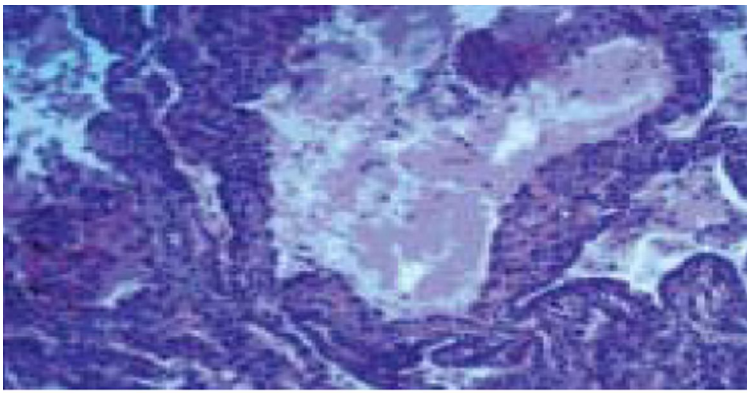
In DIP there is diffuse involvement of the lung with macrophage accumulation within most of the distal airspaces. The alveolar septa are thickened by a sparse inflammatory infiltrate. A familial form has been described.[33]



DIP: Note the large numbers of intra-alveolar macrophages.

4- Chronic interstitial pneumonitis of infancy (CIP)

CIP is characterized by marked alveolar septal thickening, alveolar type 2 cell hyperplasia, and an alveolar exudate containing numerous macrophages and foci of eosinophilic debris. Primitive mesenchymal cells predominate within the widened alveolar septa and inflammatory cells are scant.[49,50]



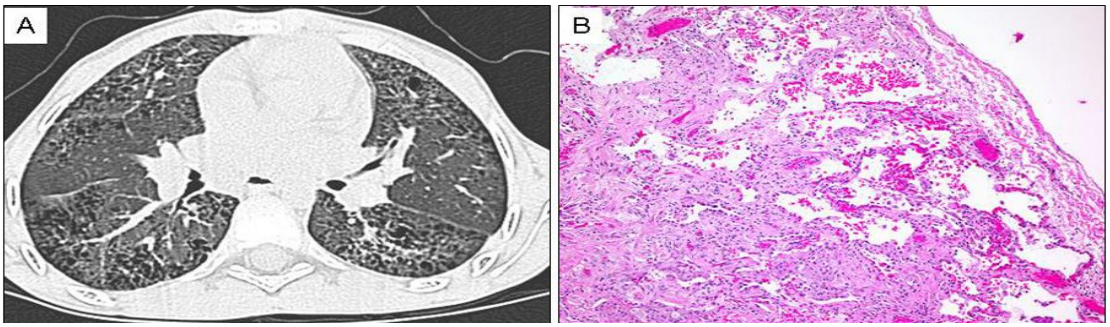
CIP
There is florid type 2 cell hyperplasia and proteinaceous intra-alveolar material.

5- Nonspecific interstitial pneumonitis (NSIP)

This term is used to describe histological findings that do not fit into the description of UIP, DIP or CIP. There is evidence of mild to moderate interstitial inflammation and evidence of fibrosis.[51]

(A) Chest high-resolution CT (HRCT) scanning from a 10-year-old with systemic sclerosis and progressive exercise intolerance.

(B) Lung biopsy showed multiple abnormalities including a relatively diffuse interstitial process with mild chronic inflammation, abundant fibroblastic tissue and patchy dense interstitial fibrosis. Accumulation of alveolar macrophages is seen in the airspaces, with rare foci of organizing pneumonia. Pulmonary arteries demonstrated focal intimal hyperplasia and medial hypertrophy, and the pleura contains patchy chronic inflammation. This overall constellation of findings is generally classified as mixed cellular and fibrotic nonspecific interstitial pneumonia (NSIP) and is a pattern most commonly seen in the setting of underlying collagen vascular disease.



