OPEN ACCESS

Original research

Acute exacerbations in children's interstitial lung disease

Elias Seidl ,[1] Nicolaus Schwerk ,[2] Julia Carlens ,[2] Martin Wetzke ,[2] Nagehan Emiralioğlu ,[3] Nural Kiper ,[3] Joanna Lange ,[4] Katarzyna Krenke ,[4] Zsolt Szepfalusi ,[5] Florian Stehling ,[6] Winfried Baden,[7] Susanne Hämmerling,[8] Silvija-Pera Jerkic ,[9] Marijke Proesmans ,[10] Nicola Ullmann ,[11] Frederik Buchvald ,[12] Katrin Knoflach,[1] Matthias Kappler ,[1] the chILD EU collaborators, Matthias Griese [1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2021-217941).

For numbered affiliations see end of article.

Correspondence to
Dr Matthias Griese;
matthias.griese@med.uni-muenchen.de

Received 12 July 2021
Accepted 22 December 2021
Published Online First
11 February 2022

ABSTRACT

Introduction Acute exacerbations (AEs) increase morbidity and mortality of patients with chronic pulmonary diseases. Little is known about the characteristics and impact of AEs on children's interstitial lung disease (chILD).

Methods The Kids Lung Register collected data on AEs, the clinical course and quality of life (patient-reported outcomes - PRO) of rare paediatric lung diseases. Characteristics of AEs were obtained.

Results Data of 2822 AEs and 2887 register visits of 719 patients with chILD were recorded. AEs were characterised by increased levels of dyspnoea (74.1%), increased respiratory rate (58.6%) and increased oxygen demand (57.4%). Mostly, infections (94.4%) were suspected causing an AE. AEs between two register visits revealed a decline in predicted FEV1 (median −1.6%, IQR −8.0 to 3.9; p=0.001), predicted FVC (median −1.8%, IQR −7.5 to 3.9; p=0.004), chILD-specific questionnaire (median −1.3%, IQR −3.6 to 4.5; p=0.034) and the physical health summary score (median −3.1%, IQR −15.6 to 4.3; p=0.005) compared with no AEs in between visits. During the median observational period of 2.5 years (IQR 1.2–4.6), 81 patients died. For 49 of these patients (60.5%), mortality was associated with an AE.

Conclusion This is the first comprehensive study analysing the characteristics and impact on the clinical course of AEs in chILD. AEs have a significant and deleterious effect on the clinical course and health-related quality of life in chILD.

Key messages

What is the key question?

⇒ In children's interstitial lung disease (chILD), what are the characteristics of acute exacerbations (AEs)?

What is the bottom line?

⇒ AEs are suspected to be mostly triggered by respiratory infections and have a significant effect on the clinical course and health-related quality of life (HrQoL) in chILD.

Why read on?

⇒ This study offers insight into the characteristics and impact on the clinical course as well as HrQoL of AEs in chILD.

INTRODUCTION

Children's interstitial lung diseases (chILDs), also labelled as diffuse parenchymal lung diseases (DPLDs), cover many rare conditions that mainly affect the lung parenchyma, leading to impaired alveolar gas exchange. Common clinical features include tachypnoea, retractions, crackles, hypoxaemia and failure to thrive.[1] The diagnosis of chILD is based on clinical, radiological, histopathological and genetical findings.[2] The current categorisation system distinguishes between the two groups 'A—DPLD disorders manifesting primary in infancy' and 'B—DPLD disorders occurring at all ages'. These are further subdivided into distinct categories and subcategories.[1 3]

Acute exacerbations (AEs) are critical events of chronic conditions and suspected to be associated with increased morbidity and mortality. As shown in diseases like asthma, cystic fibrosis (CF), non-CF bronchiectasis and primary ciliary dyskinesia, AEs have strong negative effects on disease progression and loss of pulmonary function.[4–8] In CF, AEs link to increased mortality, higher healthcare costs and reduced quality of life.[9–12]

In adult patients with idiopathic pulmonary fibrosis (IPF), AEs are associated with significant morbidity and mortality.[13–17] As important triggers mostly respiratory tract infections have been identified.[18–20] The hypothesis of an underlying infection in adult IPF is supported by the fact that AEs occur more often during the cold season.[21] There is a lack of evidence-based data on effective therapies for AEs in adult IPF, and recommendations are based on anecdotal reports.[22] Often AEs are treated with antibiotics and glucocorticosteroids.[23 24]

