Abandoning developmental silos: what can paediatricians and adult interstitial lung disease physicians learn from each other?

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Purpose of review
Interstitial lung disease (ILD) consists of a large and heterogeneous group of disorders that are classified together because of similar clinical, radiographic, physiologic or pathologic manifestations. Overall, although there is overlap between adult and childhood ILD (chILD), there are many differences in disease causes and prevalences.

Recent findings
In the last few years, our understanding of adult ILD pathobiology has improved substantially. This is particularly true for idiopathic pulmonary fibrosis, the most common of the idiopathic interstitial pneumonias, wherein recently developed guideline documents provide recommendations for the diagnosis and clinical management of patients. For chILD, similar guidelines are yet to be developed. However, complications and long-term pulmonary outcomes of paediatric disease are better appreciated, which make the implementation of a successful transition program from paediatric to adult care an urgent need. Similarly important is the development of guidelines on performance and interpretation of genetic testing in affected and unaffected relatives of familial cases and in children of adult-onset ILD patients. Lung transplantation appears to be as successful as in adult patients for end-stage disease. Paediatric pulmonologists should engage with the adult multidisciplinary teams and benefit from their much more extensive experience.

Summary
Childhood and adult ILD share a number of aspects, which give children and adult ILD specialists exciting opportunities to collaborate and learn from each other. Such collaborative effort between child and adult ILD experts is crucial for successful future development in the field.

Keywords
acute exacerbations, children, idiopathic pulmonary fibrosis, interstitial lung disease, pathogenesis

INTRODUCTION

The term interstitial lung disease (ILD) refers to a large and heterogeneous group of rare conditions characterized by various degree of inflammation and fibrosis. Although some of the childhood disorders overlap their adult counterparts, there are substantial differences in disease cause and outcome between paediatric and adult disease, and childhood ILD (chILD) poorly fits adult idiopathic interstitial pneumonia (IIP) classification (Fig. 1) [1,2]. For instance, paediatric and adult desquamative interstitial pneumonia (DIP) have different pathophysiology, the former being generally related to inborn errors of surfactant metabolism and the latter to smoking exposure, whereas usual interstitial

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KEY POINTS

- ILD represents a diagnostic and therapeutic challenge for both paediatric and adult ILD experts.
- chILDs may have late/adulthood sequelae making it a structured transition from paediatric to adult care an essential step in disease management.
- Genetics plays an important role in disease development. However, clear, evidence-based guidance on performance and interpretation of genetic testing in affected and unaffected relatives of familial cases as well as in children of adult-onset ILD patients is lacking.
- Overlapping areas of research between childhood and adult ILDs offer exciting opportunities to collaborate and may benefit both the paediatric and adult ILD community.

pneumonia, the radiological–pathological pattern that defines idiopathic pulmonary fibrosis (IPF) – the most common and severe of the IIPs – occurs extremely rarely in children [3,4]. In addition, chILD occurs far less frequently than adult disease and certain disorders are unique to infants or young children. Saddi *et al.* [5▪] recently calculated the prevalence of chILD in Australasia over a 10-year period by analysing demographics, clinical and outcome data collected by questionnaires administered to pulmonologists involved in the care of patients with chILD aged 0–18 years along with genetic data from two reference laboratories. They identified 115 cases corresponding to a period prevalence of 1.5 (range 0.8–2.1) cases/million, although, due to the retrospective nature of the study, the reliance on recall for identification of cases, and, perhaps, failure to diagnose milder cases, these figures are likely to represent an underestimate.

In recent years, growing interest in adult ILD, particularly IPF, has produced remarkable insights into disease pathogenesis and has led to the approval of two drugs (i.e. pirfenidone and nintedanib) that are able to slow down functional decline and disease progression and are recommended by current guidelines [6]. On the other hand, a number of genetic defects underlying paediatric disease have also been identified. In this review, we summarize