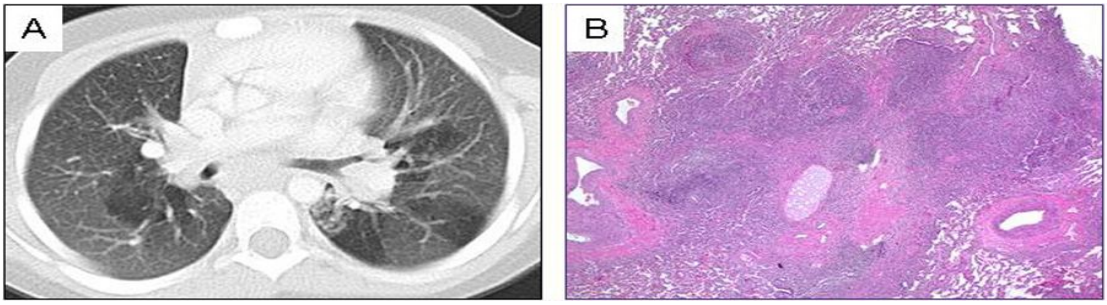
Histological diagnosis	Pathological features
CPI	Florid type-2 cell hyperplasia Mild interstitial inflammation Proteinosis-like intra-alveolar material
DIP	Homogeneous interstitial pneumonitis Dominant alveolar macrophages
NSIP	Homogeneous interstitial pneumonitis No single predominant feature May or may not be fibrosis

6- Follicular bronchiolitis /lymphoid Interstitial Pneumonia (FB/LIP)

These are thought to be part of the same spectrum of disorders causing lymphoid hyperplasia. There is a heavy lymphoid interstitial infiltrate that may contain germinal centers. If these affect the airway walls the term "FB" if often used. There is a strong association with immunodeficiency (including that caused by HIV infection), possibly combined with EBV infection. In others there may be underlying connective tissue disease.[52]

(A) Chest high-resolution CT (HRCT) scan from a 6-year-old infant with common variable immunodeficiency with history of anemia, thrombocytopenia, recurrent pneumonia, chronic cough, and exercise intolerance. Mosaic attenuation is present diffusely throughout the lungs. Extensive hilar and mediastinal lymphadenopathy is also present. Air-trapping was seen on expiratory images (not shown).

(B) Lung histopathology demonstrates severe airway-centric lymphocytic inflammation with reactive follicles, which infiltrates and obscures most bronchioles.



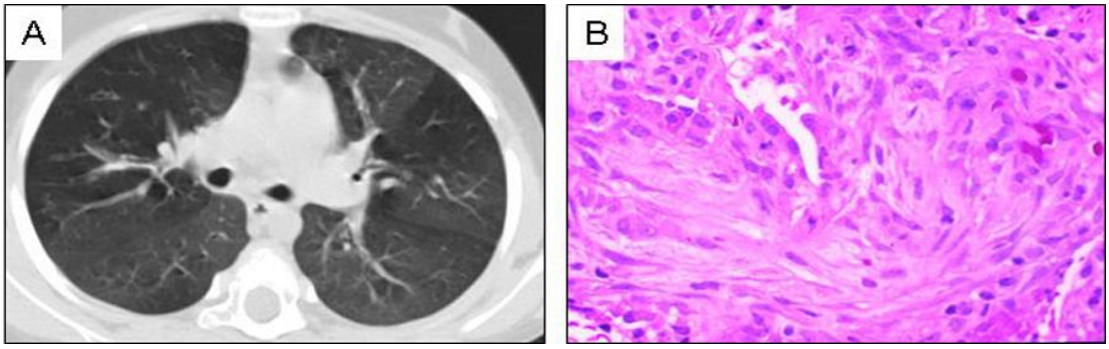
7- Bronchiolitis obliterans and organizing pneumonia (BO/OP)

OP is preferred to the previous term BOOP, because it avoids confusion with conditions predominantly affecting the airways. OP is characterized by intraluminal organizing fibrosis or polypoid masses of granulation tissue in distal airspaces (bronchioles, alveolar ducts and alveoli). OP in children is most often described after severe viral or Mycoplasma pneumoniae. It has also been associated with some connective tissue disorders.[53] There are a few case reports where no cause has been identified and these would now be called cryptogenic OP. The patchy involvement of airspaces (which can also see on CXR and CT scan) distinguishes OP from bronchiolitis

obliterans.[54]

(A) Chest CT scanning from an 8-year-old demonstrates irregular large mosaic regions of ground-glass opacity and air-trapping, as well as the presence of peribronchial thickening and bronchiectasis.

