Pulmonary function testing in children's interstitial lung disease

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Pulmonary function testing may be useful in different stages of management of children with suspected or confirmed chILD but this literature search revealed only a limited number of papers published in the last three decades. https://bit.ly/3cs0uZr

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ABSTRACT The use of pulmonary function tests (PFTs) has been widely described in airway diseases like asthma and cystic fibrosis, but for children's interstitial lung disease (chILD), which encompasses a broad spectrum of pathologies, the usefulness of PFTs is still undetermined, despite widespread use in adult interstitial lung disease.

A literature review was initiated by the COST/Enter chILD working group aiming to describe published studies, to identify gaps in knowledge and to propose future research goals in regard to spirometry, whole-body plethysmography, infant and pre-school PFTs, measurement of diffusing capacity, multiple breath washout and cardiopulmonary exercise tests in chILD. The search revealed a limited number of papers published in the past three decades, of which the majority were descriptive and did not report pulmonary function as the main outcome.

PFTs may be useful in different stages of management of children with suspected or confirmed chILD, but the chILD spectrum is diverse and includes a heterogeneous patient group in all ages. Research studies in well-defined patient cohorts are needed to establish which PFT and outcomes are most relevant for diagnosis, evaluation of disease severity and course, and monitoring individual conditions both for improvement in clinical care and as end-points in future randomised controlled trials.

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Introduction

Children's interstitial lung disease (chILD) comprises over 200 different disease entities. All these conditions are rare and, although diffuse, they differ from diffuse lung diseases (DLD) in adulthood. A classification system was proposed separating entities primarily seen in infants and preschool children from those occurring at any age [1, 2]. chILD is a basket of clinical entities and for many of the conditions no specific diagnostic tests exist, and evidence-based treatment is lacking. However, a combination of clinical symptoms and signs (such as tachypnoea, hypoxaemia, dry cough, crackles, digital clubbing), radiographic abnormalities, lung biopsy findings or genetic testing may lead to the diagnosis of a definite disease entity, but many diagnoses are nonspecific and purely descriptive [3].

Pulmonary function testing is a cornerstone in the evaluation of respiratory disease to obtain objective measures for the initial work up, diagnosis and follow-up [3, 4]. However, there are very few studies concerning the usefulness (feasibility, monitoring and treatment evaluation) of the various pulmonary function tests (PFTs) in chILD. The purpose of this narrative literature review was to give an overview of the different PFTs that may be relevant in the diagnosis and monitoring of patients with chILD in different age groups and present relevant standard operating procedures (SOPs) and age-related reference material. The further purpose was to present results from previously published studies in which PFTs were performed in chILD patients.

This literature review of lung function testing in chILD was initiated by the COST Action "Enter chILD" working group (www.cost.eu/actions/CA16125) to explore existing studies in the field and conduct a narrative review, with a view to identifying the gaps in current knowledge and to propose future research goals.

Methods

A literature search was performed in PubMed for original articles with a specific focus on lung function testing in children with interstitial/diffuse parenchymal lung diseases according to the classifications by Deutsch *et al.* [1]and Griese *et al.* [2]. The search also included SOPs and age-related reference materials for different PFTs relevant in the paediatric age group. The literature search process and inclusion and exclusion criteria are described further online in the supplementary material.

Lung function tests

A summary of all included PFTs is presented in table 1.

Spirometry and whole-body plethysmography

Spirometry is used to detect restrictive and obstructive impairment. Main outcomes are the forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) (for preschool children: 0.5 s ($FEV_{0.5}$) or 0.75 s ($FEV_{0.75}$)) as well as forced expiratory flows at different lung volumes. The technique is feasible and can be performed quickly in most clinical and outpatient settings from late pre-school age onwards. Disadvantages are the need for active cooperation and the difficulty in performing a maximal and forced expiratory manoeuvre. Falsely low FVC measurements may result from submaximal efforts, and obstructive changes can lead to reduced vital capacity (pseudo-restriction). Spirometry is well standardised and there are international SOPs and reference equations for different ages [15, 24–27]. The 2012 Global Lung Initiative reference equations are one of the most comprehensive datasets but were not available for the majority of reviewed publications [28].

The addition of specific airway resistance (sR_{aw}), airway resistance (R_{aw}) and lung volumes (functional residual capacity (FRC), residual volume and total lung capacity (TLC)) using whole-body plethysmography may help to differentiate between restrictive, combined restrictive/obstructive and pseudo-restrictive ventilatory airway disorders [21]. Restrictive lung disease is defined as a TLC below the lower limit of normal. Reference values exist for patients aged ⩾3 years for sR_{aw} measured during slightly accelerated tidal breathing [22] and ⩾6 years for R_{aw} and lung volumes, which require certain active cooperation with specific respiratory manoeuvres [23].