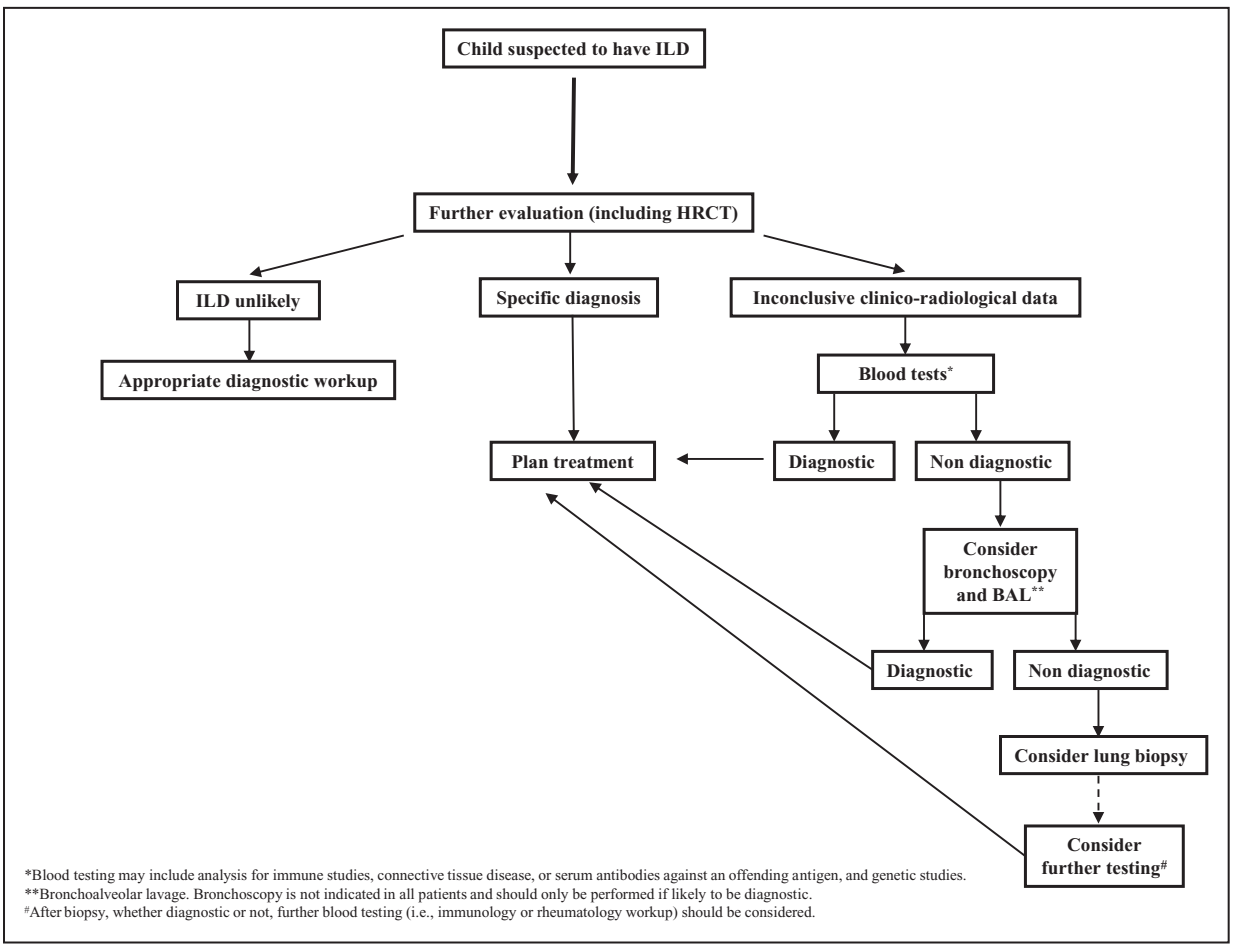

FIGURE 1. Proposed flow chart for investigating children with suspected interstitial lung disease.

and critically discuss the most relevant recent literature on paediatric and adult ILD and identify overlapping research areas that can benefit both adult and childhood disease.

