

European protocols for the diagnosis and initial treatment of interstitial lung disease in children

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ABSTRACT

Interstitial lung disease in children (chILD) is rare, and most centres will only see a few cases/year. There are numerous possible underlying diagnoses, with specific and non-specific treatment possibilities. The chILD-EU collaboration has brought together centres from across Europe to advance understanding of these considerations, and as part of this process, has created standard operating procedures and protocols for the investigation of chILD. Where established consensus documents exist already, for example, for the performance of bronchoalveolar lavage and processing of lung biopsies, these have been adopted. This manuscript reports our proposals for a staged investigation of chILD, starting from when the condition is suspected to defining the diagnosis, using pathways dependent on the clinical condition and the degree of illness of the child. These include the performance of genetic testing, echocardiography, high-resolution CT, bronchoscopy when appropriate and the definitive investigation of lung biopsy, in order to establish a precise diagnosis. Since no randomised controlled trials of treatment have ever been performed, we also report a Delphi consensus process to try to harmonise treatment protocols such as the use of intravenous and oral corticosteroids, and add-on therapies such as hydroxychloroquine and azithromycin. The aim is not to dictate to clinicians when a therapeutic trial should be performed, but to offer the possibility to collaborators of having a unified approach when a decision to treat has been made.

INTRODUCTION

Interstitial lung disease in children (chILD) is rare; there are no reliable estimates, but prevalence is likely <1 per 100 000, as against 60–80 per 100 000 in adults;¹ the average European Hospital will see no more than 5 cases/year.² chILD is more diverse than interstitial lung disease in adults, comprising more than 200 different conditions with a variety of proposed classifications.^{3–6} Since individual centres see so few chILD patients, it is unsurprising that there are no randomised controlled trials of treatment. To address this, a proposal was funded by the European Union FP7 stream⁷ to (a) create a pan-European registry; (b) peer review all potential chILD diagnoses; (c) gather prospective longitudinal data from well-defined groups of children, including the results of N of 1 therapeutic trials; (d) set up and perform the first randomised controlled trials of chILD treatment. In order to achieve this, it was essential that the diagnostic

approaches and treatment protocols were harmonised across Europe. This manuscript reports on our agreed approach, including standard operating protocols, and the Delphi consensus process used to harmonise our approach to treatment, across the entire childhood age range. The reader is also referred to an official American Thoracic Society statement, which covers only the 0–2 years age range.⁸ The aim is not to dictate to clinicians whether to undertake trials of particular treatments but to encourage and enable the use of the same protocol for treatments where there is no evidence.

THE STARTING POINT: WHEN TO SUSPECT CHILD—TYPICAL PRESENTATIONS Shortly after birth

The earliest presentation of chILD is shortly after birth, with unexplained respiratory distress in a term baby. This frequently and rapidly proceeds to intubation and ventilation, with relentlessly progressive respiratory failure^{8–9} leading to death or lung transplantation, if the latter is available. The usual causes are surfactant protein gene mutations^{9–10} and the alveolar-capillary dysplasia spectrum;¹¹ some of the former may make a partial recovery¹⁰ and the baby may survive in chronic respiratory failure. The same conditions should be considered in preterm babies with respiratory distress which does not run the normal clinical course, but the yield of positive results is much less.

First 2 years of life

Later presentations of chILD are very non-specific. In the first 2 years of life, symptoms in descending order of frequency are fast breathing, failure to thrive, typically dry cough and wheeze (this last in 25% of cases) in the absence of respiratory tract infection.³ Suggested protocols for the clinical assessment of these infants are available on the chILD-EU website (<http://www.klinikum.uni-muenchen.de/Child-EU/en/index.html>). SpC mutations may present as respiratory syncytial virus (RSV)-positive bronchiolitis, which fails to resolve;¹² there is animal evidence that RSV causes increased inflammation and worse outcomes in animals with SpC mutations.^{13–14} Signs of chILD include hypoxia, tachypnoea, recession, crackles, pulmonary hypertension and gastro-oesophageal reflux.³ Auscultation can be normal in more than a third. Chest deformity, particularly pectus excavatum, has been reported especially with ABCA3 mutations.¹⁵



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2–16 years of age

There are no large series from this age group, but it is likely that the clinical picture will not be dissimilar. In older children, exercise-induced breathlessness may be the presentation, although other, commoner causes need to be considered.

The USA group have coined the term 'chILD syndrome'⁷ which is a label mandating further evaluation in a child with diffuse lung disease who has had common causes excluded (eg, cystic fibrosis, uncoordinated swallow leading to aspiration) and who has at least three of four criteria, namely (a) respiratory symptoms; (b) respiratory signs, including digital clubbing and failure to thrive; (c) hypoxaemia; and (d) diffuse radiological changes. Clearly, another important part of the initial work-up is a full clinical evaluation of the child, looking for signs of a systemic disease (especially renal, skin, liver, eyes, joints), evidence of pulmonary hypertension and signs of reflux and aspiration.

In all cases, a careful history is mandated, including a family history, which may lead to suspicion of genetic causes of chILD, and environmental exposures if there is any possibility of hypersensitivity pneumonitis; the recent outbreak of ILD in adults and children in Korea emphasises the importance of the environmental history.^{16–18} Simple laboratory testing may give clues to the diagnosis. Anaemia and reticulocytosis are seen in pulmonary haemorrhagic syndromes. Peripheral eosinophilia suggests parasitic disease, hypersensitivity, eosinophilic lung disease and systemic eosinophilic diseases. Stool occult blood results may be positive in patients with pulmonary haemorrhage; indeed these children may have undergone extensive diagnostic work-up for iron deficiency without the possibility of pulmonary haemorrhage having been considered.¹⁹

INITIAL INVESTIGATIONS

Given the non-specific nature of the presentation of chILD the probability of a diagnosis can be enhanced by structured investigation. A simple severity score has been proposed (table 1),²⁰ which sadly has yet to be superseded by more sophisticated biomarkers:

- Clinical:** Evidence of hypoxaemia is often the first abnormality to raise concern and should be noted whether it is present at rest both awake and asleep breathing room air. In older children exercise testing should be used to unmask desaturation which is not present at rest, following standard protocols; there is insufficient evidence to recommend a particular method over others. It is unwise and uninformative to exercise a child who is desaturated at rest, without giving supplemental oxygen.
- Radiology:** The chest radiograph may be normal, but more likely reveals non-specific abnormalities. Gastro-oesophageal reflux is common in young children and also in patients with

respiratory disease; deciding if reflux may be contributory is difficult even in the presence of a barium swallow reflux study and a pH study.

