



AUDIT, RESEARCH AND GUIDELINE UPDATE

Research in progress: put the orphanage out of business

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on behalf of the ch-ILD collaborators

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ABSTRACT

Paediatric interstitial lung disease (ILD) is rare and diverse, meaning no single centre will see sufficient children to perform the studies needed to make progress. This EU FP-7 grant will standardise the evaluation of these rare conditions by establishing pan-European multidisciplinary expert panels and establish consensus on treatment protocols and standard operating procedures across Europe. We will work with patient groups to determine optimal treatment end-points and biomarkers. A biobank will be established as a Europe-wide resource for mechanistic studies. Ultimately we aim to do the first randomised controlled trial of a pharmacological treatment in paediatric ILD.

CHILD: THE WAY WE ARE

Interstitial lung disease (ILD) is a knowledge vacuum at any age (witness the recent PANTHER fiasco¹), but for a number of reasons, it is particularly challenging in children. Paediatric ILD is rare, estimated prevalence is 0.36/100 000 as against 60–80/100 000 in adults; the spectrum of conditions, particularly in infancy is much broader, with more than 200 conditions entering into the differential diagnosis; and the diseases occur in the context of the growing and developing lung, and the immature immune system, which significantly modifies pathology. There are no randomised controlled trials of treatment in childhood ILD (chILD), and no prospect of any single centre remedying this.

This work is the culmination of a number of initiatives over many years, summarised in the online supplement. The currently accepted classification of chILD in the 0–2 year age group came from the USA chILD Network.² Eleven USA centres provided data over the period 1999–2004, and 189 biopsies were reviewed. The eight categories which they described are shown in the table 1. Understanding of genetic causes of disorders of surfactant protein metabolism has moved forward, for example, mutations in the surfactant protein genes *Sp-B* and *Sp-C*, the gene encoding the surfactant processing protein ABCA3, and more recently thyroid-transcription-factor 1. Undoubtedly many more specific entities remain to be discovered. Excellent though this classification is, there are more questions than answers. Several conditions, such as pulmonary interstitial glycogenosis and neuroendocrine cell hyperplasia of infancy,

apparently specific for children, perfectly illustrate the problems of chILD; manuscripts are based on small numbers, no one knows optimal treatment, and the pathophysiology is unknown; specifically, the cells are distinguishing these entities of pathophysiological significance, or merely markers; so for example, pulmonary interstitial glycogenosis and neuroendocrine cell hyperplasia of infancy cells are seen in the normally developing lung antenatally.

The classification in older children is even more problematic, and thus the areas of ignorance even greater. The USA data are as yet only published in abstract.³ Their major categories were immune-mediated 34%, infection and postinfective 16%, and ‘Infant’ type disorders 8%. Royal Brompton, again only presented as an abstract, showed the chILD classification could be used in older children as well as those aged two and below, with ‘Infant’ type disorders, lymphoproliferative disorders, and non-specific bronchiolitis well represented.⁴ There are also combined age group data from the European Respiratory Society (ERS) Task Force.⁵ However, in all ages from all this work to date, we know that all these conditions are rare, that no centre will ever see enough to make progress, and that furthermore standardised data collection and multidisciplinary review are essential, because no one person will see enough cases spanning the whole range of the conditions.

CHILD: WHERE WE ARE GOING

Happily, the proposal ‘Orphans Unite: chILD better together—European Management Platform for Childhood ILDs’ (<http://www.childeu.net>, website under construction) under the FP7 programme has been approved. The study will run for 42 months from December 2012, and is led by Professor Matthias Griese from Munich. It is predicated on the assumption that understanding the mechanisms of disease and planning of treatment and follow-up of these rare conditions, based on identification of well phenotyped groups of patients will only be possible if individual European countries unite to join other international efforts. The components of the work-packages are to standardise diagnosis and our current management; to try to understand basic mechanisms; and to work with professionals and patient groups to disseminate knowledge and increase the profile of chILD.