For chILD, besides one study describing the characteristics of AEs in two patients diagnosed with neuroendocrine cell hyperplasia of infancy,[25] there are no studies published systematically assessing the characteristics of AEs. The management of AEs is mostly derived from other diseases.[26] The purpose

Linked

► http://dx.doi.org/10.1136/thoraxjnl-2021-217751
► http://dx.doi.org/10.1136/thoraxjnl-2022-218727

Check for updates

To cite: Seidl E, Schwerk N, Carlens J, *et al*. *Thorax* 2022;**77**:799–804.

of this study was to expand the current understanding of AEs in chILD and help to define outcome parameters for clinical investigations and research studies.

METHODS

Study design and population

The Kids Lung Register is a web-based management platform that collects data of rare paediatric lung disorders with a focus on chILDs (www.childeu.net).[27] The diagnosis of chILD was confirmed or disproved in accordance with the clinical guidelines of the American Thoracic Society[1] and European management platform for interstitial lung diseases in children[3] by a multidisciplinary peer review board, consisting of radiologists, pathologists and clinicians with expertise in chILD.[27] The clinical course of all patients included was prospectively and longitudinally followed. During the first year, after inclusion into the register, visits were scheduled every 6 months, then annually.

Assessment and characteristics of AE

AEs were defined as major unpredictable deleterious episodes of the pulmonary condition. This definition was the result of a Delphi process during the European Register and Biobank on Children's Interstitial Lung Diseases (chILD-EU) project.[26] At least two criteria of the 'seven criteria' were necessary to diagnose an AE. The seven criteria were (1) increased respiratory rate, (2) increase or development of dyspnoea, (3) newly developing or increased abnormalities on chest imaging, (4) onset/increase of oxygen demand to attain the individual baseline saturation, (5) need for an additional level of ventilatory support, (6) decrease in pulmonary function in children able to perform the tests and (7) reduced exercise tolerance. Patients experiencing an AE were asked to contact their physicians at that time for confirmation. If needed, treatment was initiated by the treating physician. The characteristics of the AE were recorded for each of these events in a standardised form (online supplemental figure 1). At the next clinical visit, the duration of the AEs was determined and noted. These information were entered into the database at the next scheduled register visit. In addition to the seven criteria, the following information was collected: hospitalisation, new feeding problems, new failure to thrive/weight loss and change in treatment prior to AE. At least one suspected cause was asked to be listed: infection, prior change of treatment, exposure to environmental irritant, extrapulmonary process, changes of treatment prior to worsening, poor treatment adherence, side effects of current medication and psychological factors.

Data on the clinical course

At every register visit, the severity of illness was assessed and categorised using the adapted Fan severity score: (1) asymptomatic; (2) symptomatic, normal room air oxygen saturation under all conditions; (3) symptomatic, normal resting room air saturation, but abnormal saturation (<90%) with sleep or exercise; (4) symptomatic, abnormal resting room air saturation (<90%); and (5) symptomatic with pulmonary hypertension.[28 29] Furthermore, patients older than 5 years were supposed to perform pulmonary function tests (PFTs). Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were recorded as absolute values and as percent predicted using values tabulated by Quanjer *et al*.[30] Also, health-related quality of life (HrQoL) was assessed. Caregivers filled validated patient-reported outcomes (PROs; chILD–quality of life for paediatric patients with interstitial lung diseases) at each register visits.[31] The following HrQoL subscales were assessed: chILD-specific questionnaire, physical health summary score, psychosocial health summary score and total score. The possible range of each score was between 0% and 100%. To assess the impact of AEs on the clinical course, the absolute changes in PFT and HrQoL between two register visits were calculated.