Infant PFTs

There are currently five methods for infant pulmonary function testing (iPFT) commercially available for usage in children aged <2 years of age. Infant whole-body plethysmography enables measurement of FRC, which is well standardised [5] with published reference values [6, 7], and assessment of (s)R_{aw}, which is less well standardised. Both tidal volume rapid thoracoabdominal compression (TVRTC) and raised volume thoracoabdominal compression (RVRTC) allow evaluation of forced expiration, providing information about peripheral airway obstruction. RVRTC has been shown to be superior to TVRTC with respect to its sensitivity in wheezing infants and infants with cystic fibrosis (CF) [45, 46]. Maximal flow at

TABLE 1 Description of included pulmonary function tests

Technique	Target age group	Main outcomes	Available SOPs[#]	Reference material	Advantages/disadvantages
Infant whole-body plethysmography	Infants <2–3 years	FRC sR_{aw}	Yes (FRC) [5]	Yes (FRC) [6, 7]	Advantages: possible to obtain simultaneous estimation of lung size and resistance Disadvantages: not widely available; time consuming; requires sedation; sR_{aw} less standardised
Compliance and resistance measurement	Infants	τ_{rs} C_{rs} R_{rs}	Yes [8]	Yes [6, 9]	Advantages: may quantify restrictive lung disease; can be performed together with infant whole-body plethysmography Disadvantages: not widely available; time consuming; requires sedation
Forced expiratory manoeuvres: RVRTC and TVRTC	Infants	V'_{maxFRC} FVC $FEV_{0.5}$ FEF_{25-75}	Yes [10, 11]	Yes [12–14]	Advantages: obtains parameters comparable to spirometry; highly reproducible; validated Disadvantages: not widely available; time consuming; requires sedation; RTC less discriminative than RVRTC
Tidal breathing analysis	Infants and pre-school children	V_T RR t_{PTEF}/t_E	Yes [15]	Yes 0–5 years [16, 17]	Advantages: high feasibility in awake infants and pre-schoolers Disadvantages: sedation is often needed
R_{int}	Pre-school children and older	R_{int}	Yes [15]	Yes 2–13 years [18]	Advantages: high feasibility in pre-schoolers Disadvantages: measures R_{aw} only
Oscillometry	Pre-school children and older	R_{rs} X_{rs}	Yes [15]	Yes (from 2 years) [19, 20]	Advantages: high feasibility in pre-schoolers; measures airway and lung tissue properties Disadvantages: may be experienced as unpleasant; requires several repetitions
Whole body plethysmography	Pre-school children and older	sRaw Raw FRC RV TLC	Yes [21]	Yes [22, 23]	Advantages: lung volume measurements; sRaw for pre-schoolers/all ages (does not require "panting"); can be combined with spirometry manoeuvre; available in most centres Disadvantages: Volume measurements for school children requires maximal in-/expiration; cooperation is needed
Spirometry	Pre-school children and older	FEV_1 $FEV_{0.5}$ $FEV_{0.75}$ FVC FEV_1/FVC FEF_{25-75}	Yes [15, 24, 25]	Yes (from 3 years) [26–28]	Advantages: feasible and well standardized technique; available in all centres; fast to perform Disadvantages: requires forced expiration

Continued

TABLE 1 Continued

Technique	Target age group	Main outcomes	Available SOPs[#]	Reference material	Advantages/disadvantages
Diffusing capacity	School children and older	T_{LCO} K_{CO} TLC VC	Yes [30]	Yes (from 5 years) [31–35]	Advantages: feasible and well standardised technique; available in most centres Disadvantages: measurement of haemoglobin is required
MBW	All ages	LCI 2,5 S_{cond} S_{acin} FRC_{gas}	Yes [37, 68]	Yes, but only for SF_6 MBW [8–40]	Advantages: only tidal breathing is required; the technique is available for all ages Disadvantages: reference material for N_2 MBW is missing; time consuming in advanced stages of the disease; the value of N_2 MBW in infants is still not clear
6-minute walk test	Pre-school and older	6-MWD	Yes [72]	Yes (from 3 years) [73]	Advantages: does not require any specific equipment Disadvantages: cannot distinguish cardiac/muscular/ pulmonary impairment
Maximal exercise test	School age and older	V'_{O_2}peak HR_{max} RER V'_E W_{max}	Yes [74, 75][¶]	Yes [78]	Advantages: a more precise estimate of the patient's maximal cardiopulmonary capacity Disadvantages: requires specific equipment; requires motivation from the patient; more risk involved than in submaximal tests; requires trained staff; skills needed to clarify cardiac/muscular/ pulmonary impairment

SOPs: standard operating procedures; FRC: functional residual capacity; sR_{aw}: specific airway resistance; τ_{rs}: respiratory tract time constant; C_{rs}: respiratory tract compliance; R_{rs}: respiratory tract resistance; RVRTC: raised volume rapid thoracoabdominal compression; TVRTC: tidal volume rapid thoracoabdominal compression; V'_{maxFRC}: maximal flow at functional residual capacity (FRC); FVC: forced vital capacity; $FEV_{0.5}$: forced expiratory volume in 0.5 s; FEF_{25-75}: forced mid-expiratory flow at 25–75% of FVC; RTC: rapid thoracoabdominal compression; V_T: tidal volume; RR: respiratory rate; t_{PTEF}/t_E: time to peak expiratory flow to expiratory time ratio; R_{int}: interrupter technique; R_{aw}: airway resistance; X_{rs}: reactance of the respiratory system; RV: residual volume; TLC: total lung capacity; FEV_1: forced expiratory volume in 1 s; T_{LCO}: transfer factor of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide; VC: vital capacity; MBW: multiple breath washout; LCI: lung clearance index; S_{cond}: resistance in conductive airways; S_{acin}: resistance in acinar airways; SF_6: sulphur hexafluoride; 6MWD: 6-min walking distance; V'_{O_2peak}: peak oxygen uptake; HR_{max}: maximal heart rate; RER: respiratory exchange ratio; V'_E: minute ventilation; W_{max}: maximal work load. [#]: SOP is only available for pre-school children, it is not available for infants; [¶]: a new European Respiratory Society task force is expected to be published soon.