Table 1 US classification of children's interstitial lung disease (ILD)

Category	Illustrative diseases
Diffuse developmental disorders (n=11)	Acinar dysplasia (n=1), congenital alveolar-capillary dysplasia (n=2) and alveolar-capillary dysplasia with misalignment of the pulmonary veins (n=8)
Growth abnormalities reflecting deficient alveolarisation (n=46)	Pulmonary hypoplasia (n=7); chronic neonatal lung disease (bronchopulmonary dysplasia) (n=20); related to chromosomal disorders (n=15); related to congenital heart disease (n=4)
Specific conditions of undefined aetiology (n=24)	Pulmonary interstitial glycogenosis (n=18); neuroendocrine cell hyperplasia of infancy (n=6)
Surfactant dysfunction disorders (n=18)	SpB gene mutations (n=0); SpC gene mutations (n=7); ABCA3 gene mutations (n=6). TTF-1 and GM-CSF α - and β - chain receptor mutations would now be added; histology consistent with Sp disorder but none detected (n=5 in total; pulmonary alveolar proteinosis (n=2), chronic pneumonitis of infancy (n=1), DIP (n=1), and NSIP (n=1))
Disorders of the normal host, presumed immune intact (n=23)	Infectious and post-infectious (n=17); Environmental agents (n=2 in total; hypersensitivity pneumonitis (n=2)); aspiration syndromes (n=3); eosinophilic pneumonia (n=1)
Disorders resulting from systemic disease processes (n=6)	Collagen vascular disease (n=4); storage disease (n=1); sarcoidosis (n=0); Langerhans cell histiocytosis (n=0); malignant infiltrates (n=1)
Disorders of the immunocompromised host (n=28)	Opportunistic infections (n=20); iatrogenic (n=3); related to transplant and rejection (n=0); diffuse alveolar damage, unknown aetiology (n=5)
Disorders masquerading as ILD (n=9)	Arterial hypertensive vasculopathy (n=8); venous engorgement secondary to heart disease (n=1); veno-occlusive disease (n=0); lymphatic disorders (n=0)

ABCA3, ATP-binding cassette subfamily A member 3; DIP, desquamative interstitial pneumonia; GM-CSF, granulocyte macrophage colony stimulating factor; NSIP, non-specific interstitial pneumonia; Sp, surfactant protein; TTF, thyroid transcription factor.

A collaboration is only as good as the patients enrolled, and uniformity of diagnosis and management is one major goal. The programme will work closely with the USA Foundation, who have a management state of the art manuscript on the cusp of acceptance, to ensure the widest possible international collaborations. We will collect clinical information, imaging, histopathological and genetic data in a standardised way, and the intention is to have each case reviewed by international panels in those four areas to ensure standardisation of diagnosis. Access to panels of international experts leading to an expert consensus diagnosis and standardised recommendations for treatment will, it is hoped, add value for the referring clinicians and the patients. So standard operating procedures will need to be developed particularly for CT scans (to minimise radiation dosage and ensure comparability of scans), bronchoscopy and handling of biopsies, drawing on existing protocols when they are available. Where available, infant lung function will be performed, using existing American Thoracic Society-ERS guidelines, but this is not a requirement for submitting cases. One weakness of the seminal USA classification paper,² acknowledged by the authors themselves, was the lack of standardisation of imaging so no useful correlations with pathology were possible. This will be remedied on both sides of the Atlantic.

We will establish a pan-European electronic database and biobank, the latter of which will collect serum, plasma, bronchoalveolar lavage fluid, and lung biopsy and any explanted lung tissue, for the much needed mechanistic studies. The database will be an extension of one already in use, and existing databases will also be integrated so previous valuable work done will not be wasted. The aim is that database and biobank will be a common resource for research groups across Europe and beyond.