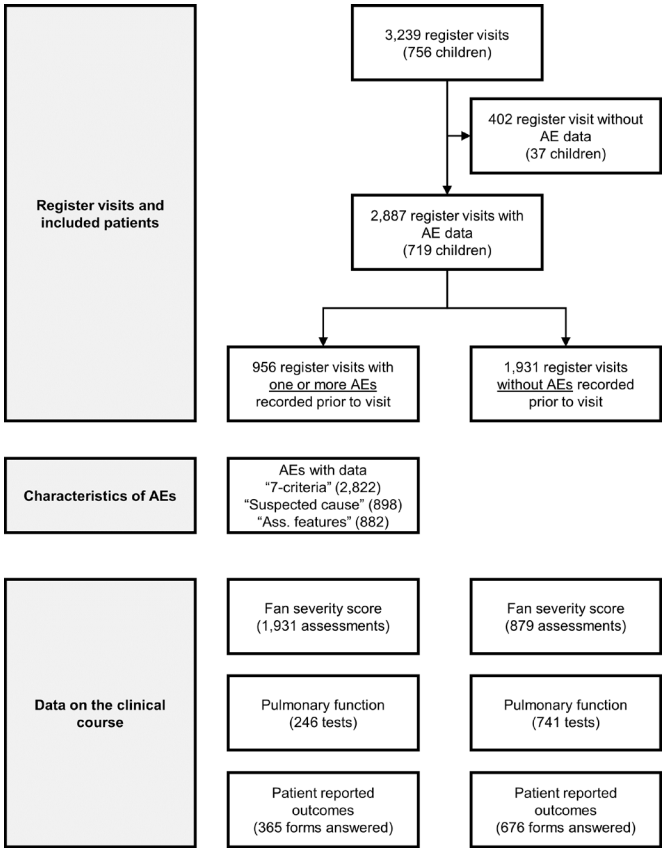

Figure 1 Flowchart of register visits, included patients, characteristics of reported AES, data on the clinical course and health-related quality of life. AE, acute exacerbation.

Statistics

The statistical evaluation of the data was done with SPSS software for statistical analyses V.26.0 and GraphPad Prism V.8.4.3. For all data median and IQR, for integers, like the Fan severity score, additionally the mean was calculated. Differences between two groups were calculated using Mann-Whitney U test for independent samples. For the comparison of more than two groups, Kruskal-Wallis test was used. Bivariate correlations were calculated using Spearman's rho correlation coefficient. It is a statistical measure of the strength of a relationship between two variables. Analysis of variance was performed if data were normally distributed and the variances among the groups were approximately equal. To identify possible confounders of the dataset, linear regression models were run. The level for statistical significance was set at 0.05.

RESULTS

Study population

When this interim analysis was conducted in early 2021, 2887 register visits from 719 children with information about AEs were entered into the Kids Lung register (figure 1). In 956 register visits, 1 or more AEs and in 1931, no AEs between two register visits were recorded. The median age at inclusion

Table 1 Characteristics of patients (N=719) included in this study

Diagnosis	
A1: DPLD—diffuse developmental disorders	27 (3.8%)
A2: DPLD—growth abnormalities deficient alveolarisation	50 (7.0%)
A3: DPLD—infant conditions of undefined aetiology	133 (18.5%)
A4: DPLD—related to alveolar surfactant region	172 (23.9%)
Ax: DPLD—unclear RDS in the mature neonate	13 (1.8%)
Ay: DPLD—unclear RDS in the almost mature neonate	14 (1.9%)
B1: DPLD—related to systemic disease processes	81 (11.3%)
B2: DPLD—in the presumed immune intact host related to exposures	96 (13.4%)
B3: DPLD—in the immunocompromised host or transplanted	40 (5.6%)
B4: DPLD—related to lung vessels' structural processes	59 (8.2%)
B5: DPLD—related to reactive lymphoid lesions	6 (.8%)
Bx: DPLD—unclear respiratory distress syndrome in the non-neonate	20 (2.8%)
By: DPLD—unclear non-neonate	8 (1.1%)
Gender	
Male	380 (52.9%)
Female	339 (47.1%)
Country the patient was treated	
Germany	386 (53.7%)
UK	90 (12.5)
Turkey	66 (9.2%)
Poland	41 (5.7%)
Italy	25 (3.5)
Other*	111 (15.4%)
Gestational age	
Mature (≥37 wga)	534 (74.3%)
Almost mature (32–36 wga)	100 (13.9%)
Immature (≤31 wga)	54 (7.5%)
Unknown	31 (4.3%)

*Switzerland, 21 (2.9%); Denmark, 16 (2.2%); Spain, 16 (2.2%); Belgium, 12 (1.7%); Austria, 9 (1.3%); Greece, 8 (1.1%); Hungary, 7 (1.0%); Portugal, 5 (0.7%); Czech Republic, 4 (0.6%); Netherlands, 4 (0.6%); South Africa, 3 (0.4%); Brazil, 2 (0.3%); Croatia, 1 (0.1%); Israel, 1 (0.1%); Luxembourg, 1 (0.1%); and Romania, 1 (0.1%).
DPLD, diffuse parenchymal lung disease.