WHAT ADULT INTERSTITIAL LUNG DISEASE PHYSICIANS SHOULD LEARN FROM CHILDHOOD INTERSTITIAL LUNG DISEASE

Long-term consequences of childhood interstitial lung disease

Neuroendocrine cell hyperplasia of infancy (NEHI), better labelled as persistent tachypnea of infancy [7], is an obstructive airway disease of childhood that typically presents in the first year of life with tachypnea, crackles and hypoxia, and generally improves over time [7,8]. However, NEHI may also result in lifelong pulmonary abnormalities. Lukkarinen *et al.* [9] reported on the prospective follow-up of nine infants with histologically and radiologically confirmed NEHI. Although respiratory symptoms (i.e. tachypnea, cough, recurrent wheezing and hypoxia) improved in all infants – with a median symptom duration of 18 months – six infants developed non-atopic airflow obstruction that persisted during follow-up. Similar time courses were observed in the largest European cohort with 50% of the patients fully recovered by age 2.6 years [7], whereas in the US cohort reported by Nevel *et al.* [8] 50% of children no longer required supplemental oxygen at 7.3 years after initiation of therapy. Differential diagnosis and labelling of conditions have to be done very carefully. For example, Nevel *et al.* [10] described four adult relatives with a history of persistent tachypnea of infancy who were found to carry an *NKX2.1*/*TTF1* mutation. Some of these cases had imaging and pulmonary function abnormalities persisting into adulthood [10]. These observations along with the variable phenotypic manifestations of the disease suggest that underlying NEHI should be considered in the differential diagnosis of children with chronic airflow obstruction.

Bronchopulmonary dysplasia (BPD) is classified as a chILD [11], and is a chronic lung disease that affects newborns (generally premature) and infants and results from lung damage caused by mechanical ventilation and long-term oxygen use [12]. Persistent lung sequelae are a common concern in BPD. For instance, teenaged or young adult survivors of BPD tend to have lower forced expiratory volume in 1 s and forced vital capacity compared with controls [13], with high-resolution computed tomography imaging of young adult survivors often revealing persistent architectural distortion [14]. Respiratory infections and exposure to tobacco smoke and pollution may complicate resolution of BPD and increase the risk of pulmonary morbidity. Dysmorphic pulmonary vasculature and altered angiogenesis increase the risk of BPD-associated pulmonary hypertension with retrospective data suggesting a prevalence of pulmonary hypertension 8–25% among infants with BPD [15]. Overall, long-term outcomes of BPD in adulthood and risk of late right ventricular dysfunction and pulmonary hypertension remain largely unknown.

Identification of novel molecular disease entities during childhood

The ATP-binding cassette subfamily A member 3 (*ABCA3*) gene encodes a 1704 amino acid protein with a critical role in surfactant production and processing, and mutations within *ABCA3* are the most common genetic cause of respiratory failure in full-term infants [16]. However, while carriers of null/null mutations leading to ABCA3 deficiency generally have a fatal outcome within the first weeks to months of life, those carrying null/other or other/other mutations display a more variable disease course and may survive into adolescence and adulthood [17▪] (Fig. 2). On histology, nonspecific interstitial pneumonia, DIP, pulmonary alveolar proteinosis (PAP) (alone or in combination) and chronic pneumonitis of infancy are the patterns most commonly found, but variability between individuals and over time in the same individual is well described [18,19]. *ABCA3* mutations may represent a rare cause of apparently idiopathic adult ILD. Notably, in such cases, family history is unlikely to be informative as the disease is inherited as an autosomal recessive.

COPA syndrome is a recently described autoimmune disorder caused by mutations in *COPA* gene, which encodes α subunit of a protein (COP1) involved in the retrograde protein trafficking from Golgi apparatus to the endoplasmic reticulum [20]. The disease is inherited as an autosomal dominant trait with variable expressivity and most patients present with ILD, kidney disease and arthritis [21]. A recent whole-genome sequencing identified a heterozygous missense mutation (Glu241Lys) in three affected individuals over two generations from an Icelandic family [22]. The absence of this mutation from a large number of sequenced genomes strongly supports its role in the pathobiology of COPA syndrome.

The tRNA synthetases catalyse the initial step during protein synthesis, providing the correct amino acids. Recessive loss-of-function mutations in the coding genes can lead to severe ILD with associated multisystem abnormalities. Biallelic mutations in the gene encoding the beta chain of