- Physiological testing:** Lung function testing in infants has little general availability and the role in infants is unclear. Neuroendocrine cell hyperplasia of infancy (NEHI) is characterised by a pattern of hyperinflation and airflow obstruction,²¹ but there is insufficient experience to rely on physiological patterns in infancy in chILD. In older children, the usual pattern is classically restrictive, with a reduced FEV₁ and FVC, a normal or even elevated FEV₁/FVC ratio and reduced lung volumes. Carbon monoxide transfer (diffusing capacity or transfer factor of the lung for carbon monoxide, DLCO) is usually reduced, and if elevated, pulmonary haemorrhage should be suspected.²² The occasional chILD may have a more obstructive pattern of physiology.
- Echocardiogram:** Should be an early investigation to estimate pulmonary artery pressure, and exclude cardiac mimics of interstitial lung disease, such as cor triatrium leading to pulmonary oedema.²³ Pulmonary hypertension, where present, should be diagnosed and treated accordingly in liaison with paediatric cardiology colleagues.
- Blood studies:** A focused approach is recommended. Tests can be grouped into (a) genetic abnormalities; (b) immune function (especially if the follicular bronchiolitis-lymphoid interstitial pneumonia spectrum is suspected); (c) auto-antibody studies (cases of pulmonary haemorrhage, alveolar proteinosis, or if there is evidence of a systemic disease); (d) environmental organic dust exposures (hypersensitivity pneumonitis); (e) miscellaneous, that is, ACE inhibitors in cases of suspected sarcoidosis. Note that novel genetic chILD entities with multisystem disease are being described,^{24 25} and the younger the child is the more carefully new or established genetic diagnoses are sought. In all cases of chILD, DNA of the patient and parents should be stored for future analyses. The clinical situation will dictate which tests are performed, and whether it is realistic to await results before proceeding to a CT or lung biopsy.

A proposed diagnostic pathway is shown in figure 1. In terms of timing of enrolment of suspected chILD patients in the registry, a preliminary discussion at an early stage would be valuable for the patient. The use of, for example, standardised scanning protocols is to be preferred.

IF CHILD IS SUSPECTED CLINICALLY: THE ROLE OF CHEST CT SCANNING

CT chest is invariably performed in the investigation of a possible case of chILD. The purpose of chest CT is to evaluate the presence and extent of disease. In some cases it can be diagnostic,²⁶ but is more usually supportive of a diagnosis that takes account of clinical history, blood results and sometimes bronchoalveolar lavage and/or biopsy material.

CT scanning for chILD should only be performed in centres experienced in paediatric radiology. The general principles of scanning are to minimise radiation dosage to the child while maximising the information obtained; a very low dose scan which is diagnostically useless benefits no one.²⁷ Detailed protocols for reducing radiation exposure while maintaining image quality are given online, and these should be audited regularly.

The optimal CT scan is a volumetric scan during inspiration, performed in tandem with a high-resolution CT (HRCT) fine-cut spaced expiratory scan. Ventilation should be controlled to ensure satisfactory, interpretable, scan output. In young children this necessitates a general anaesthetic (ie, under 5 years of

Table 1 Staging the severity of childhood interstitial lung disease (chILD)²⁰

| Score | Symptoms | Hypoxaemia <90% sleep or exercise | Hypoxaemia <90% rest | Pulmonary hypertension |
|-------|----------|-----------------------------------|----------------------|------------------------|
| 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 |

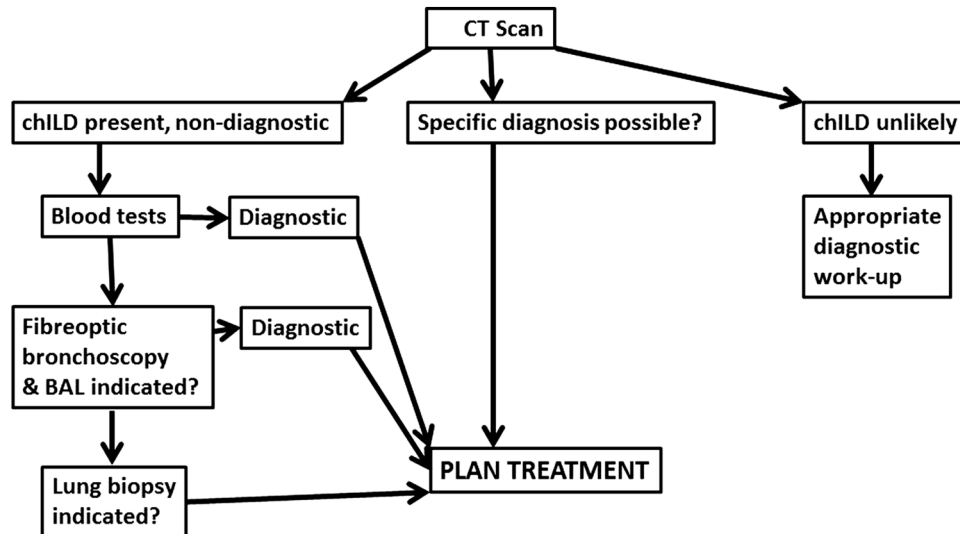


Figure 1 Proposed flow chart for investigating interstitial lung disease in children (chILD). If the child is well and stable, progress to the more invasive investigations may not be indicated. HRCT, high-resolution CT.

age), although some centres advocate sedation and controlled, bag and mask ventilation.²⁸ As always, the risk of anaesthesia or sedation should be weighed against the risk of not obtaining diagnostic information. Older children should be able to reliably hold breath in inspiration and expiration for 6–10 s. In children who are ventilated under a general anaesthetic it is important to attain appropriate ventilation pressures in both inspiration and expiration; these details are provided in our online standard operating procedure (SOP).

