CHAPTER 17

Paediatric interstitial lung disease

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Interstitial lung disease (ILD) in children (chILD) is very different in many aspects to the adult disease. First, chILD is rare, estimated at 0.36 per 100,000, compared with 60–80 per 100,000 for ILD in adults [1]. Secondly, the spectrum of conditions, in particular in infancy, is much wider than in adults. The conditions encompass growth and developmental issues, as well as immunological problems. The consequence is that paediatricians are even less advanced than adult physicians when it comes to making diagnoses by radiology and bronchoalveolar lavage (BAL), and this, combined with the rarity of the conditions, means that there have been no randomised controlled trials of treatment. Thus, chILD is very much work in progress. However, chILD is a really important topic for adult chest physicians; some of the paediatric diseases may in fact present in adult life, and if diagnostic awareness is not heightened, patients may disappear into a dustbin category such as usual interstitial pneumonia (UIP). Furthermore, rare genetic abnormalities may lead to an understanding of modifier genes important in adult ILD. In this regard, it is a pity that recent guidelines saw fit to ignore chILD altogether [2]. This chapter will first review recent advances in the classification of ILD in children, and then discuss presentation, diagnosis and differential diagnosis, as well as what little is known about treatment options.

Classification of ILD in children

There are two published classifications [3, 4], and a third is still only reported as an abstract [5]. The definitive classification in the 0–2-yr age range is from North America [4], and this is recommended for adoption. The European Respiratory Society (ERS) Task Force also contained data in the young age group, but mainly focused on 0–18 yrs [3], and the abstract from North America [5] is in children aged 2–16 yrs; this showed a very different spectrum of chILD compared with infants. The full publication is eagerly awaited at the time of writing.

ILD in infants aged 0–2 yrs

The antenatal period and the first 2 yrs of life are crucial in long-term lung health, and there is a clinical logic as well as data to suggest considering this time period separately from the 2–16-yr age range, although the cut-off is not completely clear. For example, surfactant protein gene disorders, particularly *Sp-B* and *ABCA3*, commonly present in the newborn period, but may present later in childhood or even in adult life as well (see below).

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This early time period is characterised by rapid growth of the airways, and particularly of the alveolar-capillary membrane, the maturing of the immune system, and encounters with new infectious, allergic and chemical challenges. The exact nature of the growth factors that drive the growth and maturation of the lung are ill understood, but are probably unique to this early time period. The immune system normally shows a change from the pregnancy-associated T-helper cell (Th) type 2 to a neonatal Th1 bias [6], and the infant has to switch from reliance on maternal humoral immunity during pregnancy to the development of immune responses and immune memory functions. Novel infective and allergic proteins are encountered, and acid reflux is common; pollution, including tobacco smoke exposure, will also impinge on the newborn respiratory system. The importance of a developmental perspective is shown by the study of kindreds with Sp-C deficiency [7]. In adult life, this is manifest by a pattern of UIP, but the same gene defect presenting in infancy causes a cellular nonspecific interstitial pneumonia (NSIP). One could speculate that other apparently exclusively paediatric conditions, such as pulmonary interstitial glycogenosis (PIG) and neuroendocrine cell hyperplasia of infancy (NEHI), may in fact represent the response of the immature lung to insults that in adult life might cause a very different pattern of ILD.

The North American chILD group have recently proposed dividing ILD in the 0–2-yr age group into eight categories (see below) [4]. The classification was based on 187 biopsies (of which 22 were unclassifiable) from 11 institutions over a 5-yr period. The strengths of the classification include the large number of cases reported and the independent pathological verification of the diagnoses. Ongoing issues include that it takes no account of what are the (admittedly rare) diseases that may not come to biopsy, for example idiopathic pulmonary haemosiderosis (IPH); and the need to validate the classification in a second population [8]. The classification might also be criticised as almost too broad, because it also encompasses diseases with a major airway component, such as obliterative bronchiolitis, and conditions in which there is usually no diagnostic doubt, such as bronchopulmonary dysplasia; perhaps "diffuse distal lung disease" might be a better term, but the term "chILD" is in fact probably here to stay. As in the classification of adult ILD, where organising pneumonia (a predominantly alveolar filling disorder) is included primarily as it enters the differential diagnosis of ILD, a greater number of non-interstitial disorders are included in the chILD classification, as these entities enter into the pre-operative differential diagnosis due to the lower sensitivity of investigative procedures, such as high-resolution computed tomography (HRCT), in children. Table 1 is a summary of the classification; each section is discussed in more detail below. Diagnoses made in a partially overlapping age group reported in the ERS Task Force (table 2) [3] included infection with *Pneumocystis*, Epstein–Barr virus and respiratory syncytial virus; desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP), NSIP and unclassified fibrosis; and some ILDs caused by an associated disease, such as alveolar proteinosis (unspecified), systemic lupus erythematosus, histiocytosis and aspiration. The ERS Task Force represented a large survey, but there was no independent validation of the pathological diagnoses, and it would seem that molecular studies were infrequently performed.

Category one: diffuse developmental disorders. The first two categories, "diffuse developmental disorders" and "growth abnormalities reflecting deficient alveolarisation" must surely be overlapping, since in practice growth and development are hard to separate [8]. They are, however, considered separately in the chILD group classification, and hence in this chapter. Diffuse developmental disorders are believed to be due to defects in one of the primary molecular mechanisms of the lung (and/or pulmonary vascular development, presumably on a molecular basis); they include acinar dysplasia,

Table 1. – Classification of interstitial lung disease (ILD) in children aged 0–2 yrs

Category		Illustrative diseases
1	Diffuse developmental disorders (n=11)	Acinar dysplasia (n=1) Congenital alveolar-capillary dysplasia (n=2) Alveolar-capillary dysplasia with misalignment of the pulmonary veins (n=8)
2	Growth abnormalities reflecting deficient alveolarisation (n=46)	Pulmonary hypoplasia (n=7) Chronic neonatal lung disease (bronchopulmonary dysplasia) (n=20) Related to chromosomal disorders (n=15) Related to congenital heart disease (n=4)
3	Specific conditions of undefined aetiology (n=24)	Pulmonary interstitial glycogenosis (n=18) Neuroendocrine cell hyperplasia of infancy (n=6)
4	Surfactant dysfunction disorders (n=18)	*Sp-B* gene mutations (n=0) *Sp-C* gene mutations (n=7) *ABCA3* gene mutations (n=6) Histology consistent with surfactant protein disorder but none detected (n=5 in total): Pulmonary alveolar proteinosis (n=2) Chronic pneumonitis of infancy (n=1) Desquamative interstitial pneumonia (n=1) Nonspecific interstitial pneumonia (n=1)
5	Disorders of the normal host, presumed immune intact (n=23)	Infectious and post-infectious (n=17) Environmental agents (n=2 in total): Hypersensitivity pneumonitis (n=2) Toxic inhalation (n=0) Aspiration syndromes (n=3) Eosinophilic pneumonia (n=1)
6	Disorders resulting from systemic disease processes (n=6)	Collagen vascular disease (n=4) Storage disease (n=1) Sarcoidosis (n=0) Langerhans' cell histiocytosis (n=0) Malignant infiltrates (n=1)
7	Disorders of the immunocompromised host (n=28)	Opportunistic infections (n=20) Iatrogenic (n=3) Related to transplant and rejection (n=0) Diffuse alveolar damage, unknown aetiology (n=5)
8	Disorders masquerading as ILD (n=9)	Arterial hypertensive vasculopathy (n=8) Venous engorgement secondary to heart disease (n=1) Veno-occlusive disease (n=0) Lymphatic disorders (n=0)

n=165 interpretable biopsies in total. Data taken from [4].

congenital alveolar dysplasia, and alveolar-capillary dysplasia with misalignment of the pulmonary veins (ACDMPV). Acinar dysplasia in pure form is characterised by lung growth arrest in the pseudoglandular or early canalicular phase and congenital alveolar dysplasia by growth arrest in the late canalicular or early saccular phase. However, a recent paper has stressed that overlap conditions are common [9]. The constellation of malposition of pulmonary veins adjacent to small pulmonary arteries, medial hypertrophy of pulmonary arteries and arterioles, and reduced capillary density with lobular maldevelopment was considered diagnostic for ACDMPV (fig. 1). DEUTSCH *et al.* [4] had biopsies in term infants who presented at birth with therapy-unresponsive

Table 2. – Classification of interstitial lung disease based on the European Respiratory Society Task Force [3]

Category	Commonest age yrs	Diagnoses made
Infection (n=19; 14.5%)	3–12 (n=10)	Adenovirus Mycoplasma Pneumocystis Epstein–Barr virus Respiratory syncytial virus Influenza A
Associated disease (n=51; 38.9%)	6–12 (n=17)	Hypersensitivity pneumonitis Aspiration syndromes Sarcoidosis Alveolar proteinosis Bronchiolitis obliterans Graft *versus* host disease "Chronic disease" Metabolic disorder Systemic lupus erythematosus Histiocytosis Granulomatosis Haemosiderosis Rheumatoid arthritis Vascular disorders Lymphatic disorders
Idiopathic (n=46; 35.1%)	6–12 (n=13)	Unclassified Desquamative interstitial pneumonia Usual interstitial pneumonia Nonspecific interstitial pneumonia Lymphoid interstitial pneumonia
Unclassifiable (n=14; 10.6%)	6–12 (n=5)	

hypoxia and persistent pulmonary hypertension. One child was transplanted, the rest were dead within a month. MELLY *et al.* [9] reported a larger group, in which there were four survivors. Histological features stressed by this group included the likely presence of PIG cells in 17 out of 21 cases, and the great variety of the degree of misalignment, with higher capillary apposition and density being predictive of a better prognosis. Associated abnormalities, including Down syndrome, were common. Finally, there is a single case report which describes complete resolution of severe pulmonary hypertension on sildenafil in a baby who appears to fall into this diagnostic group [10].