FRC is the main TVRTC outcome parameter, while FVC, $FEV_{0.5}$ and forced mid-expiratory flow may be derived from RVRTC. These methods are well standardised [10, 11] and reference values have been published [12–14]. Measurement of passive respiratory tract mechanics is used to assess compliance and resistance of the entire respiratory system noninvasively during spontaneous breathing. SOP [8] and reference values [6, 9, 47] are available. Tidal breath analysis utilises flow and volume measurements to calculate minute ventilation, tidal volume (V_T), respiratory rate (RR) and various indices of breath timing (for example, inspiratory time to expiratory time ratio (t_I/t_E) and time to peak expiratory flow/t_E ratio) [48, 49]. The multiple breath inert gas washout test (MBW), which may also be adapted for infants, is discussed in the following sections. iPFT has been demonstrated to provide clinically relevant information in infants with chronic lung disease of prematurity [50–52], CF [53–55] and recurrent wheezing [56]. Limitations of iPFT include the need for specialised equipment and trained staff. Usually sedation is needed (chloral hydrate or triclofos) to ensure regular breathing and enable a face mask to be tolerated, which makes iPFT time and resource intensive.

Tidal breathing indices, interrupter technique and forced oscillation technique

Tidal breathing indices, the interrupter technique (R_{int}) and the forced oscillation technique (FOT) can all be used to measure lung function in pre-school children. Since the tests are executed during tidal breathing, they are quick to perform, and also equipment is commercially available. Technical recommendations have recently been published for pre-school children [15] and, for FOT, also for adults [19]. Several indices can be measured during tidal breathing: RR, V_T, t_I and t_E. Reference values have been reported for these indices, although they are laboratory specific [16, 17]. The need to reach a stable and regular breathing pattern is the main technical limitation of these methods. An irregular breathing pattern may increase the intra-individual variability, thus limiting reproducibility and suitability for long-term follow-up. R_{int} is based on the assumption that during a sudden flow interruption during tidal breathing, mouth pressure equilibrates with alveolar pressure and resistance can hence be calculated, *i.e.* dividing mouth pressure by the flow measured just before (classical technique) or just after (opening technique) the interruption [15]. Several reference values have been published [57–59], some of which were recently unified by the Asthma UK Initiative [18]. FOT is based on the principle that respiratory impedance can be calculated by measuring the changes in mouth pressure and flow generated by small pressure oscillations at a low frequency applied to the airways [15, 19]. Respiratory impedance can be divided into resistance of respiratory system representing the frictional pressure loss, and respiratory system reactance, which at low frequencies represents the compliance (distensibility) of the respiratory system and at high frequencies inertance. Low frequency oscillations (4–48 Hz) are generated by a loudspeaker and can be based on sinusoidal waves or impulses, both as single-frequency or composite signals. Reference values starting at the age of 2 years have been published for both techniques [15, 19, 20].

Diffusing capacity measurement

The transfer factor of the lung for carbon monoxide (T_{LCO}) measures the ability of the lungs to transfer gas from inhaled air into the red blood cells in the pulmonary capillaries, and can be used to monitor disease progression and response to treatment in diffuse lung disease [60]. T_{LCO} changes with the level of haemoglobin, lung volume, carboxyhaemoglobin levels and altitude, and adjustments for these factors, in particular haemoglobin, may be needed prior to interpreting results [61, 62]. In DLD with diffuse loss of lung units, the transfer coefficient of the lung for carbon monoxide (K_{CO}) is reduced due to the reduced size of the alveolar-capillary bed, but the alveolar volume (V_A) may also be reduced because of reduced lung compliance, causing a markedly reduced T_{LCO} ($T_{LCO}=K_{CO}\times V_A$). Hence the relative changes in K_{CO} and T_{LCO} depend on the nature and severity of the condition studied. T_{LCO} may be increased if there has been recent pulmonary haemorrhage [63], as in idiopathic pulmonary haemosiderosis. In most cases of asthma, T_{LCO} is normal but may be increased. This is thought to be due to increased changes in pleural pressure needed to overcome airflow obstruction having the secondary effect of augmenting venous return and thus increasing pulmonary blood volume [64, 65]. It is important to notice that T_{LCO} may be reduced in several other conditions only loosely related to a pulmonary parenchymal disease, including hepatopulmonary syndrome, pulmonary embolic disease and primary pulmonary hypertension, or affected by factors that limit chest expansion, such as muscle weakness or chest wall deformity [66].