The administration of contrast medium will make the assessment of ground glass shadowing almost impossible, and so careful consideration should be given as to the risk/benefit of using a contrast medium based on the anticipated diagnosis. The need to assess the pulmonary vasculature will require the use of contrast, with detrimental effects on the interpretation of some lung components.

The three outcomes of HRCT scanning (figure 1) are (1) chILD unlikely including that the CT is normal. Although a normal CT scan is unusual in ChILD, it may occur in some cases early in the course of the disease process where there are very few non-diagnostic CT features; (2) chILD present and a specific diagnosis can be made²⁶; and (3) chILD present, with or without possible evidence of a comorbidity such as aspiration (eg, consolidation in a typical distribution), but a specific diagnosis cannot be made. If chILD is unlikely then appropriate diagnostic algorithms to investigate possible non-chILD findings are deployed; these are beyond the scope of this article. A specific diagnosis of chILD may allow immediate action; however, the ability for CT to be completely diagnostic is limited to relatively few conditions (ie, pulmonary alveolar proteinosis, extrinsic allergic alveolitis and NEHI), and these too are usually supported by other diagnostic tests, that is, environmental allergen and prednisolone response in hypersensitivity pneumonitis (figure 2A), or granulocyte-macrophage colony-stimulating factor-receptor auto-antibody or gene mutation studies, surfactant protein gene mutations and an immunological work-up in cases of pulmonary alveolar proteinosis (figure 2B).

It is recognised that although faster CT scanners may enable chest CT without the need for anaesthetic, we do not recommend this unless anaesthesia is thought to be unsafe, as (1) the technique frequently provides suboptimal results from

respiratory movements made by the child and (2) the variance in lung volumes during an uncontrolled respiratory cycle will reduce the value of the scans obtained and the reliability of CT to provide the supportive evidence for a diagnosis of ChILD.

Whatever the timing of investigations, planning to avoid the child having multiple general anaesthetics is essential. So fibre-optic bronchoscopy should only be done as a separate procedure if it is likely to be diagnostic; otherwise, it is better performed under the same anaesthetic as the lung biopsy.

INVASIVE TESTING: FLEXIBLE BRONCHOSCOPY

Bronchoscopy with bronchoalveolar lavage (BAL) may be diagnostic in pulmonary haemorrhage syndromes, alveolar proteinosis and eosinophilic lung disease, and a normal cell differential can rule out hypersensitivity pneumonitis. BAL target site should be chosen on the basis of radiological abnormality or airway inspection. If BAL is to be performed during the same anaesthetic as CT, then it should follow the imaging; where it is to be performed at the time of lung biopsy, the lobe designated for a lung biopsy should be avoided. Where possible flexible bronchoscopy should be performed via endotracheal or laryngeal mask to reduce suction channel contamination from the upper airway. BAL volume is adjusted to body weight using 3 mL/kg of sterile normal saline divided into three equal fractions in children weighing <20 kg and 3 mL/kg in 20 mL portions in children weighing >20 kg.²⁹ Negative suction pressure should be adjusted to avoid visible airway collapse. The first bronchoalveolar lavage fluid aliquot should be unfiltered and used for microbiological studies, and the other aliquots should be pooled (unless one is bloodstained), filtered through sterile gauze only if a lot of mucus is present, which is unlikely in chILD, and used for analysis of cellular and non-cellular components. Transport and preparation of samples is provided in our online SOP. Clinicians should liaise with their laboratories to ensure appropriate investigation of samples, to include appropriate microbiological analysis and culture (bacterial, fungal, virus), Oil Red O staining (fat-laden macrophages), periodic acid-Schiff staining (pulmonary alveolar proteinosis) and iron staining (ie, Prussian blue for haemosiderin within macrophages) to diagnose pulmonary haemorrhage syndrome. CD1a-positive cells are consistent with Langerhans cell histiocytosis. A