(B) Pathology demonstrates focal areas of fibrosis with polypoid plugs of fibroblastic cells and fibrin filling distal bronchioles and airspaces (hematoxylin and eosin).



8- Rare histological forms of chILD:

***UIP:** Usual interstitial pneuminitis the pattern associated with IPF in adults is rarely described in children. UIP is characterized by a heterogeneous appearance at low magnification, with alternating areas of normal lung, inflammation, fibrosis, and honeycomb changes, which are most prominent in the peripheral subpleural areas. Fibrotic areas contain dense collagenous deposits and characteristic foci of proliferating fibroblasts (fibroblastic foci), which have negative prognostic importance. There is only one well-characterized report of UIP in a child, and adolescent with ABCA3 deficiency.[55,56]

****Pulmonary LCH:** Langerhans cells histiocytosis X, is predominantly interstitial on histologic analysis, with features of centrally scarred, stellate nodules with a polymorphic infiltrate containing characteristic Langerhans cells. The lungs are involved in approximately 10-40% of children with LCH, but few children present with isolated lung disease. In adults, pulmonary involvement is clearly related to smoking.[57]

Recent advances in chILD syndrome

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 C chain of the granulocyte-macrophage colony stimulating factor (GM-CSF) receptor (see below); secondary, in conditions associated with functional impairment of the macrophage (such as haematological cancers, some infections;[37–40] and later onset, probably an autoimmune disease, with auto-antibodies targeting GM-CSF.[50,51] The role of GM-CSF in surfactant 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.[47,48]

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).[46] GM-CSF therapy in PAP restores PPAR 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.[60]

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 carboxy terminal 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 characterized 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 frame shift 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.

It was determined that 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.[61]

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]

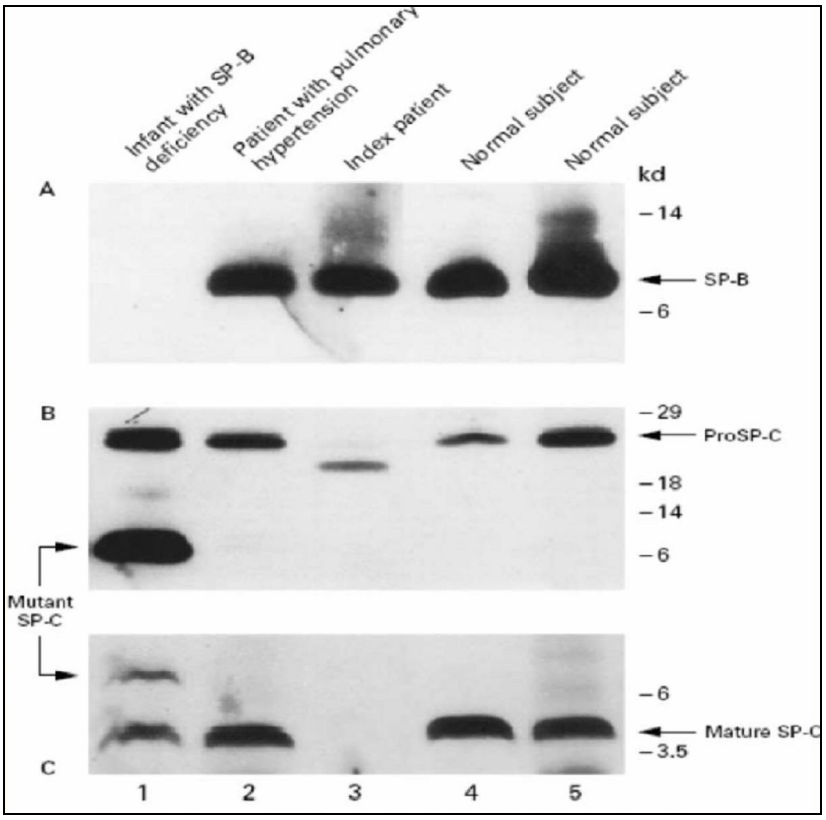
There were no normal lamellar bodies. However, the SP-B and -C genes were sequenced and found to be normal. The reasons for the abnormal surfactant accumulations within pneumocytes are unclear, but could include a primary secretory defect, a defect in surfactant phospholipids, an abnormal interaction 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.[1]