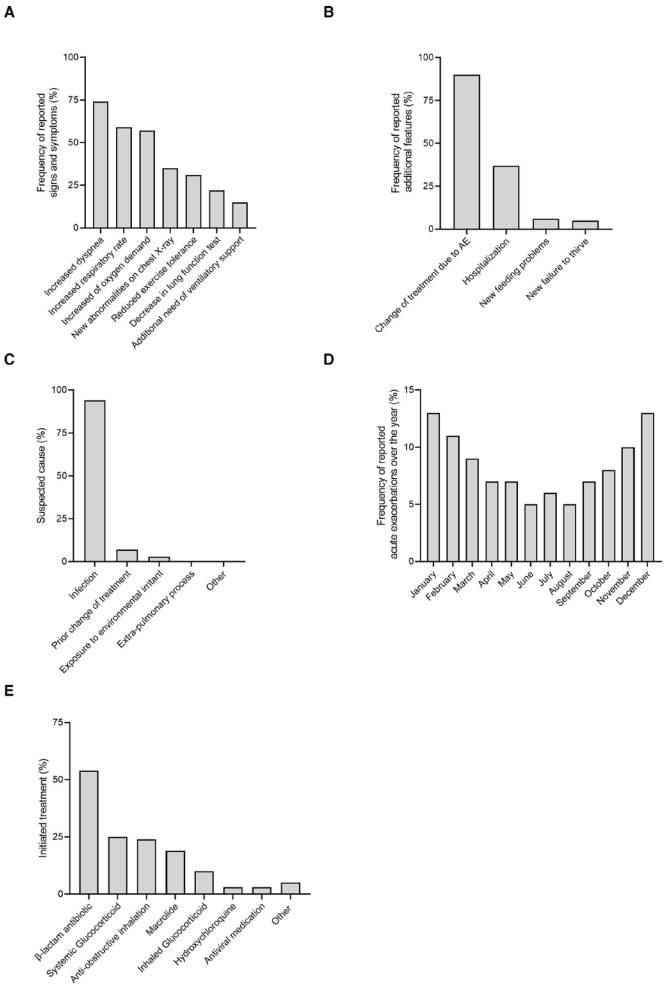

Figure 2 Characteristics of reported AEs: (A) frequency of signs and symptoms ('seven criteria') (n=2822), (B) associated features ('additional criteria') (n=882), (C) suspected cause of AEs (n=898), (D) distribution over the year (n=1252) and (E) initiated therapy (n=182). AE, acute exacerbation.

into the register was 3.2 years (IQR 0.64–9.8) and the median follow-up time was 2.5 years (IQR 1.2–4.6). The median time between AE and register visit was 11.5 weeks (IQR 7.5–22.9).

Characteristics of AEs

Characteristics of the study population are shown in table 1; characteristics of AE in online supplemental table 1. Most AEs lasted 2–3 weeks (40.3%) or longer (33.3%). In over half of the children, increased levels of dyspnoea (74.1%), increased respiratory rate (58.6%) and increased oxygen demand (57.4%) and, in almost one-third, reduced exercise tolerance (31.3%) were reported (figure 2A). Mostly, infections (94.4%) were suspected as AE cause. Only a minor proportion reported prior change of treatment (7.1%), exposure to environmental irritant (3.3%) or related extrapulmonary process (0.4%) as trigger (figure 2A–C). Most AEs were reported from September to March (figure 2D). If treatment was initiated, most patients received β-lactam antibiotics (53.8%), systemic glucocorticosteroids (25.3%), inhaled bronchodilators (24.2%) or macrolides (19.2%) (figure 2E). As multiple selection was possible, the numbers do not sum up to 100%. Over one-third of the children were admitted to the hospital (36.6%). Children admitted to the hospital were significantly younger (2.0 years, IQR 0.8–12.2) than patients with no hospital admission (10.2 years, IQR 7.8–12.6) (p<0.0001).