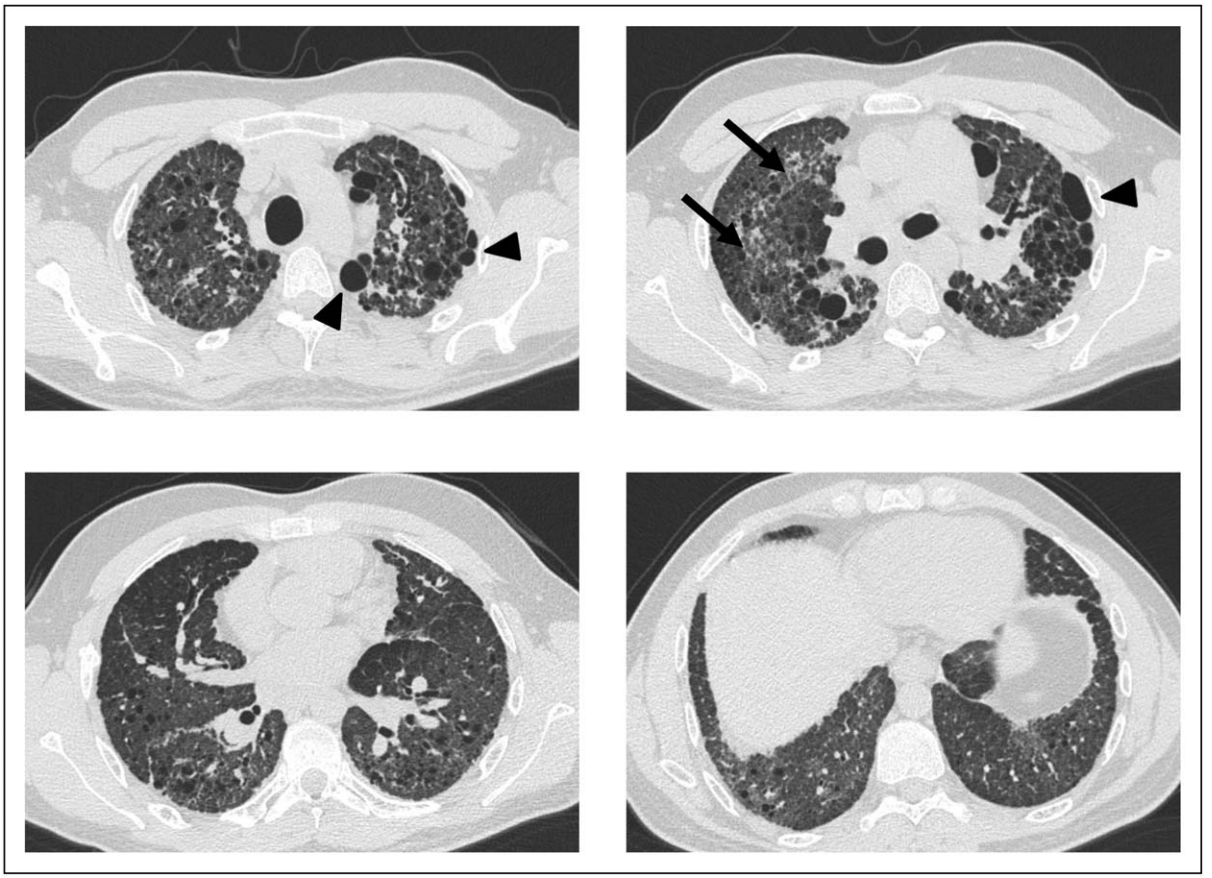

FIGURE 2. 34-Year-old man with familial pulmonary fibrosis (his father and grandfather died of idiopathic pulmonary fibrosis at the age of 55 and 80 years, respectively). High-resolution computed tomography shows ground glass opacity (arrows), and centrilobular and paraseptal emphysema (arrowheads). These abnormalities predominate in the upper zones. This patient was found to carry heterozygous *TERT* (rs7712562) and *ATP-binding cassette subfamily A member 3* (rs138092785) mutations. Both mutations, however, are of uncertain functional and clinical relevance.

the phenylalanine-tRNA synthetase (FARSB) produce a phenotype with frontal bossing, deep and narrow-set eyes, intracerebral abnormalities, scoliosis, joint hyperextensibility, liver cirrhosis, renal abnormalities and muscle hypotonia, among others [23]. In contrast, biallelic mutations of methionyl-tRNA synthetase cause a disease leading to severe pulmonary fibrosis and presenting initially with PAP [24▪▪]. COPA syndrome, ABCA3 deficiency, MARS and FARSB deficiency are novel genetically defined entities, which are diagnosed in childhood and will eventually be treated in adult pulmonary care. In addition, all these severe pulmonary entities may be associated with secondary pulmonary hypertension.