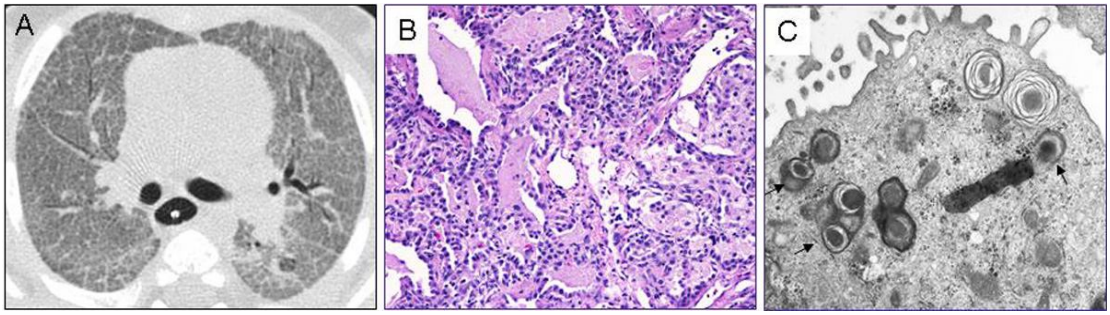
Surfactant Metabolism Dysfunction related chILD

- Surfactant is a complex mixture of phospholipids and proteins. These proteins are identified as; (SP-A, -B, -C and -D) & ABCA3.
- ABCA3 ⟶ an ATP-binding transporter of lipids.
- Mutations of SPB, SPC and ABCA3 could present as chILD

Immunoblotting for surfactant proteins in lung tissue for children with mutant surfactant proteins (SPB and SBC) compared to healthy children



Childhood ILD due to ABCA3 gene mutation[3]



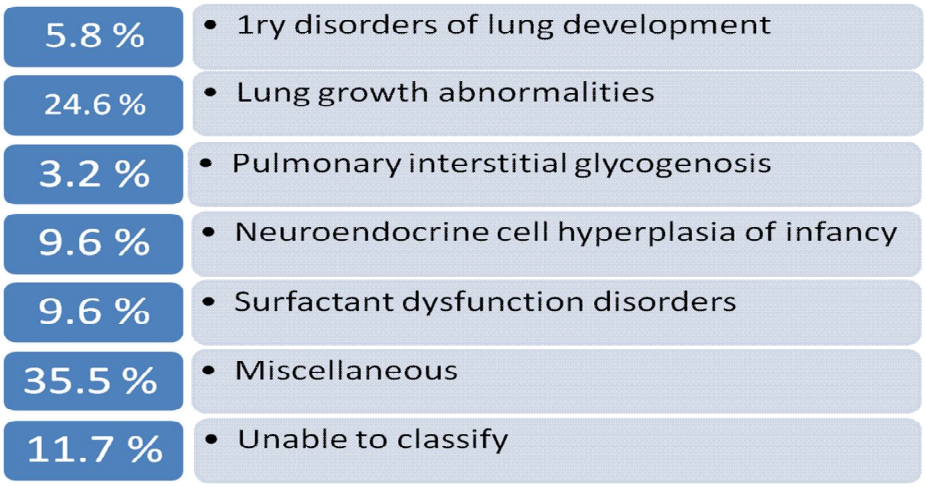
Interstitial lung disease (ILD) due to ABCA3 gene mutations.

(A) High-resolution CT (HRCT) scan from a 4-month-old infant with ABCA3 mutations. The CT scan was performed with controlled ventilation under general anesthesia. Diffuse bilateral ground glass opacities and thickened interlobular septae are present. This "crazy paving" pattern suggests alveolar proteinosis or ILD due to genetic mutations affecting surfactant function and metabolism.