Data on clinical course

A total of 2810 assessments of the Fan severity score, 987 PFTs and 1041 filled PROs were included in this analysis (online supplemental table 3 and figure 3A–C). Following one or more AEs, we found a significant decline of predicted FEV_1 (median −1.6%, IQR −8.0 to 3.9; p=0.001), predicted FVC (median −1.8%, IQR −7.5 to 3.9; p=0.004), chILD-specific questionnaire (median decline −1.3%, IQR −13.6 to 4.5; p=0.034) and physical health summary score (median −3.1%, IQR −15.6 to 4.3; p=0.005) compared with no AEs in between register visits. The median change in Fan severity score showed no difference following one or more AEs between two study visits, although statistically different (median 0, IQR −1 to 0, mean .11; p<0.0001). No differences were found for psychosocial health summary score (p=0.190) and total score (p=0.074). A lower baseline PFT was associated with a greater decline following an AE (predicted FEV_1 r=0.185, p<0.0001; predicted FVC r=0.133, p<0.0001). Baseline values of clinical assessment, PFTs and PROs are listed in online supplemental table 5. The disease category, the country in which the patients were treated,

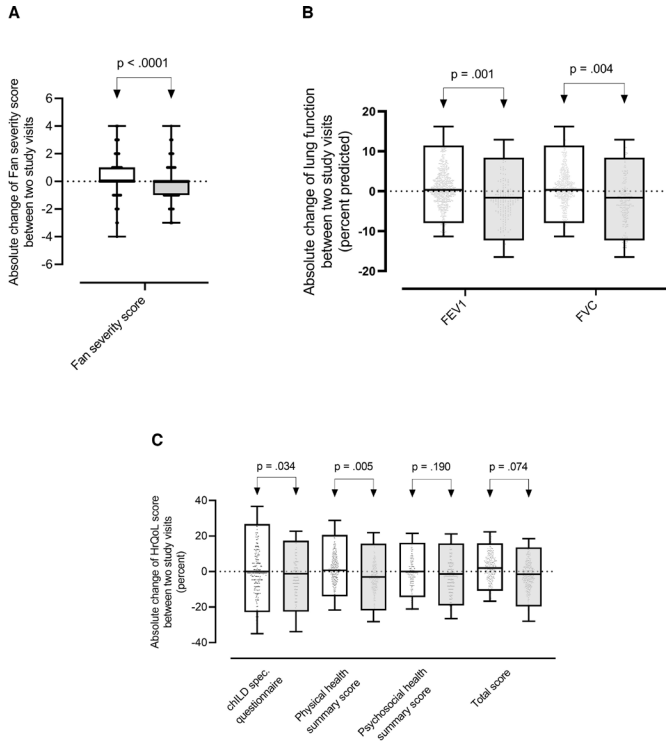

Figure 3 Absolute change in (A) Fan severity score (n=2810), (B) pulmonary function tests (n=987) and (C) patient-reported outcomes (n=1041) between two register visits without (white box) and with (grey box) acute exacerbations in between. The boxes represent 50% of patients. The end of the boxes are 25th and 75th quartile. The horizontal line within the box represents the median. The whiskers expend to the minimum and maximum. Black dots represent individual data points. chILD, children's interstitial lung disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HrQoL, health-related quality of life.

sex, gestational age or previous hospitalisation had no impact on the decline in PFT or HrQoL (online supplemental table 6).

Mortality

During the observational period, 81 patients died. Among these patients, sex was equally distributed (male 40 patients, 49.4%; female 41 patients, 50.1%). Death mostly occurred in children younger than 1 year (45 patients, 55.6%) and over 13 years (12 patients, 14.8%) (online supplemental table 2). For 49 children (60.5%), death was associated with an AE: pulmonary deterioration or infection (45 patients, 55.5%) and pulmonary hypertensive crisis (4 patients, 4.9%). A non-pulmonary cause (10 patients, 12.3%) or unknown reasons (22 patients, 27.1%) were reported less often. Over-represented were patients diagnosed with A1: DPLD—diffuse developmental disorders (11 patients, 13.6%) and A4: DPLD—related to alveolar surfactant region (29 patients, 35.8%), whereas only one patient (1.2%) diagnosed with A3: DPLD—infant conditions of undefined aetiology died. Linear regression did not show an association of decline in PFT and HrQoL between these individuals before death and the rest of the cohort.

DISCUSSION

This is the first comprehensive study analysing characteristics of AEs and the impact on the clinical course in chILD. Our results show that AEs were mostly triggered by respiratory tract infection (94.4%) causing increased levels of dyspnoea (74.1%) and an increased respiratory rate (58.6%). Other causes for AEs, like change of treatment (5.1%) or prior exposure to environmental irritants (3.3%), played only a minor role. The high hospitalisation rate (36.6%) and increased oxygen demand (57.4%) are of interest. However, the duration of a hospital admission is difficult to interpret. Differences in resource and patient management practices across different study centres might contribute more than the severity of the disease. During the observational period, 81 of the patients died. In these patients, mortality was associated with an AE in 60.4% of the cases.