Pulmonary hypertension

Bromley and Vizcaya [25] performed the first systematic review of pulmonary hypertension in chILD. Twenty articles were identified. Estimates of pulmonary hypertension in chILD ranged from 1 to 64%, although only ten studies – all observational and mostly retrospective case series – reported on the frequency of pulmonary hypertension in chILD. Notably, in those studies ($n = 5$) that described the tests used to diagnose pulmonary hypertension – cardiac catheterization and/or echocardiogram and/or ECG – the frequency of pulmonary hypertension was higher, ranging from 25 to 64%, suggesting this complication is frequently missed. Comparisons between studies were limited by differences in the study populations, composition of the case series and methods used to diagnose pulmonary hypertension. Nevertheless, the three studies that reported either mortality rates or the effect of pulmonary hypertension on mortality found that, similar to adults with ILD, the presence of pulmonary hypertension in children with ILD is associated with a significantly increased risk of mortality.

THE IMPORTANCE OF A COORDINATED TRANSITION FROM PAEDIATRIC TO ADULT CARE

Effective transition from paediatric to adult care has become a priority as survival increases for several

chILD. The main goals of a planned transition are to minimize interruption of care and to maximize independence as patients move from paediatric to adult care. One population that has been at the forefront of the discussion regarding the need for structured transition is cystic fibrosis (CF), wherein many patients spend more years under the care of adult rather than paediatric subspecialists [26]. Major barriers to overcome for a successful transition include insufficient economic/personnel resources as well as poor communication between paediatric and adult providers, often leading to the patients' perception that they are receiving suboptimal quality of care from physicians who are unfamiliar with a 'paediatric' disease. Such fragmented care may result, particularly in burnt-out chILD, in patients not seeking medical attention until a serious problem arises, not managing adequately chronic symptoms, and not engaging in preventive care [27]. The transition process should start early, although considerable variations across centres exist in the structure of such transition. Yet, without a planned, structured transition, patient transfer may occur only at a time of rapid clinical deterioration and even without patient's agreement. The main issue, however, is the extreme rarity of chILD patients surviving to transition to adult life, whereas a large CF clinic will have many transition patients per year (approximately 50% of CF patients in the United States are 18 years of age or older [28]), there may be only a single chILD patient every few years. These challenges notwithstanding, the experience of CF has demonstrated that developing a comprehensive transitional care framework is feasible in childhood onset chronic, complex diseases.

WHAT PAEDIATRIC CHILDHOOD INTERSTITIAL LUNG DISEASE DOCTORS SHOULD LEARN FROM ADULT INTERSTITIAL LUNG DISEASE PHYSICIANS

Significance and management of acute exacerbations

Acute exacerbations are episodes of acute respiratory deterioration characterized by worsening dyspnea, increased supplemental oxygen requirements and radiological evidence of new widespread alveolar abnormality. Importantly, acute exacerbations are associated with increased morbidity and mortality [29▪]. Although best characterized in IPF, acute exacerbations may complicate the course of virtually all ILDs both idiopathic and nonidiopathic [30] including chILD [31] (Fig. 3). In IPF, incidence rates of acute exacerbations range from 41 events per 1000 patient-years – as emerged from a meta-analysis of patients randomized to placebo in six clinical trials [32] – to 130 events per 1000 IPF patient-years as reported in a registry-based US study [33]. The frequency of acute exacerbation in chILD is far more difficult to estimate due to the lack of a standardized definition, the multitude of pathological conditions and the inadequacy of organized reporting systems. Similar to IPF, the definition and diagnostic criteria of acute exacerbation in chILD include any acute respiratory event regardless of its cause; this is based on both the observation that the prognosis of acute respiratory worsening in IPF is similar whether idiopathic or triggered by an identifiable cause [34] and the difficulty in determining causation in chILD [35]. Based on expert opinion, a definition of acute exacerbation of chILD and a set of diagnostic criteria have recently been proposed [31]. From an initial list of criteria derived from studies performed in multiple lung diseases and patient groups, an expert panel identified seven items that more reliably reflect a deterioration in the patient's condition (Table 1) [31]. Notably, this approach is not meant to provide rigid definition and diagnostic criteria of acute exacerbation of chILD. Instead, it aims at harmonizing inclusion criteria for future research studies of acute exacerbations of chILD, documenting their prevalence across the spectrum of chILD, standardizing the search for specific triggers (e.g. infection and aspiration) and determining management protocols.

Interstitial lung disease findings in the relatives of those with known interstitial lung disease: what should we do?

Genetic factors play an important role in the development of sporadic and familial IPF and non-IPF forms of pulmonary fibrosis with at least one-third of the risk of developing the disease being explained by common (i.e. polymorphisms) or rare (i.e. mutations) genetic variants [36]. However, there is no consensus on when to pursue genetic evaluation and testing in patients with pulmonary fibrosis or how to use test results in patient care [37▪▪,38]. Similarly, there is no guidance on when to extend genetic testing to individuals at risk of developing the disease such as unaffected family members of patients.