(B) Histopathology (hematoxylin and eosin) shows diffuse alveolar septal thickening with uniform prominent type II cell hyperplasia. Accumulations of alveolar macrophages and granular proteinosis are also present in the alveolar spaces.

(C) Electron microscopy demonstrates abnormal lamellar bodies with dense inclusions (arrows).

European spectrum classification of children presented with ILD[1]



* Those children who were unable to be classified according a definitive cause are those who are entitled to be "chILD syndrome" and usually nominated according to lung biopsy.

Treatment

General rules[62]

- Treatment depends on the cause.
- Where no cause has been identified, it is common practice to give a trial of systemic corticosteroids. Steroids may be of some help in children with SPC and ABCA3 related lung disease. The dose and duration depend on the severity of the illness and the response. In most children an initial high dose (2 mg/kg) course of 4 weeks can be used to assess response. If improvement is seen, a weaning course over a further 8 weeks, with or without a maintenance dose, can be tried.
- In children who do not respond, or who have severe oxygen dependent disease, Pulse Therapy of IV methylprednisolone (10-30mg/kg once daily for 3 days) is an alternative and can be repeated on a monthly basis for 6 months.
- There is also anecdotal response to hydroxychloroquine combined with prednisolone.
- Other immunosuppressive treatments, including azathioprine, cyclophosphamide and methotrexate, have all been tried with varying success.
- Post infectious organizing pneumonia OP usually responds to corticosteroids.
- In all forms of ILD, if medical therapy has failed, lung transplantation may be considered.

Primary treatment "treatment of the cause"

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.[2]

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.[63]

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.[2]

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.[1]

There are other therapies for specific ILDs for which no satisfactory trials have been carried out. IPH probably responds best to hydroxychloroquine,[64] 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 tobaccosmoke 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.[65]

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.[66]

Medical Care[67,68]

The multiple possible diagnostic entities and lack of randomized clinical trials make offering specific recommendations regarding treatment of children's interstitial lung disease (chILD) impossible. If the process is secondary to an underlying condition, patients should be treated for the underlying disease.

The same principles that apply to all children with chronic pulmonary diseases apply to those with interstitial lung disease (ILD). These include meticulous attention to growth and nutrition, immunizations (including influenza and pneumococcal prophylaxis), and treatment of secondary infections.

- Treatment with bronchodilators, inhaled steroids, or both may be appropriate if any component of airway reactivity is demonstrated on PFT. However, this therapy has not been proven to modify the clinical course of most types of ILD.
- Oxygen therapy, either continuously or during sleep, may be necessary to provide symptomatic relief and to decrease the risk or halt the progression of pulmonary hypertension and cor pulmonale related to alveolar hypoxia.
- Active and passive smoking should be avoided. Smoking cessation should be actively pursued for caregivers who smoke.
- Many medications have been used to treat different forms of ILD. No therapeutic regimen has been subjected to the rigors of a randomized control trial in the pediatric population. Numerous broad treatment strategies have been attempted, including anti-inflammatory medications (eg, steroids, cytotoxic agents, immunosuppressive therapies), collagen synthesis inhibitors, antifibrotic agents, hydroxychloroquine, intravenous immunoglobulin (IVIG), antioxidants, and cytokine inhibitors.
- Hypersensitivity pneumonitis is the most treatable condition among chILDs. Other steroid-responsive conditions include NSIP, LIP, COP, eosinophilic pneumonia syndromes, sarcoidosis, pulmonary hemosiderosis, and ILD associated with connective tissue disease.
- Treatment of specific conditions resulting in ILD includes antiviral agents against CMV and EBV, antiretroviral therapy in addition to prednisolone for

AIDS-associated LIP, surgical approach for lymphangiomatosis, therapeutic BAL for PAP, and PPI and Nissen fundoplication for GER-associated chronic aspiration. Reports indicate that infliximab (an inhibitor of tumor necrosis factor [TNF]-alpha) may be beneficial for ILD associated with rheumatoid arthritis.