Category two: growth abnormalities reflecting deficient alveolarisation. Abnormal alveolar development that is largely secondary is the hallmark of this group. This includes pulmonary hypoplasia due to a small fetal thorax, reduced amniotic fluid volume, diminished or absent fetal breathing movements, reduced pulmonary blood flow, abdominal wall defects and chromosomal abnormalities. Post-natally, chronic lung disease of prematurity is in this group. It is arguable whether it is useful to include these patients in a discussion of ILD, and in most (particularly chronic lung disease of prematurity), lung biopsy would rightly not be contemplated. The exception might be in children with congenital heart disease [11], but the question would be related to the operability of the abnormality, rather than a lung diagnosis. Histologically, there is variable lobular simplification with alveolar enlargement, often most prominent subpleurally. In nearly half, PIG cells were noted (often previously overlooked), and hypertensive pulmonary vasculopathy was common.

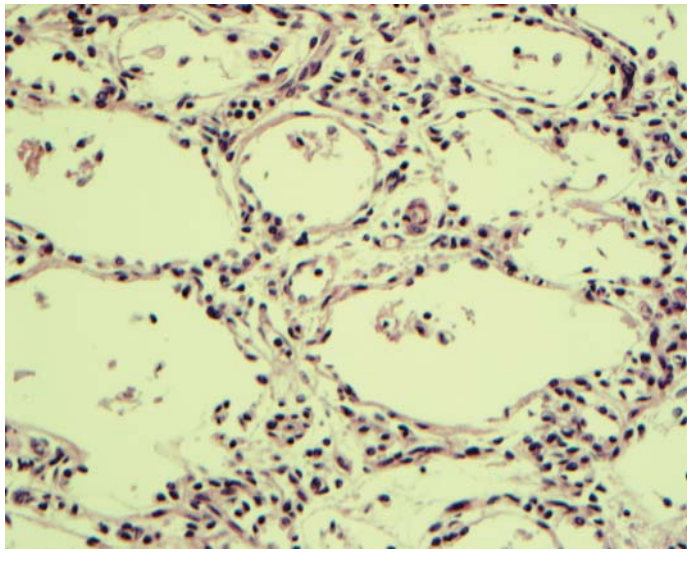

Fig. 1. – A case of alveolar capillary dysplasia shows poorly developed alveolar walls, within which there is low capillary density and poor apposition to the epithelium. Towards the centre, an intra-acinar pulmonary artery shows marked medial hypertrophy.

Category three: specific conditions of undefined aetiology. These two conditions (NEHI and PIG) appear to be found purely in infancy; whether they are specific conditions, or related nonspecifically to disordered lung development, is unclear.

Neuroendocrine cell hyperplasia of infancy. The human airway epithelium contains highly specialised pulmonary neuroendocrine cells (PNEC), either alone or as innervated neuroepithelial bodies. The ''PNEC system'' comprises both neural and endocrine cell phenotypes, the functions of which include the synthesis and release of amine (serotonin) and a variety of neuropeptides (such as bombesin) [12]. Bombesin cells peak in mid-gestation, and then reduce to the normal adult low levels by term [13]. Thus it is possible to hypothesise that NEHI may represent a failure of the normal regression of these cells. The function of the PNEC system in the lung is unknown. Complex roles have been proposed, including modulation of fetal lung growth and differentiation and airway oxygen sensors involved in neonatal adaptation at birth. Post-natally, they may provide a lung stem cell niche that is important in airway epithelial regeneration [14]. Thus, PNEC are a normal part of the lung, and not necessarily pathological cells. Characteristically, NEHI presents in the first year of life (mean age 3.8 months in the largest published series) with tachypnoea and respiratory distress, in a relatively well infant [15]. Rare cases of a NEHI-like syndrome have been described in older children, in one case in association with emphysema for which there was no underlying cause such as α_1-antitrypsin deficiency [16]. Cough and wheeze are not prominent in NEHI [15]. There is a male predominance. Presentation requiring intubation at birth has not been described [4]. Crackles are often heard. The chest radiograph (CXR) typically mimics post-viral infection airway changes. HRCT shows patchy ground-glass opacification, typically centrally and in the right middle lobe and lingula, with air trapping elsewhere. Experienced radiologists may feel sufficiently confident to diagnose NEHI on these appearances alone [17], but most paediatricians would want to proceed to lung biopsy. The pathology is of apparently almost normal lung tissue on haematoxylin and eosin staining, but occasionally there may be increased

airway macrophages, mild smooth muscle hyperplasia, and epithelial clear cells. The pathological hallmark of NEHI is increased numbers of bombesin-positive airway cells. These are also seen in healthy controls, but the upper limit of normal is 5% of the epithelial area [15]. KL-6 has been proposed to be a useful biomarker distinguishing NEHI from surfactant protein disorders; children with NEHI have normal levels of KL-6, whereas these are elevated well above the normal range in surfactant protein disorders, including *ABCA3* defects [18]. There is no treatment other than oxygen if the child is hypoxic, and the long-term outlook is relatively good, with no deaths recorded, and long-term pulmonary function at worst showing mild airflow obstruction. However, up to two-thirds of the children remained symptomatic at follow-up. Thus, parents of infants diagnosed with NEHI can probably be reassured as to the prognosis.

Scientifically, the description of bombesin-containing cells is straightforward, but the interpretation is not. First, the connection between NEHI and chronic idiopathic bronchiolitis of infancy [19] and diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) [20] is not clear. Secondly, PNEC have been reported as being increased in many other conditions, including sudden infant death syndrome [21], bronchopulmonary dysplasia [22] and Wilson–Mikity disease [23]. Finally, neuroendocrine cells are normally seen in the developing lung, and are indeed crucial in normal developmental processes such as branching morphogenesis [12]. It is not clear to us that NEHI is truly a separate entity, or overlaps with other conditions; or whether the bombesin-containing cells have any pathophysiological significance or are markers of some unknown underlying problem.

Given these concerns, and given the rarity of NEHI, we continue to recommend invasive diagnosis where possible, and always that such infants are carefully followed up. The exception to the support for an invasive diagnosis would be a well, thriving infant who has only trivial and stable oxygen dependency, and has a typical appearance on HRCT with nothing to suggest an alternative diagnosis.

However, it should be noted that we still know very little about NEHI, and even the largest papers are little more than extended case series. The possibility remains that some cases of NEHI may evolve into a chronic constrictive bronchiolitis-like picture in later childhood. We have seen at least one case, diagnosed only on HRCT because the child was well but tachypnoeic and a biopsy was refused by the family, who appears to have followed just this course, with later onset of oxygen dependency. Furthermore, although the overall prognosis is usually good, we have seen biopsy-proven NEHI relapse and require a further period of oxygen dependency. Finally, whether there is any relationship between NEHI and the adult condition of adult DIPNECH is not known.

Pulmonary interstitial glycogenosis. Glycogen-containing fetal type 2 cells are seen in normal lung development, regressing towards term [24, 25]. However, the pathological hallmark of PIG is the expansion of the interstitium by primitive mesenchymal cells rich in glycogen (fig. 2). This is specific to the lungs; there is no generalised disorder of glycogen metabolism or storage. Presentation is with nonspecific respiratory symptoms, and onset is usually early, with biopsies in the first case series being performed at 2–4 weeks of age; four out of the seven described cases were pre-term [26]. There is a male preponderance in the very small numbers of cases reported to date. Radiology is nonspecific, with interstitial infiltrates, a fine reticular pattern, hyperinflation and ground-glass shadowing. Six out of seven infants did well; one died of the complications of extreme prematurity, which begs the question of the nature of PIG cells (see below). Treatment was with corticosteroids and sometimes hydroxychloroquine. The condition may be related to ''chronic interstitial pneumonitis of infants'' [27, 28], in itself a rather generalised term, but it is not possible to be sure, because special stains for glycogen

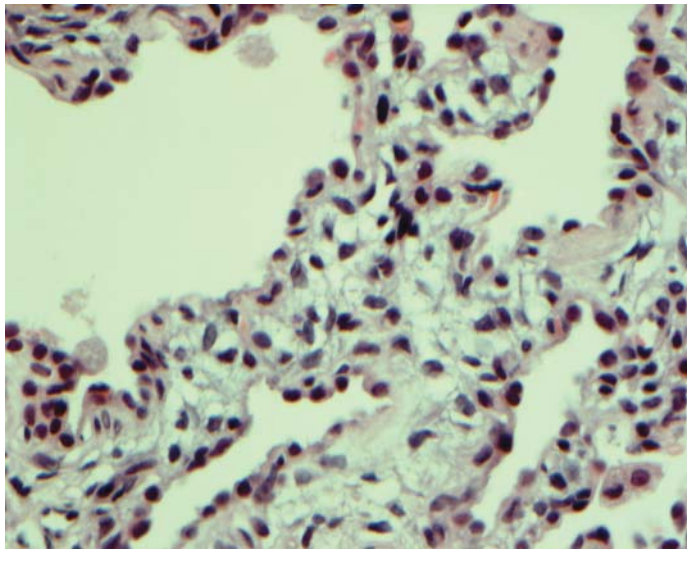

Fig. 2. – A case of pulmonary interstitial glycogenosis shows the alveolar interstitium to be expanded by cytologically bland clear cells of uncertain histogenesis.

were not performed in these cases. This underscores the need for protocol-driven handling of surgical lung biopsies (see below).

An intriguing report described PIG in pre-term twins [29], with a favourable outcome associated with systemic steroid therapy. This report begs the question as to whether 1) there is an undescribed genetic component to PIG, or 2) PIG is part of the spectrum of chronic lung disease of prematurity, or overlaps with it. However, it should be noted that nine out of the 16 cases in the published literature were in term infants [4, 26, 29, 30].

As with NEHI, it is pertinent to question the specificity of glycogen-containing cells, and to what extent they are merely a marker for some other process, or indeed whether PIG is a separate entity. First, glycogen-containing cells are seen at some stages of lung development [24, 25]. They are found in the early stages of lung development in cells lining the alveolar septa, becoming less prominent with advancing gestational age. It must be stressed that in PIG, alveolar lining cells are spared, and it is the mesenchyme which is affected. Glycogen stores are seen in association with lamellar bodies in fetal type 2 cells, suggesting a role in surfactant synthesis. Secondly, PIG cells have been reported in association with congenital lobar emphysema, but not in sufficient quantities to cause ILD [31]. There is still much to be learned about the role of these cells and the spectrum of PIG; as with NEHI, even the largest papers are mere extended case series.