Familial interstitial pneumonia (FIP) is defined as the occurrence of an IIP in two or more relatives sharing common ancestry; so far, deleterious mutations in genes related to telomere biology and surfactant production have been associated with the development of FIP. Specifically, a short telomere syndrome is suggested by a family history of cryptogenic cirrhosis, aplastic anaemia, myelodysplasia

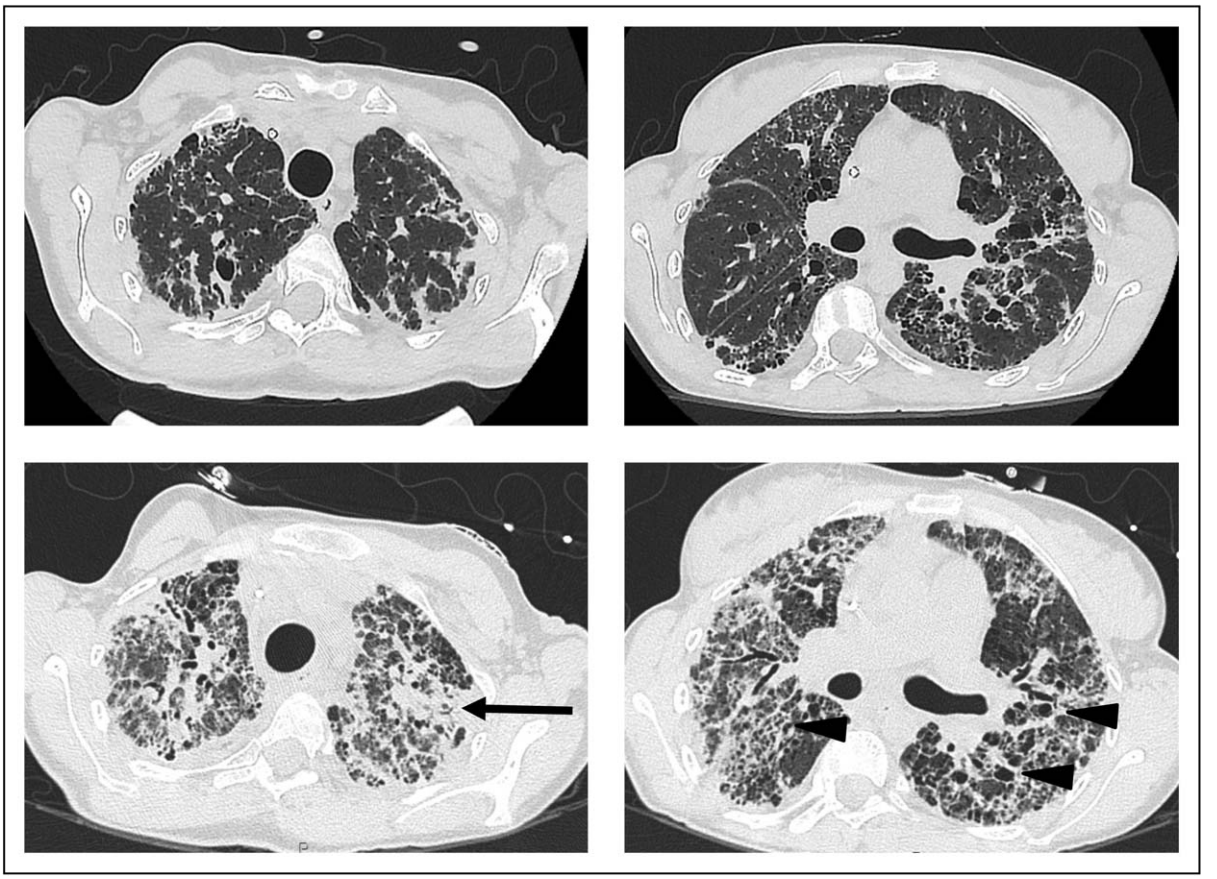

FIGURE 3. Acute exacerbation of interstitial lung disease in a 24-year-old Nigerian woman with COPA syndrome. Diffuse ground glass opacity and reticular changes mixed with areas of consolidation (arrow) are distributed predominantly in the mid-upper zones of the lung. These abnormalities, which are either peribronchovascular or diffuse in distribution, are superimposed on a background of cystic abnormalities (arrowheads). The two computed tomography scans (top left and right vs. bottom left and right) were performed 3 weeks apart.