- Several studies have demonstrated successful use of subcutaneous treatments with GM-CSF in adults with PAP.
- In patients with associated PAH, sildenafil and/or anticoagulant therapy should be considered.
- In patients with congenital PAP due to GM-CSF receptor mutation or acquired receptor dysfunction secondary to autoantibody formation, subcutaneous or inhaled GM-CSF treatment has been reported to be beneficial.[45,46]

***Surgical Care*[1,68]**

- Surgical consultation is usually sought for diagnostic biopsy (see Procedures).
- Patients with end-stage idiopathic forms of ILD, severe lung disease associated with SFTPB or ABCA3 mutations, as well as some pulmonary veno-occlusive diseases, may be candidates for lung or heart/lung transplantation. These patients are considered on an individual basis at the few centers specializing in pediatric lung transplantation.
- 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.
- In children, the establishment of lung transplantation has been slower than in adults. Only 5% of all patients receiving transplants for this reason have been younger than 18 years. For some diseases, such as SP-B and ABCA3 deficiencies and alveolar capillary dysplasia, lung transplantation remains the only effective treatment.
- The latest reported result was a 77% overall survival rate for the first year after transplantation in children.45 The 3- and 5-year survival declined to 63% and 54%, respectively. The authors observed no statistical relationship between pretransplantation diagnoses and long-term survival. The same authors reported 19 infants younger than 6 months who underwent lung transplantation: Seven had SP-B deficiency, 4 had PAP of other etiology, 3 had congenital interstitial pneumonitis, 2 had alveolar-capillary dysplasia, and 10 had pulmonary vascular disease.

***Consultations*[69-72]**

- Pediatric pulmonologist: All children with ILD should be treated in consultation with a pediatric pulmonologist.
- Pediatric ILD specialist: In addition, referral to or telephone consultation with a center with clinicians specializing in childhood ILD is advised.
- Pediatric cardiologist: As a result of the existence of cardiovascular diseases masquerading as ILD, all patients should see a pediatric cardiologist.
- Pediatric rheumatologist: A pediatric rheumatologist should be involved in the management of ILD associated with connective tissue disease.
- Pediatric radiologist: Consult a pediatric radiologist regarding interpretation of imaging studies.
- In addition, consider consultation with the following specialists:
  - Infectious disease specialist.
  - Immunologist.
  - Rheumatologist.
  - Transplantation specialist.
- ***Pathologist:*** Consultation with a pathologist is recommended before tissue is obtained to ensure that adequate specimens are collected and that they are correctly processed. Consider consultation with a pathologist knowledgeable about chILD.

***Diet*[1]**

No specific diet is necessary. However, as with patients with any chronic disease, patients with chILD should receive sufficient kilojoules to maintain adequate growth. Decreased lung compliance increases the work of breathing and energy expenditure. Energy supplementation should be undertaken with consideration to the added difficulty in handling high carbohydrate loads with chronic lung disease. Consult a nutritionist experienced in the management of chronic pulmonary conditions in children. Young infants with feeding difficulties resulting from dyspnea may require a transpyloric or gastrostomic feeding tube.

***Activity*[73]**

Activity may be limited by the patient's degree of dyspnea. Oxygen saturation during exercise should be measured. A prescribed, monitored, exercise program may be beneficial to prevent deconditioning in older children. Conditions that may exacerbate pulmonary

symptoms (high levels of ozone or other environmental pollutants) should be avoided. Patients with hypersensitivity pneumonitis should be removed from exposure to the precipitating substances (eg, birds, organic dusts). Air travel or travel to high altitudes must be carefully planned in patients with arterial desaturation.

Medication[1,74-78]

Corticosteroids have been the mainstay of therapy in most children and adults with interstitial lung disease (ILD), despite little conclusive evidence of their efficacy. The theoretical basis for the use of corticosteroids is the assumption that the lung remodeling is in large part the result of persistent inflammation. This paradigm has recently been challenged in IPF. Steroids may be administered daily or by pulse. Steroid responsiveness is often considered an important prognostic indicator. Data in adults indicate that the specific histopathologic pattern seen on biopsy specimens correlates with the degree of response to steroids. This has not been verified in children. Time to response is variable, but steroids should be continued for at least 8-12 weeks at full dose before therapy is deemed to have failed. Improvement may be seen in symptoms, physical signs, or chest radiographic appearance alone.