T_{LCO} is, in general, a feasible, rapid and non-expensive test to perform with limited discomfort for the patient, whether by single breath or rebreathing. The technique most commonly used is the single breath method which requires a 10 s breath hold and may be difficult for preschool children and for very tachypnoeic patients. Methods have been developed for measuring single breath T_{LCO} in infants and toddlers, but these are not widely used or routinely available [29, 67].

Some equipment is unable to measure T_{LCO} if the patient's vital capacity is <1.0 L [30]. There is a SOP from the European Respiratory Society (ERS)/American Thoracic Society (ATS) task force [30], and different reference values in children have been published [31–34]. In 2017 the Global Lung Function Initiative published their reference material for patients aged 5–85 years [35].

MBW

The MBW test offers important insights into any non-uniformity of gas mixing, predominantly in the distal, airways. The test is performed during tidal breathing *via* a mouthpiece or facemask. The standard MBW index is the lung clearance index (LCI), which reflects overall ventilation distribution inhomogeneity. Resistance in conductive airways (S_{cond}) and resistance in acinar airways primarily reflect heterogeneity in the conductive (airway generation 8–16) and acinar (airway generation 17–23+) lung zones, respectively [68].

MBW has primarily been used in a research setting and most published MBW studies have been conducted in children with CF [69, 70], where the technique has been shown to be an earlier and more sensitive indicator than spirometry of pulmonary disease and its progression [71]. Commercially available equipment has facilitated distribution to more centres over recent years and made the method more applicable in a clinical setting. The use of MBW indices as an outcome measure is considered attractive because the technique requires only the passive co-operation of the child. MBW testing is feasible even in infants [36, 69] and SOPs covering all age groups exist [37, 68]. A limitation is that sedation may be needed in infants and small toddlers and leaks or irregular breathing patterns (including coughing, swallowing or sighing) can impair test quality. Different reference ranges have been published [39,40] but they are mainly based on the sulfur hexafluoride technique and may be laboratory specific, and to date no robust all-age nitrogen MBW reference material exists. LCI normal values are largely independent of age and height, making it promising for long-term follow-up; however, under the age of 6 years, LCI seems to be inversely correlated with height [40]. Studying local healthy subjects is recommended to generate comparator data until robust device-specific reference equations are published for commercial systems [68].

Exercise testing

Exercise testing measures physical capacity and is measured by a submaximal or maximal method. In this review we have focused on the 6-min walk test (6MWT) and peak oxygen uptake (V'_{O_2peak}), although other well-described tests are available, *e.g.* the step test [41]. The 6MWT is a standardised exercise test which reflects impairments in functional capacity during submaximal effort. Outcome measures are the distance walked on a flat surface in 6 min (6MWD) as well as heart rate, oxygen saturation and level of exhaustion and breathlessness after self-paced walking. There is an ATS guideline and reference values for children aged ⩾3 years [72, 73]. The test is easy to perform without specialised equipment even in severely ill patients, but it does not allow differentiation of exercise limitations caused by cardiac or pulmonary impairments, *e.g.* from joint immobility or reduced muscle strength.

V'_{O_2peak} is measured during a cardiopulmonary exercise test (CPET) and is often assessed using a graded exercise test until exhaustion while measurements of pulmonary gas exchange are made. V'_{O_2peak} may be defined as the maximum capacity to uptake and transport oxygen in the pulmonary and cardiovascular system, and of the capacity of the exercising muscles to utilise oxygen. When performing a direct measurement of V'_{O_2peak}, the test must be conducted using a treadmill or a cycle ergometer, but V'_{O_2peak} can also be estimated from field tests like the 6MWT [42]. In CF, V'_{O_2peak} is significantly correlated with survival and quality of life leading to recommendations that it should be part of the annual assessment [43]. ERS and ATS statements for conducting CPET in patients with lung diseases have been published [74, 75], but without a specific paediatric focus, and a new ERS statement on standardisation of CPET in chronic lung diseases and how to report outcomes is expected to be published in the near future. Several protocols for cardiopulmonary function testing have been published, but the protocols of Godfrey [76] and Bruce *et al.* [44] are most frequently used for the cycle ergometer and the treadmill test, respectively. Several reference equations have been published and it is important to standardise testing using the procedures and methodology of the reference values used as comparators [77, 78].

Results

The results from the literature searches are listed in table S1 and are summarised for each of the different lung function tests in tables S2–S7. In total, 48 studies were included. The diseases most studied are hypersensitivity pneumonitis (HP), post-infectious bronchiolitis obliterans (PIBO) and rheumatological diseases which may reflect that they are more common in older children.

Surfactant disorders

Clinical utility of iPFT in two patients with different surfactant protein C (SFTPC) mutations (p.173T and p.138F) was demonstrated in a case report [79]. In both patients, a restrictive pattern of impairment was demonstrated, which improved with hydroxychloroquine treatment.