Treatment and follow-up will also be standardised. Currently N of 1 treatment trials, when treatment is thought to be indicated, usually start with oral or parenteral steroids, with or without additional hydroxychloroquine and azithromycin. If these fail, councils of despair include methotrexate, azathioprine, rituximab and many, many others. Every group does its own, equally irrational and non-evidence based thing, with the result that there is no increase in knowledge. The proposal includes determining the range of current practices across Europe, and using these data to standardise these trials of

treatment. At this stage of the proposal the intention is merely to ensure that treatment trials are done the same way, rather than change the direction of treatment. Since there is no evidence, it should not be difficult to agree on separate protocols for pulsed and oral steroid therapy, based on consensus of current practice, and also agree on a hierarchy of add-on treatments.

Clearly if a treatment is given, the benefits or otherwise must be accurately assessed, particularly if the treatment is potentially hazardous. The current best-practice assessment of severity is astonishingly crude, based as it is on symptoms, hypoxaemia whether at rest or only on exercise, and the presence of pulmonary hypertension.⁶ We will prospectively collect a range of samples for the biobank, with the aim of developing suitable biomarkers for future studies, as well as gaining further mechanistic insights into disease processes. The combination of observational assessment of the responses to non-specific treatments such as steroids of well phenotyped groups of patients, and the development of better biomarkers, will lead to the final and most ambitious stage of the project, namely the first randomised controlled trial of treatment in chILD.

The other really important aspects of this project will be working with patient groups and disseminating knowledge. The current uncertainty of diagnosis and prognosis and the lack of evidence-based treatments indicate the urgent need for patient participation in research. Patient reported outcomes, such as quality of life, will be assessed and will contribute to the understanding of the impact of the disease and of the subjective benefits of interventions. Clinicians have to provide disease-specific education and psychosocial support to patients and caregivers to empower chILD patients and their families. The contribution of patient charities and pressure groups to pushing chILD to the top of the European agenda cannot be overstated. If ever there was an example to people that patient power matters, this is it. All across Europe, patients matter—patients vote, and politicians run scared of voters. So patient partnership is at the epicentre of the proposal. We will use conventional means of disseminating information such as conference participation and peer review manuscripts, as well as charity websites, Facebook and Twitter, and other electronic and social media that the young understand and the old gaze at, wide-eyed and open-mouthed.

The presentation of chILD is very non-specific, and undoubtedly many cases are being misdiagnosed. We aim to make Europe 'think chILD'.

WHAT WE NEED

Key to success of the programme is buy-in from paediatric pulmonologists and above all families of chILD patients from across Europe. We acknowledge, that, as with all huge grants, there is not enough money to cover costs and we will all be working from conviction rather than for money. There are huge challenges to overcome; we need to make sure we can use existing databases, centralising the information. Many countries have advanced programmes, and all involved will need to be flexible, and be prepared to compromise to achieve a uniform approach; there is no reason not to do this, since there is so little hard evidence. There are ethical and practical considerations involved in moving material, particularly for genetic studies, between institutions and across borders, and setting up biobanks, but it will be essential for these to be overcome. We need to have referrals of chILD patients from across Europe if this once in a generation chance is to succeed. For the referring clinicians, we hope

that the assessment by multidisciplinary expert panels will be a sufficient return for submitting the case. For all concerned, we hope the chance to be part of an endeavour to replace speculation and opinion with data will be an incentive to make it work. There are so many huge gaps in our knowledge in this field.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

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On-line supplement: RESEARCH IN PROGRESS: PUT THE ORPHANAGE OUT OF BUSINESS

There has been widespread interest in paediatric interstitial lung disease over many years. Important initiatives have included European [E1] and UK [E2] wide surveys which were arguably the first European attempts to address these rare lung diseases. This was the stimulus for a European Respiratory Society taskforce, published in 2004 [E2]. Other important initiatives have been the British Paediatric Orphan Lung Disease Registry [E3], and the French [E4] and German registries [E5]. During this odyssey, there has been increasing emphasis on central evaluation of these rare conditions, drawing on wider expertise than could be expected in a single centre.

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