A. Glucocorticoids

These agents elicit anti-inflammatory properties and cause profound and varied metabolic effects. They modify the immune response of the body to diverse stimuli. Suppression of immune-mediated alveolitis and repair mechanisms may reduce the progression of fibrosis. Data from small studies suggest that pulse administration with intravenous (IV) corticosteroids may improve survival and lessen toxicity compared with prolonged courses of oral steroids.

Prednisone (Deltasone, Meticorten, Orasone, Sterapred)

Most widely used agent, particularly for UIP, DIP, and hypersensitivity pneumonitis. May decrease inflammation by reversing increased capillary permeability and suppressing polymorphonuclear (PMN) activity.

2 mg/kg/d PO for 6-8 wk; not to exceed 60-80 mg/d; continue 8-12 wk at full dose, gradually taper or adjust dose to clinical response and PFT results; symptom relapse warrants return to maximum dosing

Methylprednisolone (Solu-Medrol)

Decreases inflammation by suppressing migration of PMN leukocytes and reversing increased capillary permeability. Can decrease frequency in patients with stable clinical course.

10-30 mg/kg/d IV for 3 d each month; in patients with stable clinical course, interval may be gradually increased

B. Immunomodulating and immunosuppressive agents

The use of hydroxychloroquine and chloroquine has been reported, with variable results. Hydroxychloroquine has been used most frequently as a corticosteroid sparing agent with anecdotal success in ILD and alveolar hemorrhage syndromes. The mechanism of action is unknown. Recent data suggest that the efficacy of these agents may be related in part to alkalization of macrophages, which may reduce the secretion of TNF-alpha and impair antigen presentation.

Azathioprine, MTX, cyclophosphamide, or penicillamine may be used as second-line therapy if response to corticosteroids has not occurred, if a steroid-sparing effect is desired, or as an adjunctive agent to steroids in severe or rapidly progressive disease. The mechanism of action is presumed to be immunosuppression by means of relative myelosuppression. The potential for pulmonary toxicity from MTX and cyclophosphamide has limited their use.

Hydroxychloroquine (Plaquenil)

Inhibits chemotaxis of eosinophils and locomotion of neutrophils and impairs complement-dependent antigen-antibody reactions. Hydroxychloroquine sulfate 200 mg equivalent to 155 mg hydroxychloroquine base and 250 mg chloroquine phosphate. Dose and duration not tested in controlled trials, but, case reports describe children receiving 5-10 mg/kg/d for years. In adults, usually discontinued if no clinical response after 6 months.

Dose: 10 mg/kg/d PO hydroxychloroquine base; not to exceed 400 mg/d hydroxychloroquine sulfate

Chloroquine phosphate (Aralen)

Generally not used in young children who are unable to comply with thorough color-vision testing. Anti-inflammatory activity from lymphocyte transformation suppression. Dose and duration not tested in controlled trials, but case reports describe children receiving 5-10 mg/kg/d for years. In mostly uncontrolled case reports and small series of infants <6 mo with ILD, mortality rates 66% with corticosteroids alone vs 16% with chloroquine. Most infants responded clinically within first 2 mo of treatment.

Dose: 5 mg/kg/d (as base) PO; not to exceed 300 mg/d (as base) PO; doses up to 10 mg/kg/d PO reported

Azathioprine (Imuran)

Antagonizes purine metabolism and inhibits DNA, RNA, and protein synthesis. May decrease proliferation of immune cells, which lowers autoimmune activity.

Dose: 1 mg/kg/d PO for 6-8 wk initially; increase by 0.5 mg/kg/d q4wk up to 2.5 mg/kg/d or until response

Methotrexate (Rheumatrex)

Unknown mechanism of action in treatment of inflammatory reactions; may affect immune function.

Dose: Specific dosing for ILD not standardized In inflammatory conditions, such as JRA, 10 mg/m2/wk PO has been administered as single dose qwk; not to exceed 15 mg/wk

Precautions: Folic acid usually prescribed concurrently as 1 mg/d; may elevate hepatic enzyme levels and persistent elevation may indicate hepatotoxicity or cirrhosis; monitor blood CBC counts at baseline and monthly.