Spirometry was conducted in two studies. One study from 1994 included seven patients with histologically confirmed interstitial lung disease (six children with desquamative interstitial pneumonitis and one with chronic interstitial pneumonitis) [80], and follow-up was reported in 2014 [81] with measurements of spirometry, body plethysmography and T_{LCO}. Five of the seven patients survived and were diagnosed with SFTPC gene mutations (p.173T: n=3; p.138F: n=1; p.V39L: n=1) and two died, one from respiratory failure, a patient who had a very low FVC at the time of diagnosis (26% predicted). At the last follow-up of the remaining five patients (aged 28–37 years), three patients had normal FVC, TLC and T_{LCO} whereas two had a moderately low FVC (65% and 46%, respectively). The surviving patient with the worst lung function at age 7 years (time of first publication) showed most decline in spirometry at follow-up. T_{LCO} was also performed at the two follow-up visits [80]: in 1994 T_{LCO} was >90% pred in all four patients tested while it was clearly reduced in two patients 20 years later (42% and 58% pred), a sign of deterioration, whereas the other two patients had more stable values around 80% pred. Interestingly, V'_{O_2peak} CPET was also performed and long-term follow-up revealed a preserved fitness ⩾79% pred in three patients after 20 years of disease; two who continued with abnormal FVC and T_{LCO}.

The second study included six out of nine patients with mutations in the ATP binding cassette sub-family A (ABCA3) gene [82] with longitudinal spirometry data with last follow-up at age 8–18 years. The mean±SD FVC was 43.6±13.9% and stability was documented during follow-up.

Pulmonary interstitial glycogenosis

In a case report, a 3-month-old child with pulmonary interstitial glycogenosis (PIG) had a restrictive pattern of functional impairment measured by iPFT [83]. T_{LCO} was also measured and was markedly reduced but was normalised by steroid treatment, although FVC remained significantly reduced.

Persistent tachypnoea of infancy and neuroendocrine cell hyperplasia of infancy

Infants with persistent tachypnoea of infancy have a markedly elevated RR with increased work of breathing. If a lung biopsy is performed and hyperplasia of neuroendocrine cells is found, or characteristic computed tomography findings are present, this is termed neuroendocrine cell hyperplasia of infancy (NEHI) or NEHI syndrome, respectively. Two studies in NEHI [84, 85] and one including both NEHI and NEHI syndrome (persistent tachypnoea of infancy) patients [86] documented obstructive lung function (peripheral airway obstruction, airflow limitation and air trapping) using RVRTC and infant whole-body plethysmography, without any differences between NEHI and NEHI syndrome. There were no effects of bronchodilator or corticosteroid treatment on clinical symptoms or lung function. Some of the iPFT parameters correlated with follow-up measurements of haemoglobin saturation 6–12 months after the iPFT and with spirometry 4–5 years later.

HP

PFTs in 17 children and adolescents with HP were reported [87]. Initial spirometry predominantly showed a restrictive pattern (FVC 42.7% pred, 95% CI 38.3–47.1; FEV_1 44.2% pred, 95% CI 39.1–49.3) and these parameters improved significantly to near a normal level in more than two-thirds of patients after 3 months of avoidance of exposure and treatment with systemic corticosteroids, with further improvement during the following months of treatment. The median number of pulse steroid courses was 15 per patient (range 8 to 34). The same trend was seen with TLC, T_{LCO} and T_{LCO}/V_A, with all lung function parameters becoming normal within 6 months after completion of treatment. The same group reported long-term follow-up (median period 3.28 years) in 22 patients (median (range) age 16.7 (11.3–26.9) years) up to 10 years after initial diagnosis of HP [88]. Spirometry was stable during follow-up and was normal in >90% of patients while body plethysmography showed reduced TLC in 35% of the cohort (median z-score: −1.68).

Two studies revealed T_{LCO} to be moderately decreased at diagnosis of HP with mean values of 52% and 48%, respectively [87, 89]. T_{LCO} was found to increase significantly and normalise after 6 months of treatment [87], and a follow-up study found no further change in T_{LCO} from the end of treatment to last follow-up several years later [88]. T_{LCO} median z-score was found to be slightly reduced (median z-score: −1.02) but very variable between individuals (range −3.49 to 0.45). The follow-up study revealed abnormal LCI and S_{cond} in 47% and 53% of patients [88] despite spirometry being normal in the majority of patients (>90%). LCI z-score was significantly inversely correlated with the FEV_1 z-score even years after completion of treatment.

The above-mentioned follow-up study in patients diagnosed with HP [88] also found V'_{O_2peak} to be in the normal range in the majority of patients (>85%) at follow-up after treatment was finished, and demonstrated a significant correlation between V'_{O_2peak} and FVC.

Storage disorders

In an international cross-sectional study including 59 adult and paediatric patients with Niemann–Pick Type B (30 children aged 6–17 years), 53 had high-resolution computed tomography abnormalities suggestive of interstitial lung disease [90]. Spirometry was performed in 55 patients, showing reduced FVC in 47% and an abnormal FEV_1/FVC ratio in 22%. T_{LCO} was reduced in 79% of patients despite only 12% exhibiting respiratory symptoms. There was a significantly lower T_{LCO} % pred in patients with a history of initial shortness of breath compared to those without. 6MWT was abnormal in only 5% of the patients. No follow-up studies have been reported.