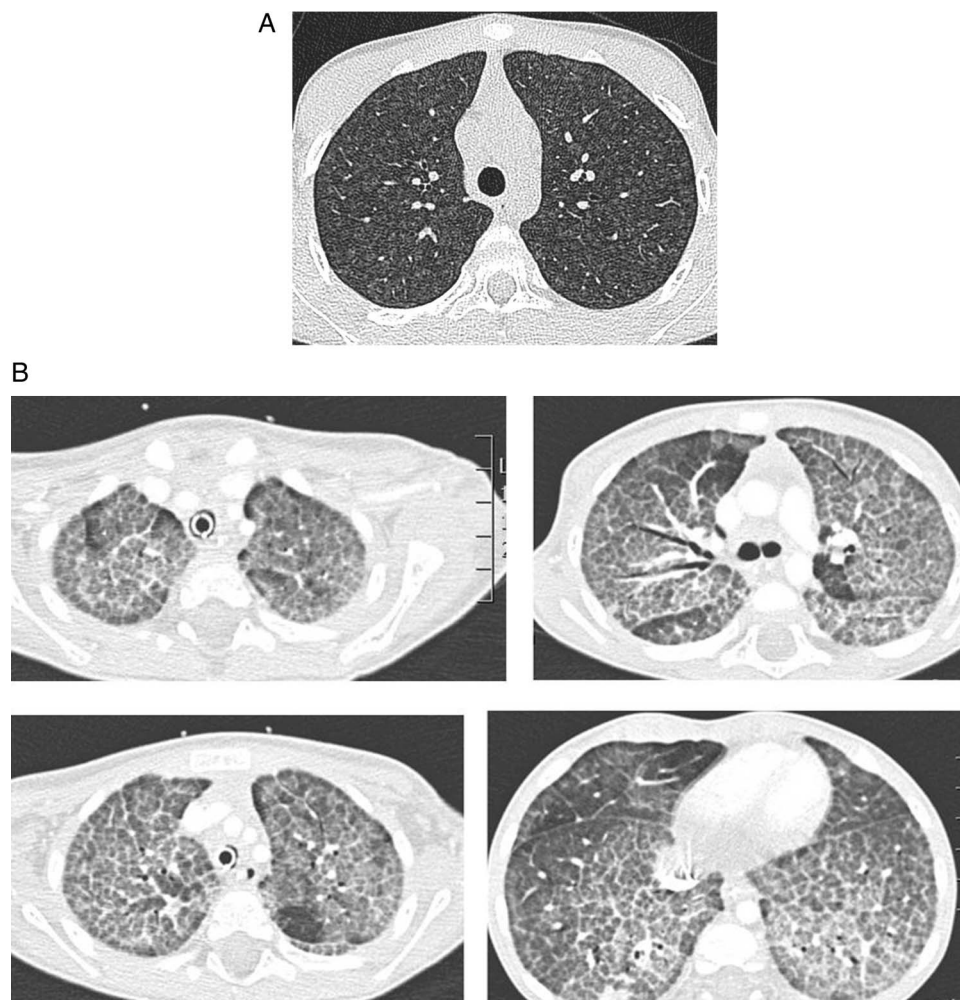


Figure 2 Diagnostic high-resolution CTs (HRCTs) in childhood interstitial lung disease (chILD). (A) There is diffuse ground glass shadowing with a widespread soft centrilobular nodular pattern. This is virtually diagnostic of hypersensitivity pneumonitis, in this case due to pet doves. (B) There is generalised ground glass opacification with thickening of the interlobular septa, giving the classical cobblestone appearance of pulmonary alveolar proteinosis. It is not possible to distinguish the different aetiologies from the HRCT appearances.

lymphocyte-predominant BAL with an elevated CD4/CD8 ratio (>2) suggests sarcoidosis with involvement of the lung.³⁰ Metabolic abnormalities may be diagnosed by BAL, for example, sea-blue macrophages.³¹

Endobronchial (EBx) and transbronchial (TBB) biopsies are rarely performed in chILD and are not recommended unless a specific diagnosis that could be made by these techniques is suspected. Specific conditions such as pulmonary alveolar microlithiasis may be diagnosed by TBB,³² but the samples are too small to diagnose most chILDs. Blind EBx may detect sarcoid granulomas,³³ but is not useful for diagnosing NEHL.³⁴ Our protocols for these procedures can be found online if needed.

INVASIVE TESTING: SURGICAL LUNG BIOPSY

The timing and need for lung biopsy is controversial. chILD patients who are well and thriving may not merit biopsy even if the CT scan appearances are not typical. Some would consider that an oxygen requirement warrants a diagnostic lung biopsy, while others would wait and see. There is clearly merit in performing an invasive procedure only if treatment will be changed as a result. Steroids are a mainstay of treatment for chILD and the timing of biopsy related to their initiation is often dictated by circumstance. Where possible, biopsy prior to steroid treatment is recommended (to minimise risk to

wound healing and to expedite specific chILD treatments, ie, TNF- α antagonist infliximab combined with methotrexate for sarcoidosis, and cyclophosphamide for angiitis with granulomatosis). The dilemma posed by the sick patient with chILD who is on the verge of ventilation (and biopsy would most likely tip to requiring ventilation) or is unstable on a ventilator often dictates that a steroid trial before a biopsy may be appropriate. If the child is already ventilated, unless the ventilatory requirements are very high, a biopsy can safely be performed.

The site of biopsy should be guided by a recent CT chest. There should be liaison between the surgeon, pathologist and paediatrician. Any other procedures which may merit general anaesthesia (eg, bronchoalveolar lavage, mucosal biopsy, placement of a vascular access device or gastrostomy) should be carefully planned. The tip of the middle lobe and lingula should be avoided, and biopsy should preferably be from two sites, and sample areas of varying disease severity. Increasingly, biopsy is using video-assisted thoracoscopic surgery rather than a mini-thoracotomy. Whatever technique is used, the procedure must only be undertaken by an experienced surgeon, who is confident of obtaining adequate biopsies (at least $10 \times 10 \times 10$ mm); a very superficial biopsy, which does not contain distal airways, may result in diagnostic error.

Samples should be rapidly transported to a waiting pathologist working in an accredited laboratory working to international standards.³⁵ There should be access to light microscopy and common special stains, immunohistochemistry, genetics services, microbiology and virology services and photographic equipment. Table 2 describes the postbiopsy sample processing. The remaining tissue should be fixed in formalin. Table 3 describes the routine stains to be used. Details of transport of specimens can be found online.

OTHER SOURCES OF LUNG TISSUE

Postmortem and explanted lung tissue should be accessed if at all possible, and handled in the same way as a lung biopsy. Even if permission for autopsy is refused, it may be possible to obtain permission for percutaneous, transthoracic True-cut needle biopsies. DNA of the patient and both parents should be stored with the family's permission, if this has not already been done. Another valuable source of tissue is the explanted lungs after lung transplantation.

THE ROLE OF PEER REVIEW

chILD is a spectrum of very rare conditions, and no centre will see many cases. The diagnosis may be obvious, as, for example, a suspected surfactant protein gene mutation when known disease causing mutations are detected. However, in many cases the interpretation of CT scans and lung biopsy material is difficult. We believe that the best practice is to peer review these cases so that patients have the benefit of a consensus view from different specialists who can pool and increase their expertise. This is an integral part of our protocols. In chILD-EU, cases are peer reviewed at point of diagnosis and revisited at 12 monthly intervals to gauge the precision of diagnosis and patient outcome.