Following an AE, the pulmonary function did not fully recover but revealed a decline in predicted FEV_1 and FVC, which was more pronounced in children with an impaired baseline PFT. Due to the duration of almost 3 months between AE and register visit, this decline might be not only temporary but also persistent because children who do not recover after this time may be at risk of never regaining. The failure to recover to previous levels of pulmonary function has also been reported in CF.[6 12 32 33] The exact reason has not been fully understood. It is unclear to what degree an AE and a chronic decline in pulmonary function individually contribute to pulmonary morbidity. Data on the natural clinical course of chILD are limited and need further investigation. Of note, the proportion of children performing spirometry following an AE was lower compared with children with no AE between register visits. There might be a selection bias, as it may be speculated, that children with a very severe clinical course are less able to perform an acceptable PFT manoeuvre and therefore were excluded from this analysis.

We did not observe a clinically relevant change in Fan severity score following one or more AEs between two study visits; the median change was 0 and the mean change was 0.11. The significant p value calculated was most likely driven by the large number of included data points. However, AEs had a lasting effect on the HrQoL as we found a decline of scores for chILD-specific questionnaire and physical health summary score. As a multidimensional construct assessing different components of well-being,[34] PROs can provide a more comprehensive description of the medical condition than reporting symptoms[35] and are frequently used for screening and monitoring of the subjective health status as well as outcome parameters in clinical trials.[31] Infants are mostly at risk of AEs and monitoring disease progression is particularly important. As infant PFTs are commonly not available,[36 37] PROs can provide a comprehensive description of the impact of the medical condition on the life of children.[35] Of note, for chILD, the threshold for the minimal important difference (MID) is unknown. The MID provides the smallest change in the quality of life that patients perceive as important, either beneficial or harmful.[38]

Similar to the findings in adult ILD, respiratory tract infections were identified as most prominent triggers[18–20] and occurred more often during the cold season,[21] but seasonal information was restricted to a smaller group. As data are missing, we cannot prove that these data represent the same information. However, we do not think that there is a strong evidence for a bias as the included data provide a conclusive picture that AEs are mostly triggered by infections as the number of AEs were declining during warmer and increasing during colder months.

Preventing infections might reduce morbidity and mortality in chILD. Some study centres use passive immunisations against the human respiratory syncytial virus during the cold season for patients diagnosed with chILD. Furthermore, the use of face masks was highly effective, reducing respiratory tract infections during the COVID-19 pandemic.[39] There is a need to investigate systematically what preventive measures are beneficial in these patients. In chILD, there are no standardised and prospectively evaluated treatments of AE yet and a broad variety of

interventions was initiated following an AE. Antibiotic treatment might be helpful in preventing further deteriorations related to bacterial superinfections. However, the use of glucocorticosteroids to modify disease progression is of interest and questionable in the face of the experience in adults with IPF.[40] As we do not know any long-term consequences, the benefit of different treatment regimens urgently need to be analysed in prospective controlled trials. Our data did not show a correlation between hospitalisation rate and decline in PFT or HrQoL, but children admitted were significantly younger. Infants might be admitted to hospital more liberally for surveillance because of the younger age and not merely due to the severity of the AE.

There are several limitations to consider in interpreting our findings. This is not a population-based study. Some AEs could be missed and not recorded. Furthermore, severe AEs could be overrepresented, as mild events might not be reported to the treating physicians and thus completely excluded from the analysis. Moreover, we did not systematically assess if the physicians confirmed AEs following a clinical visit, a telephone-based review or even retrospectively at the next clinical visit. Also, when interpreting the duration of AEs, one has to be careful as the physician's judgement might vary. The cause of an AE was defined by the physician treating the patient and proof of a causative agent (eg, positive swab test) was not mandatory. Other causes for dyspnoea (eg, aspirations) could have caused an AE and are difficult to diagnose. Lastly, for this exploratory analysis, many comparisons were made without adjustment for multiple testing.