Rheumatological disorders

There may be pulmonary involvement in the rheumatological disorders, the prevalence and severity depending on the underlying condition [91]. Secondary pulmonary involvement has been explored in several cross-sectional studies. We identified six studies reporting pulmonary function in children (range 13–40 patients) with systemic lupus erythematosus (SLE) [92–97]. All patients had abnormal spirometry, mostly restrictive, with reduced diffusing capacity, despite which many were asymptomatic. However, half of the studies in SLE found T_{LCO} was reduced in only a very few patients [93, 95, 97] while the remainder found abnormal T_{LCO} values in more than half of the patients [92, 94, 96]. In one of the studies, T_{LCO} was related to the activity of systemic inflammatory processes and disease activity score [94] A CPET was conducted in 10 children with SLE [98]. V'_{O_2peak} was reduced in all patients and in 80% of patients the exercise endurance was below the second percentile compared to age- and sex-matched healthy controls. Muscle strength was reduced in the majority of patients and 40% had <60% muscle mass for their age and sex. Unfortunately, the authors did not perform PFT and it is therefore not known whether the reduced V'_{O_2peak} was related to impaired lung function or impaired physical ability.

In one study in children with juvenile dermatomyositis [99], two studies in children with systemic sclerosis [100, 101] and one study including a mixture of different connective tissue diseases [102] demonstrated similar results with predominant varying degrees of restrictive spirometry in up to 50–60% of patients and also varying impairment in T_{LCO}. However, in a large follow-up study including 51 patients treated for juvenile dermatomyositis [103] spirometry was normal in 82% of patients, and restrictive interstitial lung disease was only diagnosed in 8%.

There were no differences in 6MWT performance in children with either systemic sclerosis or SLE, irrespective of whether there was pulmonary involvement [97, 104]. In children with systemic sclerosis, 6MWD was mostly influenced by myalgia. They had a higher incidence of lower extremity pain and shorter 6MWD compared to children with SLE and healthy controls. Only two (7%) out of 28 paediatric SLE patients had a desaturation >4% at the end of the test [97].

These studies underline the importance of regular lung function testing including spirometry and measurement of diffusing capacity in connective tissue diseases, even in those with no respiratory symptoms.

PIBO

Several studies using mostly spirometry and whole-body plethysmography in large cohorts of children from school age with PIBO [105–108] found moderate-to-severe obstructive lung function impairment (reduced FEV_1, FEV_1/FVC and flow at low lung volumes, with hyperinflation and markedly increased R_{aw}) [105]. In a prospective study, 46 school-age children with PIBO who were followed up for a mean±SD 12.5±3.5 years were found to have a persistent severe obstructive lung function with a decrease in z-score per year for FEV_1, FVC and FEV_1/FVC of 0.07, 0.09 and 0.04, respectively [106]. A similar trend was documented in another small study of 11 school children with mean follow-up time of ∼10 years with a decline of approximately 1% per year in FEV_1, forced mid-expiratory flow at 25–75% of FVC and FEV_1/FVC; FVC did not significantly change over time [107]. T_{LCO} was also moderately reduced in 10 out of 11 children at the time of diagnosis, with a median value of 55% pred while T_{LCO}/V_A was preserved in all patients [107]. Impairment of diffusion capacity *per se* is not thought of as a dominant feature in this patient group and may be related to ventilation inhomogeneity due to severe obstruction/obliteration of the bronchioles, and this may lead to the reliability of the test results in these patients being affected [30].

Also, structural abnormalities in computed tomography scans performed within the first 3 years of life in children with PIBO showed a correlation between these early CT scores and spirometry measured years later (aged 8–15 years) in the same patients [108].

FOT was performed in 12 pre-school children (aged 3–5 years) with PIBO, 135 children with asthma and 35 nonatopic controls [109]. Resistance of respiratory system 5% pred and respiratory system reactance 5% pred were significantly higher in children with PIBO than in the asthma or normal control groups. There was no significant bronchodilator reversibility in the PIBO children.

MBW has been measured in two studies. Gur *et al.* [110] compared a group of 16 children and young adults with bronchiolitis obliterans (14 PIBO and two post burn) to a group of age- and sex-matched CF patients, and found LCI to be comparably elevated in the two patient groups. In addition, the LCI z-score correlated with FEV_1 and FVC, z-scores and computed tomography scores using a modified Bhalla score. A recently published follow-up study in 15 children and young adults previously treated for post-infectious diffuse lung disease [111] revealed similar results, with abnormal z-scores for LCI and FEV_1 in a high proportion of patients (80% and 53%, respectively) and with significant associations between zLCI and $zFEV_1$.

Exercise capacity and lung function were evaluated in 20 PIBO patients [112]. 6MWD was significantly reduced compared to reference values but did not correlate with V'_{O_2peak} in maximal CPET. However, 6MWD was correlated with FEV_1, FVC and residual volume/TLC and may be an acceptable alternative when CPET is not available.

16 patients (aged 10–23 years) diagnosed with PIBO performed cycle incremental CPET and lung function tests [113]. V'_{O_2peak} was lower in patients compared to controls (84 ± 15 *versus* 101 ± 17% pred; p<0.01) but did not correlate with FEV_1 (r=0.45; p=0.09).