PROPOSED TREATMENT PROTOCOLS: THE DELPHI PROCESS

In the absence of any randomised controlled trial data, a Delphi process was undertaken to achieve a consensus on treatment protocols to harmonise treatment approaches. The full details are given in the online supplementary material. Briefly, we conducted a two-round web-based Delphi consensus of clinicians caring for chILD. Clinicians were identified from registered email addresses with national paediatric respiratory society groups, including the paediatric assembly of the American Thoracic Society. The questions were derived by the chILD-EU core management team, with adaptation by the lead representatives for clinicians in North America (Robin Deterding) and Australia (Adam Jaffe). The survey consisted of a scenario stem

Table 3 Staining of lung biopsy specimens

| Stain | Purpose |
|------------------------------------|--|
| Always: H&E | Overview of extent, distribution and nature of any pathology |
| Always: Elastic Van Gieson | Collagen/pulmonary vasculature |
| As indicated: CD34 | Vascular marker |
| As indicated: Perls stain | Iron-laden macrophages |
| As indicated: Bombesin | Diagnosis of NEHI |
| As indicated: Periodic Schiff | Glycogen-positive cells: PIG |
| If infection suspected | Ziehl-Neelsen, Grocott, others |
| As indicated: immunohistochemistry | Langerhans cells (S-100, CD1a) |

NEHI, neuroendocrine cell hyperplasia of infancy.

and related questions. All scenarios related to children with proven or highly suspected ILD. The survey was in English. Survey 1 consisted of 8 scenario stems with 75 responses required, survey 2 of 9 lead statements with 11 individual responses required. Clinicians were asked to score according to agreement: 1 Strongly Agree; 2 Agree; 3 Neutral; 4 Disagree; 5 Strongly Disagree; 6 Don't know.

Survey 1 was approached by 173 clinicians. Twenty-nine responders who provided fewer than 50% of responses were removed from the analysis. Data is presented from 144 clinician responders: Australia 14, Canada 3, France 5, Germany 15, Italy 1, USA 61, UK 37 and other 8. There were 127 respondents to the second round of Delphi. Twelve provided insufficient data responses (fewer than 50% responses) and so were removed from the complete analysis. The 115 consultant/attending pulmonologist respondents contributing to the second round of Delphi were from the UK (36), USA (30), Germany (22), Australia (9), France (6), Italy (5), Canada (2) and other countries (5).

Delphi 1 consisted of four scenarios related to the care of a patient who was very sick and ventilated or close to ventilation for whom no specific treatment was known. Delphi 2 provided statements derived from the consensus of opinion from the first Delphi round and asked how clinicians viewed the statement. Options, provided for varying doses and medicines, are summarised as (a) usual practice or (b) could happily use it if it is the consensus of the Delphi, or (c) not usual practice and would not wish to use it even if it is the consensus of the Delphi.

In all scenarios, we were clear that the suggested doses should be considered starting doses and could be changed at the discretion of the treating clinician at any time. The final consensus for treatment reached is summarised in table 4, and the consensus for a significant response in table 5.

Table 2 Handling of lung biopsy specimens

| Type of processing | Tissue material used | Processing procedure | Purpose |
|--------------------|---|---|--|
| 1 | Majority of the sample (about 80%) | 4% Formalin | For wax blocks and staining studies and storage |
| 2 | Several 1–2 mm cuboidal pieces | Glutaraldehyde-buffer | Electron microscopy, esp Sp mutations |
| 3 | 10 to 20% of tissue | Snap frozen in liquid nitrogen, place in –80 freezer RNA ^{later} solution | Genetic, biochemical studies, conserve RNA and proteins Same as snap frozen, except enzyme activity studies; however, more convenient as can be shipped at room temperature |
| 4 | Fresh tissue (can be the remnant on the proximal side of the staple line) | None | Microbiology |

Clearly all necessary clinical samples need to be taken before any is allocated for research.

Table 4 Doses of medication to be used and anticipated time to assess if there has been a clinical response

| | chILD ventilated or close to ventilation | chILD not ventilated or close to ventilation |
|---------------------------|---|---|
| Methylprednisolone | | |
| Dose | Intravenous 10 mg/kg or 500 mg/m ² | Intravenous 10 mg/kg or 500 mg/m ² |
| Response rate | 7 days | 28 days |
| Comment | 30 mg/kg used by some centres | As alternative to oral prednisolone. Use before other therapies and judge response |
| Prednisolone | | |
| Dose | Oral 1 mg/kg, used in between pulses of methylprednisolone | Oral 2 mg/kg, as alternative to methylprednisolone pulses. Use before other therapies and judge response |
| Response rate | 7 days | 28 days |
| Hydroxychloroquine | | |
| Dose | 10 mg/kg | 10 mg/kg |
| Response rate | 21–28 days | 3 months |
| Comment | In children <6 years 6.5 mg/kg in some centres to reduce toxicity | In children <6 years 6.5 mg/kg in some centres to reduce toxicity. No preference over azithromycin as second line. 54% would consider Hydroxychloroquine as sole therapy in mild stable chILD |
| Azithromycin | | |
| Dose | 10 mg/kg 3 days per week | 10 mg/kg 3 days per week |
| Response rate | 3 months | 3 months. |
| Comment | | No preference over hydroxychloroquine as second line. 51% would consider azithromycin as sole therapy in mild stable chILD |

Results are simple majority assessed by median?/mean?.

chILD, childhood interstitial lung disease; IV, intravenous; PIG, pulmonary interstitial glycogenosis.