In conclusion, this is the first study to define characteristics of AEs in a large cohort of patients with chILD. AEs are related to mortality or have a significant and deleterious effect on the clinical course and HrQoL in chILD. Prospective studies identifying children at risk of AEs and developing standardised treatment interventions are urgently needed to reduce mortality and morbidity and to improve the clinical course following AEs in chILD.

Author affiliations
[1]Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, German Center for Lung Research, Munich, Germany
[2]Clinic for Pediatric Pneumology, Allergology, and Neonatology, Hannover Medical School, German Center for Lung Research, Hannover, Germany
[3]Division of Pediatric Pulmonology, Hacettepe University Faculty of Medicine, Ankara, Turkey, Ankara, Turkey
[4]Department of Pediatric Pneumology and Allergy, Medical University of Warsaw, Warsaw, Poland
[5]Division of Pediatric Pulmonology, Allergy and Endocrinology, Departement of Pediatrics and Adolescent Medicine, Comprehensive Center of Pediatrics, Medical University of Vienna, Vienna, Austria
[6]Department of Pediatric Pulmonology and Sleep Medicine, University Children's Hospital Essen, Essen, Germany
[7]Department of Pediatrics 2, Children's Hospital, Eberhard Karls University, Tuebingen, Germany
[8]Division of Pediatric Pulmonology & Allergy and Cystic Fibrosis Center, Department of Pediatrics III, University of Heidelberg, Germany, Heidelberg, Germany
[9]Department of Allergy, Pneumology, and Cystic Fibrosis, Goethe University Frankfurt am Main, Frankfurt, Germany
[10]Department of Pediatrics, Pediatric Pulmonology, University Hospital of Leuven, Leuven, Flanders, Belgium
[11]Pediatric Pulmonology and Respiratory Intermediate Care Unit, Sleep and Long Term Ventilation Unit, Academic Department of Pediatrics (DPUO), Pediatric Hospital "Bambino Gesù" Research Institute, Roma, Italy
[12]Department of Paediatrics and Adolescent Medicine, Paediatric Pulmonary Service, Copenhagen University Hospital, Rigshospitalet, Danish PCD & chILD Centre, CF Centre Copenhagen, Copenhagen, Denmark

Acknowledgements This work was supported by the European Register and Biobank on Childhood Interstitial Lung Diseases (chILD-EU register) funded by the European Commission under FP7-HEALTH-2012-INNOVATION-1, HEALTH.2012.2.4.4-2: Observational trials in rare diseases. Participants contributing less than 2% of the analysed acute exacerbations are listed under the chILD-EU collaborators.