Miscellaneous and unspecified interstitial lung disease conditions

There were two small studies in children with sarcoidosis [114, 115]. Spirometry revealed a reduction of vital capacity in about half of the patients which correlated with respiratory symptoms. Additionally, at follow-up, improvement in spirometry correlated with better computed tomography scores [114]. In the larger (n=21) of these studies [116], sarcoidosis patients had a reduced median T_{LCO} (65% pred) at initial assessment with normalisation after 6 months treatment.

There is one retrospective single-centre follow-up study in patients diagnosed between 2 weeks and 16 years of age with multisystemic Langerhans cell histiocytosis. Lung involvement documented clinically or radiological was present in 40% of the cohort [117]. Reduction of lung volumes and lung compliance were reported in 69.2% and 76.9%, respectively. However, the iPFT methodology did not meet current standards and the results may be difficult to interpret.

Khirani *et al.* [118] used spirometry, R_{int} and other tests in a cross-sectional study of nine school-age children and one infant (1.8 years) with a variety of chILD conditions and treatments. R_{int} was abnormally increased in three out of nine patients, but not directly correlated to symptoms or diagnosis and vital capacity was severely reduced (mean 40% pred) in the seven children who could perform spirometry. Only one study published in 1982 documented tidal breathing indices (breathing pattern) and was therefore included despite being outside the time frame of our literature search [119]. In 14 children aged 4–16 years with various chILD conditions, RR and *minute ventilation* were increased whereas t_I was reduced. The ratio of t_I to the total duration (t_{tot})of the respiratory cycle (t_I/t_{tot}) was also significantly reduced. They found a significant relationship between the t_I and the increase in lung elastance.

Summary

This is the first review describing pulmonary function testing in different chILD entities. The literature search revealed 48 publications from the past almost three decades. This underlines the large gaps in knowledge in lung function monitoring of chILD. Within the limited number of publications, spirometry was most utilised to assess disease severity and changes with time and treatment. Initial levels may be very low but near normalisation may be anticipated at follow-up in HP whereas data on long-term prognosis in other subgroups of chILD is still not known. Spirometry is widely available and should be used for basic monitoring from late preschool age, but the findings are not diagnostic of a specific chILD. There is a risk of misdiagnosis and overlap with much more common diseases like asthma in older children but finding restrictive changes on spirometry may be a helpful pointer to chILD. Adding measurements of lung volumes and R_{aw} by body plethysmography can help distinguish between primarily restrictive or obstructive diseases.

iPFT has potential for use in some of the less severe infant chILD conditions (*e.g.* pulmonary interstitial glycogenosis, NEHI and NEHI syndrome, as well as surfactant disorders manifesting early and surviving from infancy), to define typical lung function patterns and monitor changes over time and with treatment. In severe neonatal onset chILD conditions, which usually require ventilation or extracorporeal membrane oxygenation (*e.g.* alveolar capillary dysplasia, surfactant protein B mutations, ABCA3 homozygous or compound heterozygous null mutations), iPFT will not be feasible or be a useful guide in diagnosis or management. Infant whole-body plethysmography, measurement of passive respiratory tract mechanics

and RVRTC were the techniques mostly used. However, more studies are needed to determine the utility of iPFT since very few centres in Europe perform routine iPFT and introducing the techniques has significant resource implications. This equally applies to tidal breathing indices, R_{int} and FOT which, however, may be useful from the preschool age. However, what is clear is that we should be using objective measurements much more to monitor chILD; the fact chILD is an orphan disease should not mean second-rate monitoring.

T_{LCO} is a rapid and non-expensive PFT which is feasible from school age and should be performed at least at baseline in all such chILD patients. Currently, gas transfer data in chILD are based on only a few small studies in heterogeneous patient groups with a limited number of longitudinal measurements. MBW is rarely performed in chILD and LCI has not been used in any prospective studies. MBW supplements traditional PFT, such as spirometry, and has increased sensitivity; at least in CF pulmonary disease with normal FEV_1[120]. Patients with severely obstructive spirometry will have an abnormal LCI, so MBW is not worth performing in addition. Furthermore, in the presence of obstruction, gas washout measurements take a very long time.

Studies of CPET in chILD are scanty but are included in this review because this test adds another dimension. The 6MWT is easy, cheap and safe to perform. Previous studies suggest 6MWT is useful in disease monitoring and probably as a prognostic marker in diseases; for example, the assessment for lung transplantation such as for transplant-free survival in childhood pulmonary arterial hypertension [121] and other lung diseases [122]. It has been shown to be a good predictive marker for death on the waiting list in adults with idiopathic pulmonary fibrosis awaiting lung transplantation [123]. V'_{O_2peak} measurement is possible in specialised centres but is time and resource intensive.

Some PFT techniques have not been included in this review, mainly because experience in chILD is limited. We did not include spot and overnight oximetry and RR studies in this review; these are standardised measures and should be part of the management of all cases of chILD to assess any requirement for supplemental oxygen. Diffusing capacity for nitric oxide is a test with many similarities to T_{LCO} but may be more feasible than T_{LCO} in younger children due to the need for a shorter breath hold. A ERS SOP was published in 2017 [124] and both paediatric (5–18 years) [125] and adult [126] reference materials exist. The MBW method is attractive because it is feasible in all age groups including infants, and the use of MBW in chILD should be further explored, especially in young children, because little else is widely feasible in this age group. Further investigations are needed to understand whether there are any correlations between exercise testing and other lung function outcomes, clinical parameters or quality of life. The hypoxic challenge test could be useful in the future [127] as it may reflect subclinical disease in chILD. However, changes over time for the individual child seem to be the most important outcome as variability is seen in even healthy children [128].