Category four: surfactant dysfunction disorders. These illustrate an important principle which may find wide application in genetic disorders. Of the four surfactant proteins known (Sp-A, -B, -C and -D), Sp-A and -D are not surface active, and are members of the collectin family, along with mannose-binding lectin. Mutations in *Sp-B* and *Sp-C* have been shown to cause ILD (see below). The intracellular processing of these proteins is of great complexity. *ABCA3* encodes for a protein that is not itself surface active but is involved in the processing of pulmonary surfactant [32]. Deficiency produces ILD closely resembling Sp-B or Sp-C deficiency (see below). Some of the other conditions described below, which mimic surfactant protein disorders, may in fact be caused by defects in other surfactant protein processing genes. It is also interesting to speculate that

other apparently single-gene disorders may be caused by gene defects encoding processing proteins. Thus, cystic fibrosis (CF) has been described with apparently no mutation in the *CF* gene locus [33]. However, CF transmembrane conductance regulator (CFTR) interacts with numerous other proteins [34], and one could speculate that mutations in some or all of these could produce a CF-like disease. Given the complex post-translational processing of the surfactant protein gene products, this may be a relevant mechanism in chILD. It has been suggested as being important in Hermansky–Pudlak syndrome (HPS; see below), which is characterised pathologically by abnormal lamellar bodies, among other features. It should be noted that, although a family history of ILD should always be sought, 50% of patients with one of the three genetic diseases described below have disease occurring *de novo*. It is likely that the significance of these gene defects and polymorphisms is underappreciated in adult ILD [35].

Sp-B *gene mutations.* Sp-B deficiency is an autosomal recessive, loss of function mutation. It is a rare condition, with estimated prevalence being one in a million live births [36]. The gene is located on chromosome 2, comprises approximately 10,000 base pairs (bp) in 11 exons (of which only the first 10 are translated), and encodes a 381-amino-acid pre-protein. 23 amino acids are removed co-translationally to produce pro-Sp-B, which then undergoes complex processing to produce the mature protein. Production is primarily by the type 2 cells [37]. The most common mutation is a 2-bp insertion in codon 121 (121ins2), which accounts for about two-thirds of mutant alleles; more than 30 others have been described [37, 38]. The classical presentation is with relentlessly progressive respiratory distress, mimicking hyaline membrane disease in the pre-term, with no response to treatment and death within months, unless lung transplantation can be offered. The pathology is often but not invariably a pulmonary alveolar proteinosis (PAP)-like picture (fig. 3), but there may be more of a type 2 cell hyperplasia. These infants may also have secondary abnormalities in Sp-C processing, (pro-Sp-C to Sp-C), with poorly organised lamellar bodies [39–41].

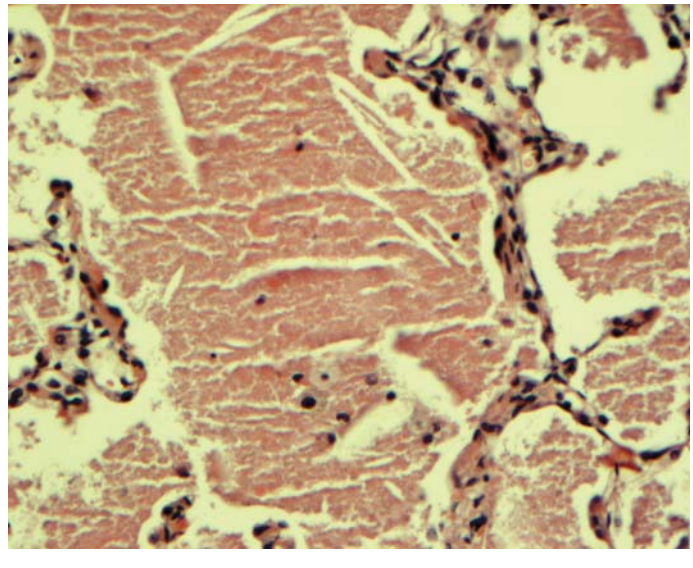

Fig. 3. – A case of alveolar proteinosis shows alveolar spaces filled by acellular eosinophilic proteinaceous debris, within which cholesterol clefts can be seen.

Although the classical disease is lethal in infancy, rare partial deficiencies have been described, with prolonged survival [42, 43]. Furthermore, it is hypothesised that heterozygosity for Sp-B deficiency, or some *Sp-B* single nucleotide polymorphisms, may confer an increased risk of acute lung injury and oxygen toxicity. Further work is needed to determine whether *Sp-B* may be a modifier gene for adult respiratory distress syndrome or chronic respiratory diseases, including inorganic dust exposure [44–47].

Sp-C *gene mutations.* Sp-C deficiency is an autosomal dominant condition caused by a gain-of-function mutation (*i.e.* the disease is produced not by loss of function of the normal protein, but by an abnormal new function in the mutated protein) [48]. Sporadic disease has also been reported, about equally frequently with the inherited condition. The *Sp-C* gene is located on the short arm of chromosome 8, and is transcribed to a 900-bp mRNA, which after post-translational processing yields one of either a 191 or 197 amino acid protein. At least 35 mutations have been described [49]. Several have been shown to reside in the COOH-terminal domain, a ~100-amino-acid region known as BRICHOS (group A mutations) [50]. These mutations result in endoplasmic stress due to accumulation of misfolded protein and ultimately to cell apoptosis *via* a CASPASE 3 and CASPASE 4 pathway, among other intracellular metabolic problems. Group B mutations are clustered in exon 3, and these result in cytosolic accumulation; the exact mechanism of toxicity has not been determined. A (single) group C mutation has been described in the cytosolic nontransmembrane NH_2-domain; this mutant protein fails to traffic to the Golgi. The dominant negative effect of the abnormal Sp-C (failure of translation of the normal allele to leads to some normal Sp-C) is attributed to effects on the trafficking and processing of the abnormal gene product [49].

In addition to being surface active, Sp-C may have other functions, including the modulation of inflammation. It binds to lipopolysaccharide, inhibiting its interactions with macrophages and CD14. The role of these functions in Sp-C deficiency disease is unclear [49].

The clinical phenotype is extremely variable, and studies of several generations in families detect presentation with the same *Sp-C* mutation in the newborn period with relentlessly progressive respiratory distress, and onset of UIP in late middle age [7]. It has been suggested that *ABCA3* mutations may be modifier genes, in part accounting for the varying clinical features of *Sp-C* mutations. *ABCA3* mutations from four symptomatic infants with the same *Sp-C* mutation, I73T, were studied. These infants were part of a series of 55 children with chILD secondary to Sp-C deficiency. Three out of the four infants were also heterozygous for an *ABCA3* mutation inherited from the parent who did not carry I73T (E292V, n=2; L212M, n=1). This suggests that the combination was predictive of early onset of lung disease in Sp-C deficiency [51]. In newborns, the histology may suggest chronic pneumonitis of infancy (CPI; see below), NSIP or DIP [49]. Spontaneous and prolonged remission of the childhood disease has been described. Virtually any histological pattern of ILD can be caused by Sp-C deficiency [49]. ILD characterised by absence of mature Sp-C, but no *Sp-C* gene mutations, has been described, and was presumably due to a mutation in a critical enzyme in the processing pathway [52]. There is no known treatment; corticosteroids and hydroxychloroquine have been used, but data are at the level of anecdote.

ABCA3 *gene mutations. ABCA3* deficiency is an autosomal recessive condition of unknown prevalence. This very large gene is located on chromosome 16, and contains 60,000 bp in 33 exons (the first three of which are not translated) that encode a 1,704-amino-acid protein [53, 54]. The disease is thought to be due to loss of function mutations. *ABCA3* is part of a family of genes, some of which are associated with

human disease (table 3). More than 100 mutations have been described [55]; the huge size of the gene means that many more mutations are likely to be so far undetected. The gene is most highly expressed in lung tissue, but also in heart, brain, platelets and kidney; however, *ABCA3* deficiency has no known clinical phenotype in these tissues. The commonest mutation, E292V, was found in 5% of older chILD patients [56, 57]. However, as might be expected in such a complex gene, many different mutations have been described [55]. It has also been speculated that some cases may be related to mutations in the noncoding regions of the gene [55]. ABCA3 is a member of the ATP-binding cassette family, and although its precise function is not known, it is probably involved in surfactant protein processing, given that 1) other ABCA proteins are involved in lipid transport; 2) it is developmentally regulated, increasing in late gestation; and 3) it is localised to lamellar bodies of type 2 cells [55, 58, 59].

Typically, presentation mimics Sp-B deficiency, with onset in infancy, and indeed *ABCA3* deficiency may be the commonest genetic cause of neonatal respiratory failure. Rarely, *ABCA3* deficiency may mimic primary pulmonary hypertension of the newborn [60]. Initially, the disease was thought to be uniformly fatal [61]. However, it is becoming clear that late-presenting disease with a better prognosis can also be due to *ABCA3* deficiency. Lung function may remain stable over a period of years, but poor growth is common [62]. As with Sp-C deficiency, a wide variety of lung histopathology is found, including PAP, DIP, NSIP and CPI, and the pathology may change over time; UIP has been described in a teenager with *ABCA3* deficiency (see below). Confusingly, Sp-B staining may be reduced as a secondary phenomenon in *ABCA3* deficiency (and also rarely in Sp-C deficiency), underscoring the need for careful evaluation of children with suspected disorders of surfactant metabolism [57]. Indications for surfactant protein studies are given in table 4. Electron microscopy shows abnormally formed lamellar bodies, which can be distinguished by the skilled electron microscopist from those of Sp-B deficiency.

The mechanisms leading to late presentation of *ABCA3* deficiency are not known; late presentation may, however, be associated with mis-sense mutations such as E292V, N1076K, G1302E, P1301L, T1114M and E690K. One diagnostic clue to the diagnosis of *ABCA3* deficiency in children with late-presenting chILD was the presence of pectus excavatum. In this series, presentation in infancy carried a poor prognosis, but chILD presenting in later childhood seemed to stabilise for prolonged periods [63]. There is no known effective treatment, but prednisolone and hydroxychloroquine have been used, with anecdotal reports of success.

Others: pulmonary alveolar proteinosis. This umbrella term is used to describe a histological picture in which the alveolar spaces are filled with amorphous periodic acid-Schiff-positive proteinaceous material, with little evidence of interstitial inflammation. Presentation can be from the newborn period to old age. The picture of PAP can be produced by at least six separate entities and although many cases are not caused by surfactant protein gene disorders, it seems logical to consider PAP in this section.

