One-year outcomes in a multicentre cohort study of incident rare diffuse parenchymal lung disease in children (ChILD)

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ABSTRACT
We performed a prospective, observational, cohort study of children newly diagnosed with children’s interstitial lung disease (ChILD), with structured follow-up at 4, 8, 12 weeks and 6 and 12 months. 127 children, median age 0.9 (IQR 0.3–7.9) years had dyspnoea (68%, 69/102), tachypnoea (75%, 77/103) and low oxygen saturation (SpO2) median 92% (IQR 88–96). Death (n=20, 16%) was the most common in those <6 months of age with SpO2<94% and developmental/surfactant disorders. We report for the first time that ChILD survivors improved multiple clinical parameters within 8–12 weeks of diagnosis. These data can inform family discussions and support clinical trial measurements.

INTRODUCTION
Interstitial lung disease in children (ChILD) encompasses more than 200 entities,2 many so rare that there is no reported prospective longitudinal disease phenotyping.6 Recent improvements in adult interstitial lung disease phenotyping has led to better disease management. We aimed to use the first international study for ChILD to systematically study new diagnoses for 12 months, to better understand disease progression and support the development of clinical outcomes.

METHODS
This was an observational cohort study of children (<18 years) presenting to participating hospitals with a new clinical presentation of longitudinal disease phenotyping.7 Recent outcomes that is, baseline oxygen levels. Missing SpO2 values were imputed (see online supplementary methods). Height, weight and body mass index were converted to Centre for Disease Control z-scores and percentiles.8 FEV1 and FVC were converted into Global Lung Initiative z-scores and percentiles.9 The trial is registered on clinical trials (https://clinicaltrials.gov/ct2/show/NCT02852928).

RESULTS
Participants were from nine European countries, predominantly Germany, UK and Poland (online supplementary table 1). The proportion of participants providing follow-up data (or death) at each time point ranged from 76%–83% (online supplementary table 2). Median age at baseline was 0.9 (IQR 0.3–7.9) years (online supplementary table 1). Peer review diagnosis, investigations and treatments were provided in supplementary information (online supplementary tables 3–5). At baseline, dyspnoea (68%, 69/102) and tachypnoea (75%, 77/103) were frequent, with failure to thrive in 49% (61/125) and developmental/surfactant related disorders in 68%, 69/102 and tachypnoea (75%, 77/103) were frequent, with failure to thrive in 49% (61/125) and developmental/surfactant related disorders (online supplementary table 3, figure 1).
There were 20 deaths (16%) over 12 months. Age at death, time from enrolment to death and diagnostic group are provided in online supplementary table 3. Most deaths occurred in diffuse developmental disorders (n=6), alveolar surfactant disorders (n=6) and lung growth abnormalities (n=3). Age at baseline was significantly associated with survival, with deaths in 33% (15/45) of those <6 months of age compared with 7% (5/74) in those ≥6 months of age (log-rank statistic, p=0.0001) (figure 1A). SpO₂ at baseline ≥94% was associated with better survival (4% died: 2/52), compared with 29% (18/63) of those with SpO₂<94% (p=0.0006) (figure 1B).

Over 12 months, ventilatory support was used in 49 (39%) children, decreasing steeply over time with improvement or death (table 1). Of the 31 children ventilated at baseline, 15 died (11 invasive, 4 non-invasive ventilation). Supplemental oxygen was provided to 72% (92/127) at any point from baseline to 12 months. The percentage of children in follow-up recorded as receiving oxygen supplementation declined most markedly from baseline (63%, 74/117) to 12 week observations (31%, 23/74). For 33 children (26%), SpO₂ in air was never ≥94%, mostly in those who subsequently died or were aged <6 months of age at baseline (table 1). Most improvement in SpO₂ in air was observed in the first 8 weeks following enrolment (online supplementary figures 1A,B and 3).