In general, most published work consists of descriptive, cross-sectional single-centre studies with small numbers due to the rarity of the diseases. Details of the reported lung function data varied significantly and, especially in older studies, the different disease entities were often not specified. Follow-up studies are mostly in systemic diseases with secondary pulmonary involvement, mainly rheumatological; probably as children more frequently grow into adolescence and adulthood with these diseases, and diagnostic specificity and treatment has improved significantly in the past decades. Most studies are conducted in patients from school age and onwards, albeit many incident cases of chILD occur at a younger age [1].

The PFTs we have discussed are all well-established methods with published ERS/ATS consensus statements for standardised test performance in paediatric patients and commercially available equipment (table 1). However, for a large proportion of the studies, the SOP/guideline used was not specified in the publication and it was therefore impossible to conclude whether the technique was standardised or the report of outcomes acceptable. Not all techniques are widely available, but patients suspected of having chILD are usually referred to specialised centres for a diagnostic work-up. Age-related reference material is available for most techniques for the target age range, except for nitrogen MBW, but not all reference materials cover diverse ethnic groups. The methods are generally considered safe and without adverse effects or discomfort for the patient, but some iPFTs require sedation and in each case the patient's clinical condition and the value of the information must be balanced against the procedural risks. Patients with severe restrictive or obstructive ventilatory impairments may not have large enough lung volumes or tolerate breath hold for some manoeuvres, even if they are of an age to cooperate. Table 2 describes suggestions for the minimal indications for PFT in patients with chILD.

Limitations of this review include that only selected PFTs have been discussed, and only publications from 1990 and onwards were included. However, earlier publications long predate the classifications of chILD, and pulmonary function testing has changed dramatically from before this time [1, 2]. Another limitation is the necessity of excluding studies with adult patients as well as children, other than one follow-up study in five patients with SFTPC mutations [80].

TABLE 2 Main clinical indications for testing lung function in children's interstitial lung disease (chILD)

Indication	Pulmonary function test
Diagnostics#	Restrictive lung disease in older children? Low FEV_1 and FVC, FEV_1/FVC ratio normal or high, low lung volumes
	bstructive lung disease (PIBO suspected)? Low FEV_1, FVC normal or low, FEV_1/FVC ratio low, raised lung volumes and resistance
	Alveolar haemorrhage? Raised D_{LCO}
	NEHI? Obstructive RVRTC, raised lung volumes
	chILD with interstitial thickening/fibrosis or prominent involvement of pulmonary vasculature (*e.g.* hepatopulmonary syndrome)? Low D_{LCO}
Disease monitoring	Spirometry in older children
	Recurrent pulmonary haemorrhage: increasing D_{LCO}; progressive fibrosis: decreasing D_{LCO}
	Cardiopulmonary exercise testing
Monitoring extrapulmonary co-morbidities of chILD	Respiratory muscle weakness, *e.g.* in juvenile dermatomyositis: lying and standing VC, MIP and MEP

FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PIBO: post-infectious bronchiolitis obliterans; D_{LCO} : diffusing capacity of the lung for carbon monoxide; NEHI: neuroendocrine cell hyperplasia of infancy; RVRTC: raised volume rapid thoracoabdominal compression; VC: vital capacity; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure. #: it is not possible to make specific pathological diagnoses from lung function testing, but it may be helpful to direct further diagnostic approach.

Conclusion

In summary, guidelines on chILD diagnosis recommend including PFTs [3, 129]. However, the existing literature on both diagnosis and follow-up and the added value of PFTs to clinical examination, radiology or other diagnostic testing is sparse and, in most cases, not disease specific. chILD is diverse and includes more than 200 different and heterogeneous conditions. There are some data to indicate that PFT may be useful in some stages of management of children with suspected chILD. PFTs help to distinguish obstructive and restrictive impairments, the latter thus suggesting chILD rather than much more common primary airway diseases. PFTs may be used for follow-up of patients with chILD. Clearly, the evidence gaps we have identified need to be addressed. The first prerequisite is to enrol all children with interstitial lung disease in national and/or international registries. All patients should regularly have lung function testing, but the tools will inevitably depend on the highly variable resources across Europe. Observational studies will inform guidelines into which tests are most sensitive in a disease-specific fashion. We must also beware of collecting data for its own sake, in particular if the techniques are resource-intensive or involve risk (*e.g.* sedation of a tachypnoeic child). Specifically, infant PFTs have yet to be shown to have added value to standard techniques in any chILD, but this should not preclude focussed explorations of their clinical role. As with adult ILD, it is highly unlikely that many if any specific diagnoses of chILD will be made in the physiology laboratory, but lung function techniques may well be used to place monitoring of treatment benefit on an objective footing.

An international approach and platforms like the chILD-EU registry and Enter chILD COST action (CA-16125) and other international research networks are essential if respiratory specialists are to fill the evidence gaps in the management of these rare, and often serious diseases.

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