Table 3. – Disease caused by *ABCA* family members

Gene	Disease
ABCA1	Tangier disease (results in reduction of high-density lipoprotein)
ABCA3	Interstitial lung disease
ABCA4	Juvenile macular degeneration, Stargardt disease
ABCA7 (CFTR)	Cystic fibrosis

Table 4. – Indications for surfactant protein studies

Severe unexplained newborn respiratory distress
Any diffuse lung disease on HRCT, particularly if there is a family history of ILD
Histopathology reported as showing PAP, NSIP, DIP, UIP or CPI
Acute ILD (diffuse alveolar damage) with no obvious aetiology
Abnormal lamellar bodies on electron microscopy in ILD
Well adult with family history of ILD or chILD, after genetic counselling

HRCT: high-resolution computed tomography; ILD: interstitial lung disease; PAP: pulmonary alveolar proteinosis; NSIP: nonspecific interstitial pneumonia; DIP: desquamative interstitial pneumonia; UIP: usual interstitial pneumonia; CPI: chronic pneumonitis of infancy; chILD: ILD in children.

As aforementioned, surfactant protein abnormalities caused by *Sp-B*, *Sp-C* and *ABCA3* mutations may lead to many histological appearances, but in particular to PAP, especially when presentation is in the newborn period.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor abnormalities can also lead to PAP. Clearance of surfactant by alveolar macrophages requires a functional GM-CSF receptor. Mutations in the β- [62, 64] and more recently the α-chain of the GM-CSF receptor have been shown to be a rare cause of PAP [65, 66].

GM-CSF auto-antibody disease is a form of PAP more classically seen in adults [67], but paediatric cases have been described [68]. Diagnosis is confirmed by finding auto-antibodies to GM-CSF in serum or BAL. Initially, this variant of PAP was successfully treated with serial large-volume lung lavage [69], but increasingly it is now treated with inhaled or systemic GM-CSF [70, 71].

PAP has been rarely described in association with immunodeficiency (agammaglobulinaemia) [72]. The exact mechanisms are poorly defined; coincidence cannot be excluded.

Macrophage blockade can also potentially lead to PAP, and is seen exclusively in adults [73]. Causes include haematological malignancy and inorganic dust inhalation.

PAP may be a manifestation of the metabolic diseases lysinuric protein intolerance or Niemann–Pick disease (the latter only rarely).

Lysinuric protein intolerance is an autosomal recessive condition with multisystem manifestations, including vomiting, diarrhoea, failure to thrive, hepatosplenomegaly, mental retardation, chronic renal disease and altered immune responses. It is caused by mutations in the solute carrier family 7A member 7 (*SLC7A7*) gene [74]. The disease may present solely with pulmonary manifestations, which may be of an acute life-threatening ILD, or more typically, a PAP-like picture. Successful treatment of the latter by whole lung lavage has been reported [75]. Unfortunately, PAP secondary to lysinuric protein intolerance recurs after lung transplantation [76].

Niemann–Pick disease is a rare, autosomal recessive lipid storage disease, which is characterised by sphingomyelin deposition in a number of tissues due to deficiency of the lysosomal enzyme acid sphingomyelinase. It is a systemic disease, but is considered here as it enters the differential diagnosis of PAP. There are six known types (A–F) [77]. The prevalence of lung disease in this condition is difficult to determine in the absence of any big series. Types B and C2 are typically associated with restrictive lung disease in older patients, and in particular, HRCT reveals abnormalities, typically thickened interlobular septa, intralobular lines and ground-glass shadowing, in almost all type B patients; these do not correlate well with pulmonary function abnormalities [78]. Nodules, some of which may be calcified, are also reported. Typically, patients present with endogenous lipid pneumonia, with foamy macrophages primarily filling alveolar spaces, but also involving the interstitium [79–83]. An unusual feature in type B disease is the presence of lipid accumulation within ciliated respiratory epithelial cells (fig. 4).

Some cases of pulmonary involvement by Niemann–Pick disease may respond to whole-lung lavage [84, 85], but rare cases of early disease, nonresponsive to large-volume lung lavage, have been described [86]. BAL and lung biopsy show foamy macrophages, which May–Grunewald–Giemsa staining reveals to have blue granulations, known as the "sea-blue histiocytes" [87]. Electron microscopy may show abnormal lamellar bodies. Rare cases with cysts and a congenital lobar emphysema-like picture, not ILD, have been described [88, 89]. Type C1 may rarely be associated with lung disease responding to whole-lung lavage; bronchial casts have been described. Type E is very rare indeed, but may also be a cause of lung disease. Bone marrow or stem cell transplantation is the current treatment of choice [90], but enzyme replacement therapy may be an option in the future for some patients [91].

Others: chronic pneumonitis of infancy. This category is a histological diagnosis, and is made with increasing rarity as molecular studies allow for more precise diagnoses to be made. It is considered here because of its relationship with abnormalities of surfactant protein metabolism, as aforementioned. The first description of this condition predated the understanding of the role of surfactant protein and other genes in chILD. The disease was characterised by marked alveolar septal thickening, striking type 2 cell hyperplasia and an alveolar exudate containing numerous macrophages and foci of eosinophilic debris (fig. 5). There were primitive mesenchymal cells within the widened alveolar septa, but little inflammation. CPI occurs only in infants and very young children [92]. Typically, the children were initially well, but respiratory symptoms appeared at the age of 1–9 months, with a fatal course despite treatment [93]. Occasional long-term survivors have been described [94]. It is likely that many cases in fact had abnormalities of surfactant protein genes, and certainly a pathological report of CPI should prompt DNA studies on the *Sp-B*, *-C* and *ABCA3* genes and preservation of DNA for future work, which will likely reveal further genetic abnormalities causing this histopathological appearance.

Disorders related to systemic disease processes. Four children in the North American classification study by DEUTSCH *et al.* [4] had pulmonary capillaritis, all presenting with a suspected pulmonary haemorrhage syndrome. Surgical lung biopsy may not necessarily be performed in all children with suspected pulmonary haemorrhage (see

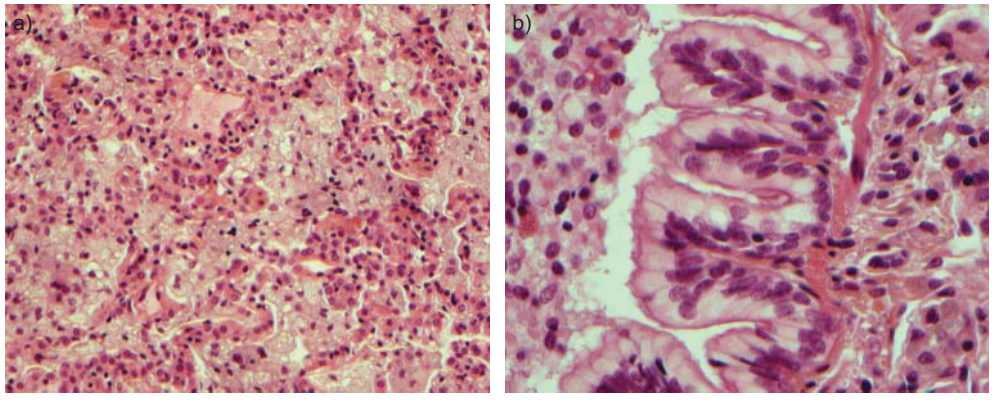

Fig. 4. – a) A case of Niemann–Pick disease shows filling of alveolar spaces by foamy macrophages. b) An unusual feature of type B disease is that the presence of fine intracytoplasmic vacuolation is also seen in the ciliated epithelial cells within airways.

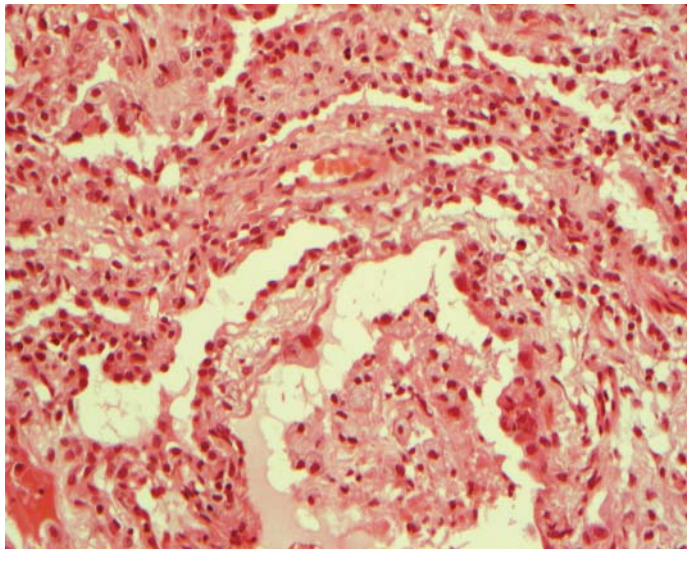

Fig. 5. – A case of chronic pneumonitis of infancy shows the alveolar interstitium to be markedly expanded by plump fibroblasts mixed with a relatively mild nonspecific chronic inflammatory cell infiltrate. There is marked type 2 cell hyperplasia and also proteinaceous debris within alveolar spaces as a minor component.

below and table 5), but should certainly be considered in those whose disease appears refractory to therapy.

Category five: disorders of the normal host, presumed immune intact. Many of these are airway diseases, such as post-adenoviral obliterative bronchiolitis, which few would consider an ILD, and would usually be diagnosed on HRCT without recourse to biopsy. Hypersensitivity pneumonia at all ages may also commonly be diagnosed on serology (positive precipitins, as described below) and HRCT appearances, again without biopsy [95–97]; at this age, likely allergen sources are avian, either pets, pigeon antigen from the clothes of an adult pigeon-fancier who lives with the child, or feathers in the bedding. Treatment is with allergen avoidance and prednisolone. Aspiration syndromes may easily be confused with surfactant protein disorders, or may be a comorbidity. It is wise, if any doubt exists, to perform both surfactant protein studies and a work-up for aspiration (pH study, exclude H-type fistula (congenital direct connection between the trachea and oesophagus, with no oesophageal atresia) and laryngeal cleft, the latter requiring a rigid bronchoscopy, speech and language assessment including video-fluoroscopy) in children presenting with ILD in whom either diagnosis is being considered.