There was a progressive reduction over time in Fan scores (figure 2 and online supplementary figure 1C), predominantly in the first 12 weeks, but continuing up to 12months (online supplementary figure 4), with deaths more frequent at higher baseline scores (5 (36%, 8/22) and 4 (23%, 9/40)).

Weight for age at baseline was low and remained so at 12 months (online supplementary table 7). Most improvements in weight and height occurred in the first 4 weeks, with slower gains thereafter. Lower weight and height z-score at baseline was significantly associated with lower baseline SpO₂ and death (online supplementary figure 5).

Median respiratory rate tended to be higher than age related reference values at baseline but similar to age-adjusted reference values by 12 months. Median heart rate was similar to age related reference values across observations (online supplementary figure 6A–D).

Improvement in FEV₁ % predicted and z score continued up to 12 weeks, with little subsequent change (table 1). FVC had a more progressive change over the 12-month observation period, again most marked in the first 12 weeks (FVC % predicted median 48% to 65% and to 80% by 12 months). At baseline 19/25 (76%) spirometry demonstrated a restrictive (FEV₁/FVC≥0.8) and 6/25 (24%) an obstructive pattern (ratio<0.8).

Systemic corticosteroids were provided to 58% (73/125), hydroxychloroquine 28% (35/126) and azithromycin 36% (45/126) of cases over the observation period (online supplementary information).

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### Table 1  Deaths, clinical support and physiology by study visit

<table>
<thead>
<tr>
<th>Deaths</th>
<th>Non-invasive ventilation</th>
<th>Invasive ventilation</th>
<th>Supplemental oxygen</th>
<th>SpO₂≥94% in air</th>
<th>Spirometry</th>
<th>FVC (% predicted)</th>
<th>FEV₁ (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Prior to baseline</td>
<td>0</td>
<td>41/126</td>
<td>33</td>
<td>N</td>
<td>34</td>
<td>N</td>
<td>93/125</td>
</tr>
<tr>
<td>At baseline</td>
<td>0</td>
<td>18/114</td>
<td>16</td>
<td>6/80</td>
<td>8</td>
<td>6/80</td>
<td>8</td>
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<td>4 weeks</td>
<td>10</td>
<td>6/80</td>
<td>8</td>
<td>6/80</td>
<td>8</td>
<td>37/80</td>
<td>46</td>
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<tr>
<td>8 weeks</td>
<td>15</td>
<td>6/80</td>
<td>8</td>
<td>3/75</td>
<td>4</td>
<td>29/75</td>
<td>39</td>
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<tr>
<td>12 weeks</td>
<td>16</td>
<td>6/80</td>
<td>8</td>
<td>3/75</td>
<td>4</td>
<td>29/75</td>
<td>39</td>
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<tr>
<td>6 months</td>
<td>20</td>
<td>6/80</td>
<td>8</td>
<td>6/80</td>
<td>8</td>
<td>37/80</td>
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<tr>
<td>12 months</td>
<td>20</td>
<td>6/80</td>
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<td>6/80</td>
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<td>37/80</td>
<td>46</td>
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DISCUSSION
We report that many clinical parameters appeared to improve within 8–12 weeks of diagnosis and starting treatment in children with ChILD. To our knowledge, this is the first prospective, longitudinal, cohort assessment of ChILD. At 12 weeks, when compared with baseline, provision of oxygen supplementation was observed in 31% fewer children, and lung function was 29% greater for FVC and 24% for FEV1. Mean Fan scores were 29% lower at 12 weeks. Differences in respiratory rate (and heart rate) across timepoints when related to normative data were not observed to have notable differences. We did not, however, provide a formal longitudinal analysis and this together with missing data may have impacted the results. We also acknowledge potential bias may have occurred from the effect of funding limitations on recruitment in some EU countries and translation of study materials. In summary, we have identified key parameters responsive to change in ChILD which could be used in trials of treatment and inform prognostic discussions with families. Furthermore, we suggest that patients with ChILD should be seen more frequently in the first 3 months following diagnosis, so treatment can be adjusted with any clinical improvement.

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REFERENCES