Table 1. Acute exacerbation criteria in interstitial lung disease in children

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

and/or premature greying, whereas a family history of early-onset lung disease (especially in childhood), or a family history of disease onset before age 45 years and lung cancer raises the suspicion of an underlying surfactant-related disorder [39]. If a short telomere syndrome is suspected, experts recommend peripheral blood mononuclear cell telomere length measurement. Notably, while in the presence of short telomeres (<10% for age) the likelihood of identifying a pathogenic mutation in a known telomerase-related gene is high, short telomeres can also be inherited without inheriting a mutation (i.e. 'occult genetic disease') [40].

Expert opinion suggests genetic testing looking for mutations in disease-associated genes be offered to all patients with FIP as a positive genetic diagnosis in FIP can aid predicting disease behaviour and anticipating complications after lung transplantation [37▪▪]. Conversely, the utility of a genetic diagnosis in estimating the risk for unaffected family members is limited by the difficulty to predict with high confidence the

penetrance of disease-associated mutations. Nevertheless, knowledge of mutation carrier status may be particularly relevant in families with telomerase mutations due to the occurrence of earlier onset disease and severe extrapulmonary manifestations in successively younger generations (i.e. genetic anticipation), which makes it reasonable and potentially beneficial to offer closer monitoring of asymptomatic mutation carriers [37▪▪]. Genetic testing in asymptomatic children within families with FIP is more problematic and expert centres tend to postpone consideration for genetic testing until adult age unless manifestations of the disease in childhood are likely.

Additional data are required before developing comprehensive, evidence-based guidelines for genetic testing and screening for patients suffering from disease and their relatives.

Lung transplantation in adults and children

Lung transplantation is an area where paediatric pulmonologists can engage with adult multidisciplinary teams and profit from their extensive experience. Indeed, in 2017, 2478 lung transplants have been performed in the United States only, approximately half of which were for ILD [41]. In patients with IPF, lung transplantation can prolong survival and improve quality of life [42,43], although only two-thirds of transplant recipients survive for more than 3 years after transplantation and only half survive for more than 5 years [44]. Conversely, in 2017, in the United States, only 13 child paediatric lung transplants were performed, including three recipients younger than 1 year [41]. Eldridge *et al.* [45] have recently reported on their experience at St Louis Children's Hospital. They compared outcomes of infants (<1 year of age, $n = 28$) and children (>1 year of age, $n = 16$) who underwent bilateral lung transplantation for genetic disorders of surfactant metabolism (*SFTPB*, *SFTPC*, *ABCA3* and *NKX2-1*) over two epochs (1993–2003 and 2004–2015) and observed that infants were more likely to be transplanted for SFTPB deficiency while children were more likely to be transplanted for *SFTPC* mutations. Both infants and children underwent transplantation for ABCA3 deficiency. Compared with children, infants experienced shorter times from listing to transplantation ($P = 0.014$), were more likely to be mechanically ventilated at the time of transplantation ($P < 0.0001$) and were less likely to develop bronchiolitis obliterans post-transplantation ($P = 0.021$). However, 5-year mortality remained substantial and did not differ between infants (56%) and children (76%) or between epochs.

CONCLUDING REMARKS

In adult ILD, specifically IPF, improved understanding of disease pathogenesis and better defined diagnostic criteria coupled with better design of clinical trials and international collaborative efforts have culminated in the approval worldwide of two antifibrotic drugs, although there is no cure for IPF and the unmet need remains substantial. Despite inherent (and inevitable) differences, childhood and adult ILD share a number of aspects – mainly related to their rarity and orphan status – which give children and adult ILD specialists the opportunity to learn from each other. For instance, monogenic diseases that manifest in infancy but with consequences in adulthood highlight the importance of a coordinated transition as paediatric patients transfer to adult care and represent a unique opportunity for clinicians, radiologists, pathologists and geneticists to collaborate towards a personalized diagnostic and therapeutic approach. Collaborative effort between child and adult expert centres has the potential to fill some of these gaps and represents, we believe, the way forward.

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Conflicts of interest

A.B. is an emeritus NIHR Senior Investigator. There are no conflicts of interest.

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