Table 5. – Causes of diffuse alveolar haemorrhage with pulmonary capillaritis

Wegener's granulomatosis
Systemic necrotising vasculitis (microscopic polyarteritis)
Mixed connective tissue disease
Behcet's syndrome (may also have large vessel bleeding)
Henoch–Schonlein purpura
Goodpasture's syndrome
Nephritis with or without immune complex disease

Category six: disorders resulting from systemic disease processes. All but two rare cases (sialidosis, previous myelomonocytic proliferative disorder) were related to pulmonary capillaritis. Pulmonary haemorrhagic syndromes are described in detail below.

Category seven: disorders of the immunocompromised host. ILD may be the first presenting feature of an immunodeficiency, or occur in a known immunocompromised child. In the former case, histological findings may be of a lymphoproliferative state on the follicular bronchiolitis (FB)–LIP spectrum (described in more detail below), which should always prompt an immune work-up including HIV testing and testing for an opportunistic infection. In the known immunocompromised child, the differential diagnosis is wide, and includes many conditions that most would not consider as ILD. Possibilities would include opportunistic infection, drug- or radiation-induced lung damage, transplant complications (lung rejection, graft *versus* host disease), pulmonary oedema secondary to iatrogenic cardiac dysfunction, pulmonary haemorrhage, and recurrence of an original malignant condition such as leukaemia. Space precludes a further discussion of these issues in this chapter.

Category eight: disorders masquerading as ILD. These include pulmonary hypertensive changes, either arterial or venous, secondary to heart disease [98], and the spectrum of lymphatic disorders. Lung biopsy should be avoided in the latter if possible, because the procedure may be complicated by prolonged lymphatic effusions that may be difficult to deal with. Pulmonary lymphangiectasia, once thought to be a uniformly fatal condition, is compatible with prolonged survival [99]. Subtypes include diffuse isolated pulmonary; as part of generalised lymphangiectasia; secondary to cardiac disease, for example in Williams syndrome [100]; and late-presenting, localised forms [101].

Unclassifiable biopsies. Even with this detailed review, 22 biopsies were unclassifiable, largely due to inadequate tissue sampling or the child having end-stage disease. The important lessons are only to refer children for lung biopsy to really experienced surgeons; and, if the child presents with end-stage disease, consider carefully whether a biopsy is 1) safe, and 2) likely to yield important information.

ILD in infants aged 2–16 yrs

The major classification paper came from an ERS Task Force that spans the entire age range. This survey did not rely solely on biopsy, and rightly excluded immunodeficiency, but did not feature an independent review of the biopsies [3]. 187 centres were contacted, and 38 returned questionnaires on 155 cases, of which 24 were excluded. Of the 131 cases at all ages, idiopathic interstitial pneumonia was diagnosed in 46 (35%), chronic infection in 19 (14.5%) and associated diseases in 51 (39%), of which the commonest were hypersensitivity pneumonitis and aspiration syndromes. The findings are summarised in table 2.

DETERDING *et al.* [5] in the USA have published, as an abstract, data from 101 biopsies in the 2–18-yr age range, which are still too preliminary to use in clinical practice; the categories were very different from the 0–2-yr age range paper, and confirm the European findings; cases included ILD that was immune mediated (34%); infection and post-infective (16%); and only 8% were ''infant'' disorders; however, late-presenting surfactant deficiency disorders should always be remembered.

Auto-immune diseases must be considered in this age group. Wegener's granulomatosis in children is characterised by combinations of glomerulonephritis and upper and lower airway disease [102]. Most patients are cytoplasmic antineutrophil cytoplasmic antibody (cANCA) positive, with a raised erythrocyte sedimentation rate. In the largest series in the literature, upper airway disease (sinusitis and epistaxis) was the third most common presenting feature [102]. More than half had pulmonary involvement at presentation, and positive pressure ventilation was not uncommonly required. Lung disease included haemorrhage and nodules, but nonhaemorrhagic air space disease was also reported. Multiple pulmonary emboli secondary to a thrombotic tendency have been described. Lung biopsy findings included vasculitis without granulomas, chronic necro-inflammatory changes with giant cells, and metastatic calcification and haemosiderosis. Space precludes detailed discussion of the pulmonary manifestations of other childhood connective tissue disorders, such as juvenile chronic rheumatoid, systemic lupus erythematosus, and scleroderma [103], but these are summarised in table 6. Presentation of these conditions with isolated lung disease is rare, but has been described. Pulmonary sarcoidosis is very rare in childhood [104]; there are no particularly different features compared with adult disease. In a large recent series, CXRs were normal in 10%, there was bilateral hilar lymphadenopathy in 71% (stage 1), 8% had parenchymal involvement (stage 2) and only one patient had stage 3 disease [105]. Irreversible fibrosis was not seen in this series, but we have rarely seen severe, end-stage fibrosis in children with sarcoidosis.

Important conditions with a specific histopathological pattern.

DIP and NSIP. The pathological diagnostic criteria are similar in adults and children. NSIP may be cellular or fibrotic in children. These histological diagnoses should trigger a search for surfactant protein abnormality. Otherwise, it is unusual to find a specific underlying cause in childhood.

Cryptogenic organising pneumonia. This has been described in children as an isolated phenomenon, or in association with asthma [106], infections [107], drug reactions [108], chemotherapy [109, 110], bone marrow transplantation [111], autoimmune disorders [112, 113] and even CF [114]. The prognosis is usually excellent with corticosteroid treatment.

Acute interstitial pneumonia. This is rare as an idiopathic illness in childhood. Some cases given this label in the past turned out subsequently to have surfactant protein mutations [115].

Table 6. – Pulmonary manifestations of paediatric rheumatological conditions

Condition	Manifestations
Systemic lupus erythematosus	Pleural disease, diffuse alveolar damage and chronic chILD, pulmonary haemorrhage, distal airway disease, diaphragmatic weakness
Dermatomyositis	Obliterative bronchiolitis, pulmonary vascular disease, pulmonary fibrosis
Scleroderma	Pulmonary fibrosis, typically a pattern of nonspecific interstitial pneumonia, pulmonary hypertension, extra-pulmonary restriction due to thickened truncal skin; aspiration due to oesophageal dysmotility is an important comorbidity
Juvenile chronic rheumatoid	Pulmonary haemorrhage, pulmonary fibrosis (variable patterns, often with associated lymphoid hyperplasia)
All	Drug toxicity, and opportunistic infection if immunosuppressive therapy is used

chILD: interstitial lung disease in children.

UIP. True UIP is virtually unheard of in children. Although there are reports of UIP in more than 100 children, the diagnostic pathological feature, fibroblastic foci at the leading edge of the fibrotic process, has not been described. UIP has recently been described in an adolescent who had *ABCA3* deficiency [116], so this diagnosis should also prompt at least consideration of surfactant protein studies.

In summary, a systematic classification has yet to be developed for the 2–16-yr age group. It is suggested that a pragmatic approach, summarised in table 7, is taken pending the publication of further data. The main feature distinguishing children from adults is the almost complete absence of UIP in children. The reasons for this are unclear.

Table 7. – Pragmatic classification of interstitial lung disease in children (chILD) in the 2–16-yr age range

Category of chILD	Examples
chILD of known aetiology	Infective or post-infective disorders
	Environmental inhalants (toxic substances, antigenic dusts)
	Drug-induced disorders
	Radiation-induced disorders
	Neoplastic diseases
	Lymphoproliferative disorders
	Genetic disorders
	Neurocutaneous syndromes
	Degenerative disorders
chILD associated with other conditions	Collagen vascular disease
	Pulmonary vasculitis syndromes
	Langerhans' cell histiocytosis
	Liver disease
	Bowel disease (*e.g.* granulomatous lung disease associated with Crohn's disease)
	Renal disease (*e.g.* pulmonary fibrosis associated with chronic renal failure)
	Organ failure (cardiac, renal)
	Amyloidosis
	Sarcoidosis
	Graft *versus* host disease
	ARDS (recovering phase)
	Hyper-eosinophilic syndromes
	Pulmonary veno-occlusive disease
Primary pulmonary disorders	DIP
	LIP/FB spectrum
	NSIP
	Alveolar haemorrhagic syndromes
	Eosinophilic syndromes
	Obliterative bronchiolitis
	Some PAP syndromes
	Langerhans' cell histiocytosis (adult type)
	Pulmonary vascular disorders
	Pulmonary lymphatic disorders
	Pulmonary alveolar microlithiasis

ARDS: acute respiratory distress syndrome; DIP: desquamative interstitial pneumonia; LIP: lymphoid interstitial pneumonia; FB: follicular bronchiolitis; NSIP: nonspecific interstitial pneumonia; PAP: pulmonary alveolar proteinosis.

Other groups of conditions which are diagnostic considerations in children with ILD

Genetic causes of ILD

There are a number of genetic disorders other than the surfactant protein abnormalities described in detail above, which may cause ILD. Some may also present in adult life. They are summarised in table 8. They are mostly very rare, and the principal interest is the insight they give into mechanisms of disease.

Specific conditions: pulmonary alveolar microlithiasis. This condition is an autosomal recessive condition characterised by the slow formation of microliths in the intra-alveolar spaces (fig. 6). It is found in Turkish people in particular. Although onset is usually in adult life, paediatric cases have been described [129]. The clinical course may be very indolent. Recently, a candidate gene, encoding the type 2b sodium phosphate co-transporter SLC34A2, has been proposed [130]. There is no known treatment; hydroxyapatite, which inhibits ectopic calcification, is not useful. One personal case treated with lobar large-volume lavage showed no benefit. However, the recent gene discovery suggests that strategies targeting phosphate metabolism may be of more interest.

Specific conditions: Hermansky–Pudlak syndrome. Although rare in most areas (prevalence approximately one in 1,000,000), in some parts of the world (*e.g.* Puerto Rico) the disease is common, attaining a frequency of one in 1,800. HPS is thought to be a manifestation of defective formation or trafficking of intracellular vesicles [131, 132]. There are eight different HPS genes, some of which lead to a relatively mild phenotype. All exhibit some degree of hypopigmentation and a bleeding diathesis. Pulmonary fibrosis occurs in types 1, 2 and 4 (80% of HPS-1 and -4 patients; mild lung disease has been reported in some of the four cases of HPS-2 in the literature), usually in adults aged >40 yrs; it is not seen in types 3, 5 and 6, and there is insufficient information for types 7 and 8. Clues to this condition in the biopsy include vacuolated cells, giant lamellar bodies and increased autofluorescence. Anecdotally, pirfenidone may be beneficial in the fibrotic forms [133].