Cyclophosphamide (Cytoxan)

Chemically related to nitrogen mustards. As an alkylating agent, mechanism of action of active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells.

Dose: 5-10 mg/kg IV q2-3wk; not to exceed adult range of 500-1800 mg/dose

Penicillamine (Cuprimine)

Metal-chelating agent. Use in patients with ILD reported. Mechanism of action unknown.

Dose: 3 mg/kg/d PO for 3 mo, not to exceed 250 mg/d; then 6 mg/kg/d PO divided bid for 3 mo, not to exceed 500 mg/d; not to exceed final maximum dose of 10 mg/kg/d PO divided tid/qid

Treatment of sarcoidosis with infliximab[2]

Infliximab is a chimeric immunoglobulin G monoclonal antibody against tumour necrosis factor (TNF)-alpha, 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- alpha,[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.

Patient Education[1]

- Stress the importance of compliance with medication and nutritional regimens, rehabilitation, and regular follow-up visits.
- Carefully instruct patients and parents about the need to report possible adverse effects of medications and to monitor for signs and symptoms of superinfection.
- Counsel patients and caregivers of patients with hypersensitivity pneumonitis to avoid precipitating exposures.
- Strongly advise smoking cessation and prevention, and inform patients and caregivers about specific support programs.
- Encourage involvement in support groups for rare disorders such as the Children's Interstitial Lung Disease (chILD) Foundation.
- Caregivers and patients should receive education and counseling appropriate for families of children with chronic respiratory diseases, including financial counseling and transplantation preparedness.

Follow-up[3]

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.[2]

Further Inpatient Care

- Admit patients to the hospital for diagnostic workup and initial therapy, pulse courses of IV corticosteroids, management of superimposed infections, and management of any serious adverse drug reactions.

Further Outpatient Care

- A pediatric pulmonologist should regularly follow up patients with interstitial lung disease (ILD).
- The patient's oxygen saturation, nutritional status, and incidence of adverse drug reactions should be monitored at each visit.
- PFTs and imaging studies should be used to monitor disease progression and the patient's response to treatment.
- Echocardiography should be repeated to assess for the development of pulmonary hypertension or corpulmonale.

Inpatient & Outpatient Medications

- New therapies, particularly use of cytotoxic or immunosuppressive drugs, should be initiated in the hospital.

- Long-term therapeutic agents are usually administered and monitored on an outpatient basis.

Transfer

- Transfer may be necessary for further diagnostic workup or lung transplantation.
- Pretransplantation evaluation should be initiated before end-stage disease develops to allow sufficient time for evaluation and donor identification.

Complications[5]

- Superinfection can be life threatening, particularly if the patient is receiving immunosuppressive medications. Immunosuppressive drugs can mask signs and symptoms of infection. Prevention and careful monitoring are crucial.
- Drug toxicity causes much of the morbidity associated with ILD. Again, prevention and monitoring are the keys to management.
- Hemoptysis may occur in some types of ILD and suggests vasculitis or venoocclusive disease as possible underlying causes.
- Death is usually the result of respiratory failure or cor pulmonale and right heart failure.

Prognosis[1]

- Mortality rates as high as 90% have been reported in children who develop ILD when younger than 1 year (predominantly DIP); other studies have reported much better survival with conservative management.
- Fan and Kozinetz reviewed the outcomes of 99 children with ILD over 15 years. Survival rates at 24, 48, and 60 months after the appearance of initial symptoms were 83%, 72%, and 64%, respectively. Patients with histopathologic DIP and pulmonary vascular disorders have a prognosis worse than this.
- Familial IPF manifesting in the neonatal period is associated with a high mortality rate.
- 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 counseling 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 pediatric ILD and all through it, children are far away from adulthood spectrum.

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 open lung biopsy is the method of choice. Repeated anesthetics 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 pediatric ILD.

May be it is a long journey to solve the chILD's mystery, but it deserves to go through it!

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