OTHER POTENTIAL THERAPIES

There is even less evidence for other regimes and no recommendations are made. If there is evidence of systemic disease, and if cytotoxic or biological therapies are contemplated, it would usually be wise to involve a paediatric rheumatologist.

MONITORING CHILD

The variety of ChILD diagnoses makes a single common monitoring plan of little value. chILD-EU has looked to enable reference across diagnoses by the development of an observational trial protocol focused on the first year of diagnosis. Monitoring is at months 1, 2, 3, 6 and 12 and annually thereafter. Key observations are clinical (respiratory rate, heart rate, weight, oxygen saturation in air awake, oxygen saturation including overnight while asleep and on exercise, evidence of pulmonary hypertension) and radiological monitoring (chest X-ray at diagnosis, 6 and 12 months; CT not recommended, however, if considered justifiable, a limited cut thin-section HRCT of areas of interest should provide sufficient information). In older children spirometry at each observational monitoring visit should be recorded, with DLCO (pulmonary haemorrhage monitoring)

and body plethysmography recommended as indicated but at least once per year.

PULMONARY EXACERBATIONS

Acute pulmonary events associated with instability are a characteristic of many chronic diseases. Although recognised, they are often difficult to define. No definition exists for a pulmonary exacerbation in chILD and so we have sought, through the Delphi process and a review of the evidence, to define what is a clinically significant change in chILD as a first step towards a definition of a pulmonary exacerbation (table 5). The period of stability before and between exacerbations must be defined; for ChILD this is arbitrarily considered to be at least 7 days of stability at baseline values. More work is ongoing to define the definition of a pulmonary exacerbation and its relationship with other respiratory events such as upper respiratory tract infection and aspiration.

SUMMARY AND CONCLUSIONS

We have proposed a sequence of investigations for chILD, and provided SOPs for performance of these tests. We aim to harmonise investigation of chILD to facilitate future research; this manuscript is the framework on which this will be based.

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Table 5 Improvement in physiological outcomes considered to be a treatment response

| | Possible response (%) | Response (%) | Best response |
|---|-----------------------|--------------|---------------|
| Heart Rate | 10 | 20 | – |
| Respiratory Rate | 5 | 10 | 20% |
| SpO ₂ | 5 | 10 | – |
| Loss of need for supplemental oxygen | – | – | Yes |
| Loss of need for mechanical ventilation | – | – | Yes |

Conversely, a deterioration of this size would be considered a significant decline. SpO₂, arterial oxygen saturation.

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Contributors AB drafted the manuscript, all authors reviewed it and agreed on the contents. SC led the Delphi consensus, and wrote the online supplement. All authors reviewed it and agreed with the contents.

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**EUROPEAN PROTOCOLS FOR THE DIAGNOSIS AND INITIAL TREATMENT
OF INTERSTITIAL LUNG DISEASE IN CHILDREN: ON-LINE SUPPLEMENT**

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Delphi Consensus of Approaches to the Management of Children with Interstitial Lung Disease

We conducted a two round Survey Monkey questionnaire Delphi consensus of paediatric pulmonologists in Europe, North America and Australasia. The aim was to gauge current practice and treatment expectation. Clinicians were identified from national paediatric respiratory society groups. The survey referred to children with proven or highly suspected interstitial lung disease.

Survey 1

Survey 1: 8 scenario stems, total 75 responses on 1-5 scale (from strongly agree to strongly disagree). Data is presented for 144 responses (29 removed as fewer than 50% answers provided): Australia 14, Canada 3, France 5, Germany 15, Italy 1, USA 61, UK 37, Other 8.

(a) Scenario patient very sick and ventilated or close to ventilation with no known specific treatment.

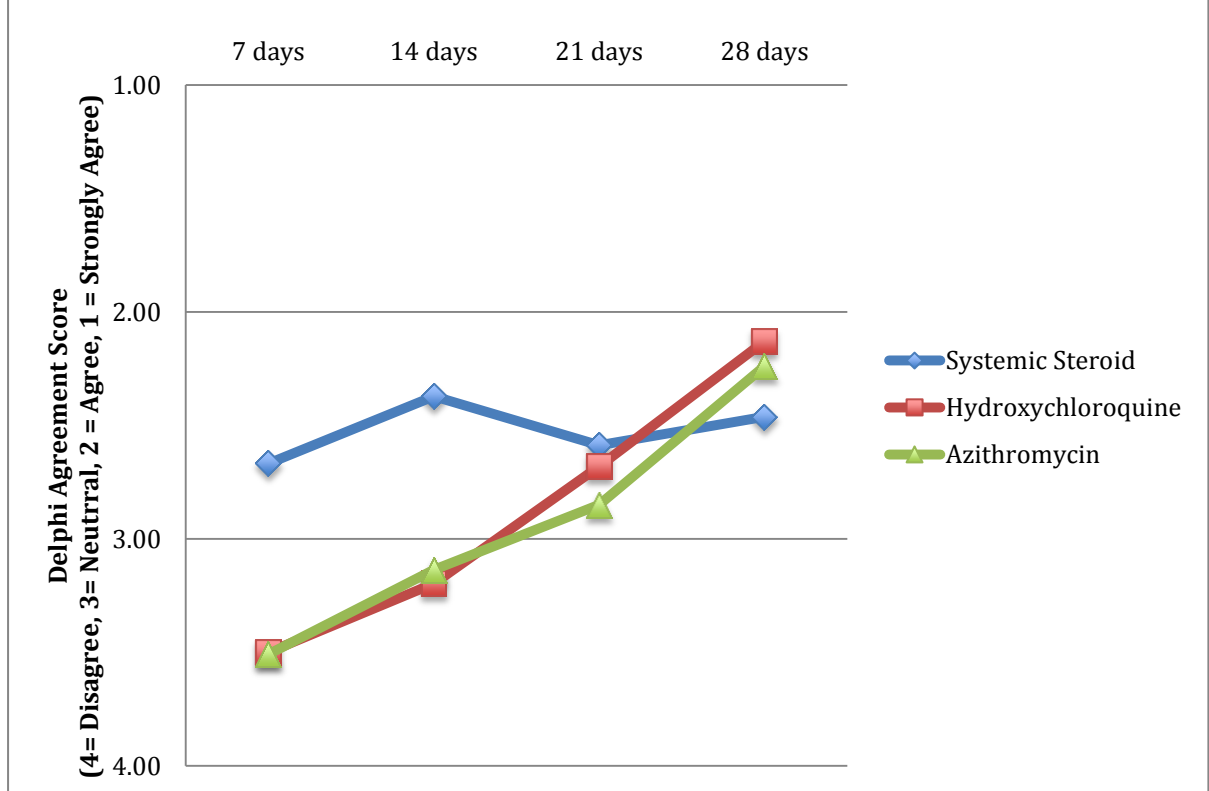
Q1. Initial approach to treatment: Most popular systemic steroids alone (median 2, mode 1). Three other options median response 3 (Systemic Steroids with hydroxychloroquine, or azithromycin or both).