Table 8. – Genetic disorders presenting as interstitial lung disease

Genetic disorder	Ref.[#]
Sp-B, *Sp-C*, *ABCA3* deficiency	
GM-CSF receptor abnormalities	
Storage disorders, *e.g.* Gaucher's disease, Niemann–Pick disease	
Hermansky–Pudlak syndrome	
Lysinuric protein intolerance	
GM_1 gangliosidosis	[117]
Fabry's disease	[118]
Neurofibromatosis	[119]
FOXP3 deficiency	[120]
Pulmonary alveolar microlithiasis (mutations in the *SLC34A2* gene)	
STRA6 deficiency	[121, 122]
Telomerase gene mutations (*TERC*, *TERT*)	[123–126]
"Brain-lung-thyroid syndrome"	[127, 128]

GM-CSF: granulocyte-macrophage colony-stimulating factor. [#]: conditions not referenced are discussed in more detail in the text.

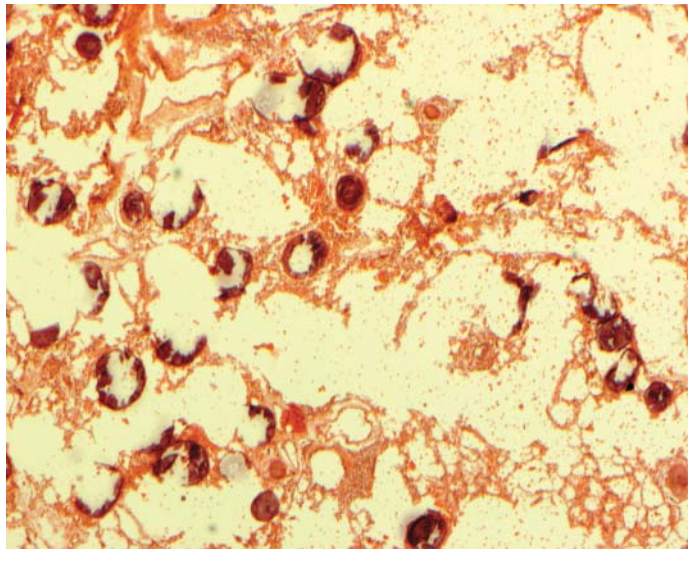

Fig. 6. – A case of alveolar microlithiasis shows abundant calcific spherites lying both within alveolar spaces and in the interstitium. Many of these have shattered during processing.

Pulmonary haemorrhagic syndromes

These may present acutely, mimicking acute respiratory distress syndrome with severe hypoxaemia and widespread alveolar filling, or with chronic haemoptysis and anaemia. In young children, presentation may be with iron deficiency anaemia rather than haemoptysis, and indeed the anaemia may respond to iron therapy [134]. The broad diagnostic categories to exclude are as follows: 1) secondary haemorrhage, *e.g.* pulmonary venous hypertension; 2) localised anatomical abnormalities, such as bronchiectasis or pulmonary arteriovenous malformation; 3) other bleeding syndromes without capillaritis; and 4) pulmonary capillaritis, which may be associated with systemic disease, as has been described above. Neonatal pulmonary haemorrhage is not a presentation of chILD. When these entities have been ruled out, the diagnosis of exclusion is IPH. The original descriptions suggested it was related to immunoglobulin (Ig)D anti-milk antibodies, and that a milk exclusion diet would be beneficial. Nowadays, these antibodies are rarely if ever measured, and milk exclusion diets are not thought to be helpful. We have never seen a case of anti-cow's-milk-protein IgD antibody-positive Heiner's syndrome (cow's milk protein hypersensitivity), nor met anyone who has.

Diffuse pulmonary haemorrhage can be suspected on HRCT and confirmed by the BAL and/or biopsy finding of haemosiderin-laden macrophages (fig. 7). It must be stressed that this is not specific for IPH. In uncomplicated cases, surgical lung biopsy is not required, but if capillaritis is suspected [135], or there is a poor response to treatment, then surgical lung biopsy should be considered.

Treatment of IPH is anecdote driven. Most would use pulsed intravenous methyl prednisolone in a dose such as 500 $mg \cdot m^{-2}$ on three successive days, followed by monthly pulses for 6 months, with maintenance oral corticosteroids and hydroxychloroquine. If this approach fails, then a number of cytotoxic agents and other therapies have been suggested [136–139]. The prognosis must be guarded, but prolonged remission has been described, and probably treatment should be weaned if there has been no overt bleeding for 2–3 yrs and there are no haemosiderin-laden macrophages on surveillance BAL.

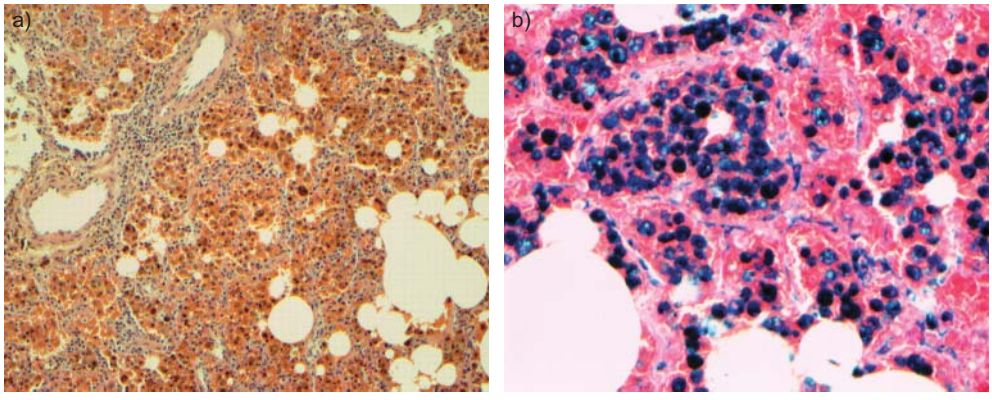

Fig. 7. – a) A case of pulmonary haemosiderosis shows abundant filling of alveolar spaces by haemosiderin-laden macrophages. There is a mild nonspecific chronic inflammatory cell infiltrate within the interstitium. b) A Perls' stain highlights the haemosiderin as blue, in addition showing deposition of haemosiderin within the interstitium.

Pulmonary eosinophilic syndromes

These are rare in childhood [140]. Diagnostic categories are broadly similar to those in adults. There is a female preponderance, which is unexplained. Presentation can be at any age, including infancy, and rarely there may be no peripheral eosinophilia. The radiological features may be atypical, and bronchoscopy or lung biopsy may be needed to make the diagnosis. If there is no specific underlying cause (*e.g.* parasitic infection) then treatment is with corticosteroids, generally with a good outcome in children.

Reactive pulmonary lymphoid disorders mimicking chILD

These are a spectrum, which includes at one end FB and LIP and, at the other end, diffuse pulmonary lymphoma, which is very rare in children [141–143]. FB is characterised by the presence of bronchocentric lymphoid follicles, and LIP is a more diffuse, polyclonal infiltration of lymphocytes. FB may be suggested by the radiological features, and can be classified as acute, subacute or resolved. FB and in particular LIP may be associated with an underlying immunodeficiency, and the child should be evaluated by an immunologist. Auto-immune disease is another aetiology, and familial cases have been described [144]. B-cell expansion is a feature, but the mechanisms are speculative. Familial cases may also be associated with pulmonary fibrosis. The prognosis is of the underlying condition; idiopathic cases of FB have a good prognosis, perhaps worse in children than in adults [142], and tend to resolve over time [145, 146]. The differential diagnosis for LIP in particular is a pulmonary marginal zone lymphoma of mucosa-associated lymphoid tissue origin, but these are very rare in children and typically present with mass-like areas of consolidation rather than diffuse disease [147]. Secondary involvement of the lung by lymphoma and other lymphoproliferative disorders may also occur and should be investigated for, if clinically suspected.

Presentation of paediatric ILD

This is very nonspecific [3, 4]. Unsurprisingly, there was a high incidence of prematurity and neonatal onset of symptoms (28% pre-term, 38% intubated at birth and

57% needing oxygen). 58% were male, and 34% had a family history of lung disease. 30% were biopsied by 3 months of age, 52% by 6 months, and 72% in the first year of life. Presenting features (descending order of frequency, more than one permitted per child) were hypoxaemia, tachypnoea, subcostal recession and other signs of respiratory distress, gastro-oesophageal reflux, pulmonary hypertension, failure to thrive, crackles, cough and wheeze (surprisingly ~20%). 25% had no abnormal auscultatory findings. The network has defined "chILD syndrome" [148] to try to refine referrals for more detailed work-up for ILD. This requires at least three of the following criteria in the absence of any other aetiology as the primary cause: 1) symptoms of impaired respiratory function, 2) hypoxaemia, 3) diffuse infiltrates, 4) presence of adventitious sounds (crackles), and 5) abnormal lung function. It should be noted that, although this is a good guide to the presence of ILD, it cannot replace clinical judgement, and over-reliance on the index may lead to false negatives and positives. There is less information to guide referral in older children.

Differential diagnosis of paediatric ILD

This has been partially covered above, and a full list of all possible diseases that may mimic ILD would encompass most of the spectrum of paediatric respirology. From the previous section, it is clear that the presentation is very nonspecific. The CXR rarely leads to diagnostic certainty, and further imaging is required. The most important thing for the paediatrician faced with a child referred with a presumed airway disease is to consider whether it could in fact be an ILD. A diffuse airway disease with distal airway obstruction may lead to patchy air trapping and cause diagnostic confusion. If proximal airway disease (bronchiectasis) is also present, this helps to exclude an ILD, but chILD may be complicated by traction bronchiectasis. Also, the CXR may be normal, and the ILD only revealed by a computed tomography (CT) scan. Clearly, not all children with any form of airway disease merit CT scanning: diagnostic alertness and clinical skill and acumen are essential.

Diagnostic work-up of the child with suspected ILD

Overview

The child with ILD undergoes a staged work-up (table 9). Not all stages are essential; if there is a clear cut diagnosis of NEHI, for example, assessment of aspiration may be omitted.

Role of HRCT

A diagnostic work-up should be performed in a staged and focused manner. The first step is to confirm that the child does have an ILD, almost invariably with HRCT, if this has not already been performed. In addition to confirming the presence of ILD, HRCT may allow specific diagnoses to be made, which include hypersensitivity pneumonitis, adult-type Langerhans' cell histiocytosis, pulmonary haemorrhage and idiopathic alveolar microlithiasis [149, 150]. Some would include NEHI on this list. Increasingly, CT is performed with suspended respiration after bag and mask ventilation of a sedated child, or under a full general anaesthetic in those too young to breath-hold to order [151]. There has been no formal comparison of scan techniques to determine whether

Table 9. – Staged work-up of interstitial lung disease (ILD) in children

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

HRCT: high-resolution computed tomography; VATS: video-assisted thoracic surgery.

suspended respiration improves rate of diagnosis. In cooperative patients, inspiratory and expiratory scans can be obtained to look for air trapping. The same can be achieved by scanning in alternate side-lying in uncooperative children. A recent manuscript reviewed 59 CT scans and reported that PAP was most frequently correctly diagnosed (n=18), but it was only the first-choice diagnosis in fewer than half of the cases [150]. All single cases of what was called ''pulmonary fibrosis with calcification'', lymphangiectasia and Langerhans' cell histiocytosis were correctly diagnosed. Thus, for most chILD patients, CT is not a definitive diagnostic investigation. Other roles of HRCT would include guiding the best site of any biopsy, and (perhaps) in follow-up. Finally, it is to be hoped that by increasing the numbers of paired scans and definitive diagnoses (usually by surgical lung biopsy) we will be able to diminish the number of biopsies performed in the future. At the present time, obtaining a reliable, confident and specific diagnosis on HRCT must be considered exceptional.

Assessment of disease severity

Once the presence of ILD has been confirmed, the next step is to define the severity of the disease, and subsequently work through programmed investigations to reach a definitive diagnosis, before hopefully finding a treatment. A five-point severity score has been proposed based on symptoms, level of arterial saturation and the presence or otherwise of pulmonary hypertension (table 10) [115]. This requires assessment of oxygenation by an overnight pulse oximetry as a minimum, and the performance of an echocardiogram. The score does not include pulmonary function testing, but this should always be performed in the older child at least.

Echocardiography. This test is used to noninvasively measure pulmonary artery pressure, a routine test in all cases of chILD. The test may also be diagnostic; cardiac mimics of ILD are excluded, *e.g.* left to right shunting causing pulmonary oedema.

Pulmonary function testing. Older children with ILD will often have the characteristic restrictive physiology, with low lung volumes, reduced forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), with a normal or increased FEV_1/FVC ratio. These can be very useful in confirming the diagnosis and monitoring therapy. An elevated diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) in the setting of

Table 10. – Illness severity score used in interstitial lung disease in children

Score	Symptoms	Hypoxaemia <90%		Pulmonary hypertension
		Sleep or exercise	Rest	
1	No	No	No	No
2	Yes	No	No	No
3	Yes	Yes	No	No
4	Yes	Yes	Yes	No
5	Yes	Yes	Yes	Yes

ILD suggests pulmonary haemorrhage or pulmonary venous hypertension; a low $D_{L,CO}$ is very nonspecific. Infant and pre-school pulmonary function is a rapidly expanding field, but experience in ILD is substantially less in this age group and tests should be interpreted with caution. Currently, we would consider them a research technique in this age group.

Determination of aetiology

The planning of investigations, and their timing, will depend on the clinical picture and the level of sickness of the child. Ideally, testing should precede blind trials of treatment, but if the child is very sick on a ventilator, this may be thought inappropriate. In most cases, the first step will be the performance of a panel of blood tests to try to determine the cause noninvasively [152]. Possible tests are summarised in table 11; a selective approach is advisable. Depending on the degree of clinical urgency, it may be appropriate to await the results before any further testing; a positive surfactant protein gene result may obviate the need for any further investigation. The next decision is whether to perform fibreoptic bronchoscopy (FOB) or proceed directly to a lung biopsy.

The role of bronchoscopy. This requires relatively heavy sedation or, more usually, a general anaesthetic [153], and is only indicated if it is thought likely that the results will preclude the need for a lung biopsy. If opportunistic infection is thought likely, then FOB and BAL are the next choice investigation [154]. If this is negative, then the evidence is that it is better to proceed directly to a lung biopsy rather than waste time performing further BALs. Pulmonary haemorrhage can be confirmed by the presence of haemosiderin-laden macrophages in BAL [155, 156], but the test does not distinguish between primary and secondary causes, nor allow the diagnosis of pulmonary capillaritis, which may require different treatment (see below). Other chILD diagnoses that may be made on BAL include Niemann–Pick disease [87], Langerhans' cell histiocytosis [157, 158] and PAP [159]. There is insufficient paediatric experience to recommend BAL cytology as a means of definitive diagnosis of other chILDs. Transbronchial biopsy has only a limited role, exclusive of course in the management of lung transplant rejection. The samples obtained are very small, and, unless the suspected ILD has very specific and focal features that are uniformly distributed within the lung [160], such as pulmonary alveolar microlithiasis or metastatic thyroid cancer, the samples are usually not adequate for the pathologist to make a diagnosis. Furthermore, morbidity from the procedure (bleeding, pneumothorax) is not trivial [161].

The timing and role of lung biopsy. Some teams would advocate a blind trial of oral corticosteroids, and only biopsy children who do not respond. We would not support this, although we have to acknowledge the lack of an evidence base. First, with modern surgical techniques, the morbidity of a lung biopsy is small [162]. Secondly, many ILDs

Table 11. – Blood work to be considered in the work-up of interstitial lung disease (ILD) in children

Test	Disease	Comment
Serum KL-6	NEHI, surfactant protein deficiency	Normal levels in NEHI, raised in surfactant protein deficiency
Sp-B, *Sp-C*, *ABCA3* genes	Surfactant protein deficiency	Indicated in most children with ILD, unless there are extra-pulmonary features or another obvious diagnosis
Angiotensin-converting enzyme	Sarcoidosis	Especially if extra-pulmonary features
Antineutrophil cytoplasmic antibodies	Wegener's granuloma, other vasculitides	Especially if upper airway disease, renal disease or pulmonary haemorrhage
Avian and *Micropolyspora faeni* precipitins	Hypersensitivity pneumonitis	CT scan may be suggestive of this diagnosis
Viral and mycoplasma serology	Obliterative bronchiolitis	Not a true ILD, but may be confused on CT
Immune work-up including HIV	Lymphoproliferative syndromes, including follicular bronchiolitis	Also perform if ILD in fact proves to be an opportunistic infection
Auto-antibody studies	Systemic lupus, rheumatoid diseases, scleroderma and other collagen vascular disease	Especially if extra-pulmonary features and renal disease
GM-CSF studies (serum auto-antibody, receptor genetic studies)	Some of the variants of pulmonary alveolar proteinosis	Adult type with response to GM-CSF has been described in children

Note that not all tests need to be performed in all cases. NEHI: neuroendocrine cell hyperplasia of infancy; CT: computed tomography; GM-CSF: granulocyte-macrophage colony-stimulating factor.

are not steroid responsive, and indeed, if there is an occult undiagnosed infection, steroids may actually be harmful. Thirdly, the morbidity of high-dose corticosteroids may be considerable, and this includes complications of surgery if biopsy is undertaken after a high-dose steroid trial. Fourthly, there are specific treatments for particular ILDs (see below), and these will not be offered if the diagnosis is not made. Fifthly, some conditions may have a genetic basis, and if a specific diagnosis is not made, the family may miss out on crucial information. A final and subsidiary issue, more important to the general population than the individual, is that our ignorance of these conditions is profound, and only by finding out as much as we can about each case will we make progress. Thus, our recommendation is for a lung biopsy to be performed ahead of blind trials of treatment unless the child is too sick, or a specific diagnosis has been made by other techniques.

Techniques of lung biopsy. These are percutaneous, CT-guided needle biopsy [163], video-assisted thoracic surgery (VATS) or *via* a mini-thoracotomy. We have no hesitation in discarding percutaneous biopsy [164]. There is a risk of bleeding and pneumothorax, a patchy abnormality may be missed, and the child needs a general anaesthetic anyway. A surgical biopsy is the method of choice. We recommend that ideally this should be preceded by a BAL, best performed with a flexible bronchoscope to get a good wedge position before lavage. This will maximise clinical information, making diagnosis of occult infection more probable; possibly indicating occult reflux from the quantification of lipid-laden macrophages, or, more specifically, by measuring BAL pepsin [165]; and BAL will be useful as a research tool to correlate BAL cytology with the clinical picture and histology, hopefully in the future minimising the number of

biopsies undertaken. The choice of biopsy technique (mini-thoracotomy or VATS) depends on local surgical expertise; increasingly VATS is the method of choice. Absolutely crucial is close collaboration between surgeon and pathology laboratory. Biopsies should be taken from areas of differing severity, avoiding the tips of the middle lobe and lingula. The biopsy should ideally be a wedge at least 10 mm depth and 20 mm along the pleural axis, unless precluded by the size of the patient (*i.e.* a neonate). The samples should be handled according to standard protocols (table 12) [166], and not left in formalin over the weekend, to await analysis sometime in the following week. The biopsy should be placed in a container with no fixative, and rapidly transported to the laboratory for the pathologist to divide up the specimens. Samples should be taken for electron microscopy (the morphology of the lamellar bodies, for example, may allow diagnosis of a surfactant protein abnormality) and ideally a small portion is snap frozen. The remainder should undergo gentle inflation with formalin, prior to fixation overnight. Care should be taken not to over-inflate the specimen, as this may artefactually cause widening of the interlobular septa and mimic lymphangiectasia. After analysis of the biopsy, a full multidisciplinary approach should be undertaken to plan treatment.

Treatment options in paediatric ILD

There are no randomised, double-blind, placebo-controlled trials in paediatric ILD, and so all recommendations are based on anecdote and low-level evidence. There are treatments to be considered for specific conditions, which will be discussed below, after the various nonspecific therapies that are offered.

Oxygen

If the child is hypoxaemic, then oxygen therapy is given. This is probably the only noncontroversial therapeutic statement. If the child is otherwise well and thriving, no further treatment may be indicated, for example in NEHI patients. Some children with ILD will show spontaneous improvement over time, and come out of oxygen with no additional treatment.