Q2. Both intravenous methylprednisolone (500mg/m² or 10mg/kg) scored median response 2 (mode 1). Oral prednisolone (2mg/kg) scored median response 3. Three further options (daily oral prednisolone 1mg/kg, three days per month oral methylprednisolone at either 500mg/m² or 10mg/kg) had median scores of 4. Some responders at larger centres expressed a preference for intravenous methylprednisolone at 30mg/kg (consistent with Rheumatology dosing).

Q3. Clinical response to treatment: Improvements in respiratory rate demonstrated progressive increase in agreement from 5% (neutral 3) to 10% (agree 2) to 20% (strongly agree 1). Improvements in heart rate produced more muted agreement as both 5% and 10% improvements produced neutral responses (3) and a 20% improvement agreement (2). Improvement in weight by 5% was neutral (3), but agreed as a response when 10% (2). Improvement in oxygen saturation were associated with better agreement; a 2% improvement was neutral (3), but a 5% increase caused agreement (2) and a 10% increase was strongly agreed as a sign of improvement (1). The loss of need for supplemental oxygen or mechanical ventilator support were both strongly agreed as demonstrating improvement (1).

Q4. Time to respond to treatment (Figure X). Systemic steroids were considered to work from 7 days, but hydroxychloroquine and azithromycin had 21-28 days for perceived benefit.

Figure 1 Time to respond to treatment very sick ChILD



(b) Scenario patient not ventilated or close to ventilation, needing treatment but no specific treatment known. Similar stem questions repeated.

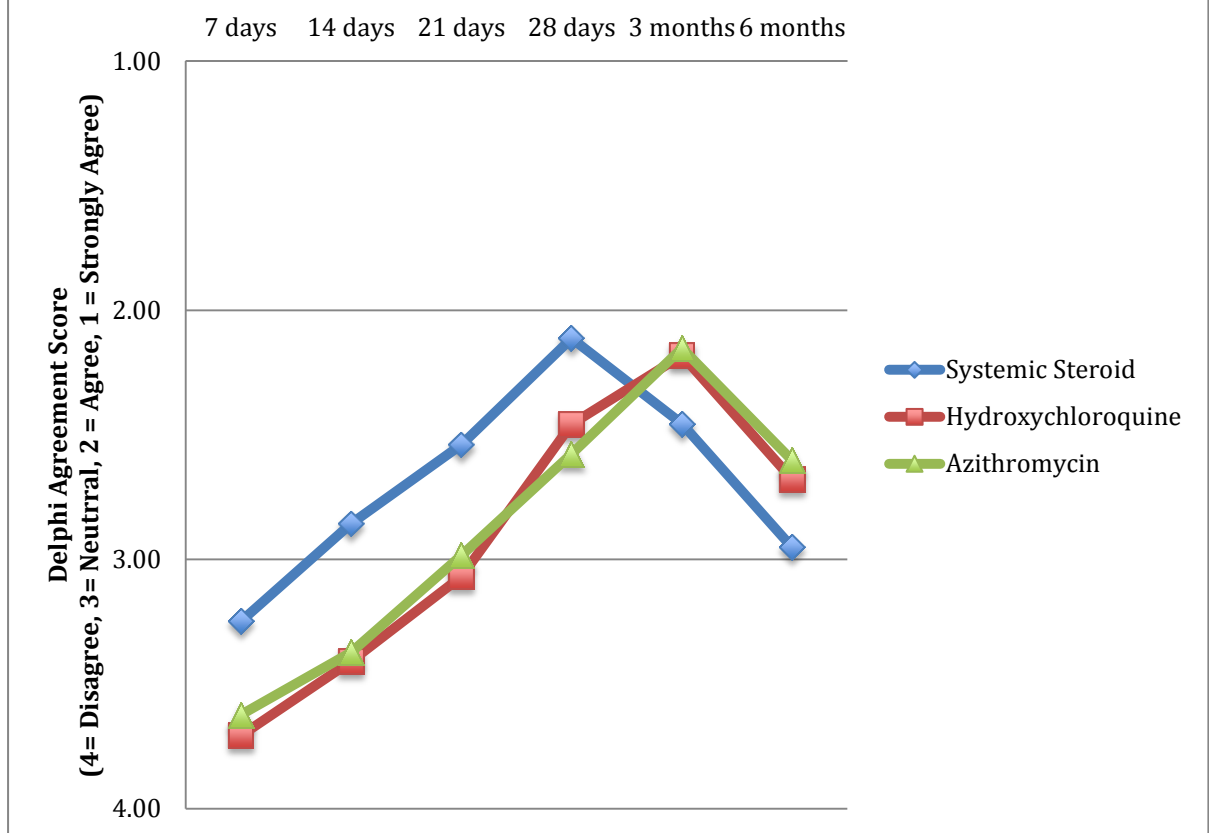
Q5. Initial approach to treatment: . As in infants who were more sick, most popular was use of Systemic Steroids alone (median 2, mode 1). Three other options median response of 3 (Systemic Steroids with hydroxychloroquine, or azithromycin or both). The responders did not significantly differentiate initial treatment response dependent on disease severity.