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

This section refers to DIP and NSIP when no underlying diagnosis has been made, and IPH. Therapeutic choices are corticosteroids, hydroxychloroquine and other cytotoxic agents, with lung transplantation as a last resort.

Table 12. – Handling the biopsy in interstitial lung disease in children

Microbiology: viruses, bacteria, fungus, mycobacteria
Snap-frozen for PCR and molecular studies
Snap-frozen in cryomatrix for immunofluorescent, laser capture or other studies
Fixed in glutaraldehyde for electron microscopy
Imprints for cytology and rapid identification of organisms
Expanded by gentle distension and fixed in formalin for light microscopy

Data from [166].

Corticosteroid therapy. Depending on severity, this is given orally or as pulses. Pulses may anecdotally be less toxic [167]. The dose and timing are empirical (*i.e.* based on guesswork). We use methyl prednisolone, 500 $mg \cdot m^{-2}$ daily for three successive days, followed by single monthly pulses at the same dose for 6 months. Ideally, oral prednisolone is avoided between pulses, but this may not be possible; our start dose would be 0.5 $mg \cdot kg^{-1}$ prednisolone on alternate days. If oral prednisolone is given from the outset instead of pulses, a reasonable starting dose is 2 $mg \cdot kg^{-1} \cdot day^{-1}$, tapering according to response. There are anecdotal reports of the use of inhaled corticosteroids as maintenance, but the evidence that these are deposited sufficiently distally and in an effective dose is scanty, and we do not recommend them.

The hardest therapeutic decision may be to determine when there is no further response to steroids, and the time has come to taper the dose to avoid substantial steroid morbidity. Our non-evidence-based policy would be to try three more pulses of methyl prednisolone, and, if there is no improvement, assume that the limit of steroid usefulness has been reached. This is important, because fruitlessly prolonging steroid therapy, leading to osteoporosis, may lead to the child being turned down for lung transplantation.

Hydroxychloroquine. This anti-malarial agent has a number of immunological effects that are possibly beneficial in ILD [168, 169]. There is evidence from case series that it may be helpful, and it is very safe. There are reports of deafness complicating its use in IPH [170], and our own practice is to refer for an ophthalmic check at the start of treatment. Nevertheless, our current practice is to add it to steroids in paediatric ILD, and maintain hydroxychloroquine therapy as an aid to steroid tapering.

Other cytotoxic agents. Evidence is even more anecdotal. There are isolated case reports and small case series advocating azathioprine, methotrexate, cyclosporin and plasmapheresis when steroids have failed. Our own experience with these agents is almost universally dismal. A recent case series has suggested that 6-mercaptopurine may be helpful in IPH [136]; the cynic would state that no medication can be considered to be wholly useless until it has been tried in this condition.

Lung transplantation. A small number of children with ILD have been successfully transplanted, more commonly older children. Both cadaver and living related donation may be considered. Other than in Langerhans' cell histiocytosis (see below), the risk of the disease returning in the transplanted lung is minimal.

Treatment of specific conditions

The increasing availability of specific therapies is an important reason for pursuing a specific diagnosis. Only a few examples are given, which serve to illustrate that there is more to chILD therapy than "steroids for everyone". These therapies have potential benefit, but the high fiscal cost and the potential for very severe side-effects militate against their indiscriminate application. It is likely that more disease-specific therapies will become available in the future, making diagnostic precision even more important. Furthermore, the era of mutation-specific therapies is dawning, for example with PTC124® (ataluren; PTC Therapeutics, Inc., South Plainfield, NJ, USA), a treatment for genetic diseases caused by a premature stop codon, in which the agent overrides the premature but not the normal stop signal [171]. Whether this may apply to some of the genetic conditions described earlier in this chapter is unknown; and the lesson that abnormal Sp-C may be toxic serves as a warning that overcoming a premature stop codon may not always be beneficial.

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

Wegener's granulomatosis and neutrophilic pulmonary capillaritis. Pulsed cyclophosphamide treatment should be considered. For refractory cases, there has been interest in using anti-B-cell strategies, employing the anti-CD20 monoclonal antibody, rituximab [172]. The potential toxicity of these therapies precludes their blind application.

Anti-tumour necrosis factor strategies for sarcoidosis and other conditions. The soluble tumour necrosis factor (TNF)-α receptor, etanercept, has been used on an anecdotal basis for refractory paediatric sarcoidosis [173], in combination with methotrexate. Other causes of ILD that have been successfully treated with etanercept include polyarteritis nodosa and other rare vasculitic diseases [174]. If etanercept fails, the anti-TNF-α monoclonal antibody, infliximab, may be worth trying. The largest dataset is in adult patients.

Pulmonary alveolar proteinosis. Treatment depends on the underlying cause, but large-volume lavage [69, 175–177] and inhaled or subcutaneous GM-CSF have been used successfully [68, 70, 177]. Rituximab has been trialled in refractory cases [178].

Langerhans' cell histiocytosis. Although Langerhans' cell histiocytosis is usually a multisystem disease in children (fig. 8), predominantly pulmonary disease has been described. Cytotoxic therapy supervised by an oncologist is the treatment of choice for both forms of the condition. Many different combinations of therapies have been used. Passive and active tobacco smoking must be discouraged.

Monitoring treatment and progress

In older children who can perform pulmonary function tests, these are the technique of choice. In younger children, we routinely employ overnight pulse oximetry monitoring. CXRs are probably of little use. Repeat HRCT, possibly using a limited

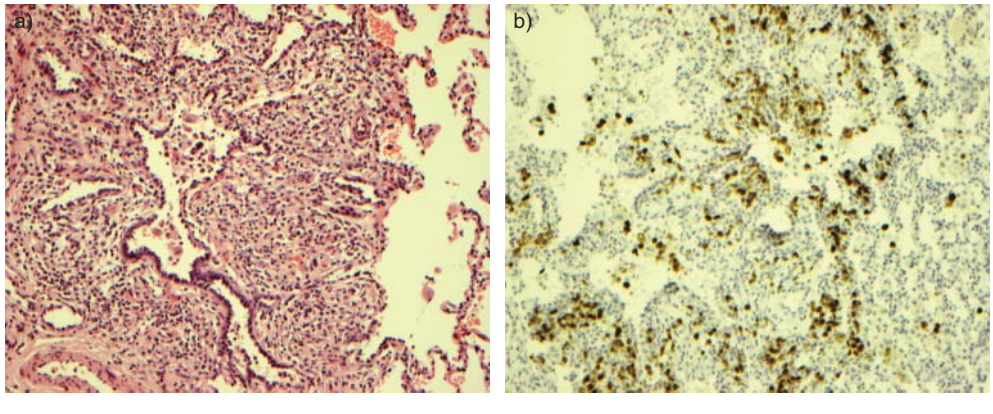

Fig. 8. – a) A case of systemic histiocytosis shows a localised area of Langerhans' cell accumulation around a bronchiole, with admixed lymphocytes and eosinophils. b) Staining for S-100 highlights the presence of abundant Langerhans' cells.

number of cuts, is another option, but should be used with caution to minimise radiation exposure. In most conditions, there is no role for repeat surveillance bronchoscopy. The exception may be the pulmonary haemorrhagic syndromes, where after a period of remission, it may be appropriate to re-bronchoscope the child before stopping treatment, to ensure there is no occult, ongoing bleeding. Repeat lung biopsy would be indicated only under the most exceptional circumstances.

Making progress: the way forward

There is a crying need for focused, randomised, controlled therapeutic trials in well characterised cohorts of patients. We also need to develop a greater understanding of these diseases. Paediatric ILD is a rare diagnosis, and no one centre will see enough cases to run such trials. Thus, the only way forward is multinational collaboration. The first pre-requisite for this is protocol-driven assessment of all these patients, specifically ensuring that information on presentation, imaging and investigations is collated in a uniform manner. There needs to be a panel of radiologists who will assess the imaging, and pathologists to assess lung biopsies. The US chILD Research Network has been a great example of how to do this, but even in their classification paper they had to admit that the imaging was so patchy that no correlations with pathology were possible. In parallel, we need hypothesis-generating studies, so that we can understand the pathophysiology of carefully characterised patients and develop novel therapies. Both novel and standard treatments must be tested in large cohorts using a randomised, double-blind, placebo-controlled methodology, with the confidence that all participating centres are characterising the patients in the same, meticulously careful way. The alternative, too bad to contemplate, is continued, anecdote-based therapy for these sick, vulnerable children.

Summary

Interstitial lung disease in children (chILD) is rare, and shows age-related differences in nature. In children aged 0–2 yrs, it is classified into diffuse developmental disorders; growth abnormalities reflecting deficient alveolarisation; specific disorders of undefined aetiology (pulmonary interstitial glycogenosis, neuroendocrine cell hyperplasia of infancy); surfactant dysfunction disorders; disorders of the normal host, presumed immune intact; disorders resulting from systemic processes; disorders of the immunocompromised host; and disorders masquerading as chILD. In older children (aged 2–16 yrs) the classification is less well worked out: immune-mediated, often systemic disease, infective and post-infective disease is more common. There are a large number of rare genetic conditions, which may also present in adult life; the same genetic disease may cause many different histological appearances, which may be age related.

Presentation is usually nonspecific, and a systematic protocol of investigation is necessary. The presence of chILD is usually confirmed by high-resolution computed tomography, and the severity is determined by physiological tests. Although less invasive testing, such as surfactant protein genetics, may be diagnostic, most will need to proceed to a surgical lung biopsy for definitive diagnosis. Precise diagnosis is important, because of the genetic implications for some families and also because increasingly there are specific cytokine-targeted therapies, *e.g.* rituximab and etanercept, which are being used for specific indications.

There are no randomised controlled trials of treatment in chILD. Oxygen therapy for the hypoxaemic, while spontaneous recovery occurs, may be all that is necessary, but many will need steroid therapy (pulse methyl prednisolone or oral prednisolone), which may be combined with hydroxychloroquine. There is even less evidence for the use of cytotoxic therapies such as methotrexate, azathioprine and cyclosporin. International collaborations, with protocol-driven evaluation of chILD, are urgently required if evidence-based treatment is to be determined.

Keywords: Neuroendocrine cell, pulmonary haemorrhage, sarcoid, storage disorder, surfactant, Wegener's granulomatosis.

Statement of interest
None declared.

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