Q6. There was equal agreement for the use of either oral prednisolone 2mg/kg/day or intravenous methylprednisolone 10mg/kg 3 days per month (both agreement level 2). Oral prednisolone 1mg/kg and intravenous methylprednisolone 500mg/m2 both had neutral responses (3), and oral methylprednisolone at either dose disagreement (4).

Q7. Clinical response to treatment responses were identical to those provided in Q3. What clinicians consider a clinical pharmacological benefit are the same in different disease states in children with interstitial lung disease.

Q8. In less sick infants (Fig Y) clinicians considered steroids could take 28 days for maximal effect, with hydroxychloroquine or azithromycin upto 3 months.

Figure 2. Time to respond to Treatment in not very sick CHILD



Continental Differences

In Survey 1 there were roughly equivalent number of responders from North America and Europe. There were no major differences of opinion in responders from the EU and North America, with concurrence for all major findings above.

Many respondents considered that pulsed intravenous steroids have a lower side effect profile compared with daily oral steroids at a corresponding dose.

Survey 2

Survey 2: 9 lead statements requiring 11 individual responses. All results are presented descriptively. Data is presented for 114 responses (Consultant/Attending Pulmonologist) (12 removed as fewer than 50% answers provided): Australia 9, Canada 2, France 6, Germany 22, Italy 5, USA 30, UK 36, Other 5.

Survey stems provided consensus of opinion survey 1 and asked clinicians to choose as (a) Usual practice or (b) could happily use it if the consensus of the Delphi, or (c) Not usual practice and would not wish to use it even if the consensus of the Delphi. Doses were to be considered starting doses that could be varied at the discretion of the treating clinician.

Q9. In survey 1 large consensus to for both sick and less sick to judge the effect of systemic steroids before commencing additional therapies. Survey 2 confirmed this as usual practice in 76% (N=87). A remaining, 23% (N=26) agreed to approach even though not their usual practice One respondent (1%) did not wish to consider this approach.

Q10. In survey 1 large consensus for use of pulsed intravenous methylprednisolone for 3 days every 4 weeks at a dose of 10mg/kg/dose in those who were very sick. Survey 2 confirmed this as normal practice in 80% (N=91). A remaining 19% (N=22) agreed to approach even though not their usual practice One respondent (1%) did not wish to consider this approach.

Q11. In sicker patients use of oral prednisolone inbetween pulsed methylprednisolone a common comment in survey 1; In survey 2, the majority of respondents, 63% (N=72) favoured prednisolone at 1mg/kg/day, with 23% favouring prednisolone at 2mg/kg/day (N=26), and 14% (N=16) not wishing to use oral prednisolone between intravenous methylprednisolone even if it were the consensus of the Delphi.

Q12. In survey 1 in less sick ChILD there was no overall consensus between intravenous pulsed methylprednisolone or daily oral prednisolone 2mg/kg/day. Initial preference was fairly evenly split with 46% (N= 47) responders using oral prednisolone alone, 45% (N= 46) methylprednisolone alone and 9% (N= 9) combining both. When asked to consider the alternative strategy respondents were fairly flexible; 31 of the 54 (54%) respondents who had not chosen oral prednisolone would be happy to use it if that were the consensus, but 18 others would not consider using oral prednisolone even if it were the consensus. Of those whose first preference was not for methylprednisolone alone, 43 of the 56 (55%) respondents would be happy to use it were that the consensus of the Delphi; 8 others would not consider this approach even if it were the consensus. Finally those who did not identify combination of pulsed methylprednisolone and intervening oral prednisolone as their first preference, 42 of the 93 (45%) would consider using a combination of therapies were there consensus, whilst 34 would not wish to consider a combination even if that were the consensus.

Q13. In survey 1 a consensus was for hydroxychloroquine to be used in the treatment of ChILD. In survey 2, 89%, (N=100) of respondents used hydroxychloroquine at 10mg/kg and would be happy to continue to do so. 4% (N=4) used a different dose but could adapt if there were consensus, and 7% (N=8) did not use hydroxychloroquine and would not wish to do so.

Q14. Similarly for Azithromycin, in survey 2, a dose of 10mg/kg 3 days per week was favoured by 79% (N=89) of respondents, with a daily dose of 10mg/kg preferred by 12% (N=13). One (1%) respondent had a fixed alternative and 8% (N=9) respondents did not use azithromycin and would not wish to do so.

Q15. In survey 1 there was no consensus on the order of medication to follow initiation of systemic steroids. Respondents were fairly divided with the options provided in survey 2 with 38% (N=43) starting azithromycin first, 44% (N=49) commencing hydroxychloroquine first and 13% (N=15) commencing both at the same time. 4% (N=5) would not commence these medicines.

Q 16. In survey 1 there was no consensus as to whether Hydroxychloroquine could be used in the absence of systemic steroids. In survey 2 respondents were split between the 54% (N=61) who could use hydroxychloroquine alone (at 10mg/kg) and the 46% (N=51) who would not wish to do so even if consensus. There were no responses for option b.

Q17. Similarly for Azithromycin used as sole treatment for ChILD in the absence of systemic steroids the responses again were evenly divided by those who could consider Azithromycin as sole therapy in ChILD , 51% (N=57) for 3 days per week and 4% (N=4) for 7 days per week, or at an alternative dose 1% (N=1), and the 47% (N= 50) who would not consider Azithromycin as a sole therapy in the absence of systemic steroids and would not wish to do so even if consensus.

Continental Differences

In Survey 2 again there were no major differences of opinion in responders from the EU (N=73) and North America (N=32), with concurrence for all major findings above.