Collaborators The chILD-EU collaborators areTugba Sysmanlar (Ankara Gazi University, Turkey), Ayse Aslan (Ankara Gazi University, Turkey), Susanne Zeidler (Asklepios Sankt Augustin Krankenhaus, Germany), Veronika Baumeister (Bochum Ruhr Universität, Germany), Folke Brinkmann (Bochum Ruhr Universität, Germany), Isabelle Rochat (Centre hospitalier universitaire vaudois Lausanne, Switzerland), Sebastian Becker (Darmstädter Kinderkliniken, Germany), Meike Köhler (Dr. von Hauner Children's Hospital, University Hospital LMU Munich, Germany), Andrea Schams (Dr. von Hauner Children's Hospital, University Hospital LMU Munich, Germany), Waltraud Wesselak (Dr. von Hauner Children's Hospital, University Hospital LMU Munich, Germany), Mandeep Kaur (Dr. von Hauner Children's Hospital, University Hospital LMU Munich, Germany), Silvia Castillo Corullón (Fundación de Investigación del Hospital Clínico Universitario de Valencia, Spain), Lale Bayir (Hannover Medical School, Germany), Nagehan Ciftci (Hannover Medical School, Germany), Steve Cunningham (Centre for Inflammation Research, University of Edinburgh, UK), Lauren McCann (Imperial College London, United Kingdom), Chiara Carolina Abbas (Inselspital Bern, Switzerland), Tobias Ehrenreich (Inselspital Bern, Switzerland), Philipp Latzin (Inselspital Bern, Switzerland), Ayse Aizit Kilinc (Istanbul Cerrahpasa University, Medicine Faculty Hospital, Turkey), Tobias Hübner (Kinderklinik Oldenburg, Germany), Holger Köster (Kinderklinik Oldenburg, Germany), Martin Schebek (Klinikum Kassel, Germany), Matteo Fontana (Luzerner Kantonsspital, Switzerland), Nicolas Regamey (Luzerner Kantonsspital, Switzerland), Stanislaw Boguslawski (Medical University of Warsaw, Poland), Honorata Marczak (Medical University of Warsaw, Poland), Deborah Adelsberger (Oldenburg Zentrum für Kinder- und Jugendmedizin, Germany), Achim Freihorst (Ostalab Klinikum Aalen, Germany), Frederik Buchvald (Rigshospitalet Copenhagen, Denmark), Gemma Donohoe (Royal Children's Hospital Manchester, United Kingdom), Morag MacLean (Royal Hospital for Sick Children Edinburgh, United Kingdom), Fiona Redmond (Royal Hospital for Sick Children Edinburgh, United Kingdom), Cordula Koerner-Rettberg (Ruhr University-Bochum, Germany), Abigel Kolonics-Farkas (Semmelweis University, Hungary), Sarah Shortland (Sheffield Children's Hospital, United Kingdom), Amy Collier (Southampton General Hospital, United Kingdom), Kathrin Seidemann (Städtische Klinikum Karlsruhe, Germany), Lutz Nährlich (Universität Giessen, Germany), Peter Meißner (Universität Ulm, Germany), Susanne Hämmerling (Universitätsklinikum Heidelberg, Germany), Benjamin Hanebeck (Universitätsklinikum Heidelberg, Germany), Dominik Schöndorf (Universitätsklinikum Heidelberg, Germany), Olaf Sommerburg (Universitätsklinikum Heidelberg, Germany), Winfried Baden (Universitätsklinikum Tübingen, Germany), Sune Rubak (University Aarhus, Denmark), Steve Turner (University Aberdeen, United Kingdom), Martin Rosewich (University Frankfurt/Main, Germany), Stefan Zielen (University Frankfurt/Main, Germany), Johannes Schulze (University Frankfurt/Main, Germany), Christiane Lex (University Göttignen, Germany), Frans De Baets (University Hospital Gent, Belgium), Edyta Glowacka (University Krakau, Poland), Freerk Prenzel (University Leipzig, Germany), Nazan Cobanoglu (University of Ankara, Turkey), Gisela Anthony (University of Marburg, Germany), Hans Rock (University of Marburg, Germany), Angelo Barbato (University of Padua, Italy), Deborah Snijders (University of Padua, Italy), Andrea Heinzmann (Universtätsklinikum Freiburg, Germany), Dora Krikovszky (Semmelweis University, Budapest, Hungary).

Contributors ES developed the theoretical framework, processed the analytic calculations, performed the data interpretation and wrote the manuscript. MG is full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. He is responsible for the overall content as the guarantor. MG designed the project, organised and developed the platform and reviewed the cases. Clinical principal site investigators of the project were ES, NK, JC, MW, NE, NK, JL, KK, ZS, FS, WB, SH, S-PJ, MP, NU, FB, KK, MK and MG. All authors participated in discussions for conclusion of the project and reviewed the manuscript.

Funding MG is supported by DFG (Gr 970/9-1), FP7 Coordination of Non-Community Research Programmes (Gr FP7-305653-chILD-EU), Cost CA (Gr 16125 ENTeR-chILD) and European Respiratory Society Clinical Research Collaboration (Gr not applicable).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by ethics committee of the Ludwig Maximilians University of Munich, Pettenkoferstr. 8, 80336 München (EK 026-06, 257-10, 111-13, 20-329). Participants gave informed consent to participate in the study before taking part.All caregivers of the patients provided written informed consent and the participants' verbal assent to participate in the Kids Lung Register.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Elias Seidl http://orcid.org/0000-0001-6610-3756
Nicolaus Schwerk http://orcid.org/0000-0002-5496-7749
Julia Carlens http://orcid.org/0000-0001-8578-864X
Martin Wetzke http://orcid.org/0000-0002-1462-9569
Nagehan Emiralioğlu http://orcid.org/0000-0002-1405-8401
Nural Kiper http://orcid.org/0000-0003-1261-7393
Joanna Lange http://orcid.org/0000-0003-4165-6455
Katarzyna Krenke http://orcid.org/0000-0002-8370-784X
Zsolt Szepfalusi http://orcid.org/0000-0003-4852-3102
Florian Stehling http://orcid.org/0000-0002-2417-2048
Silvija-Pera Jerkic http://orcid.org/0000-0003-2972-649X
Marijke Proesmans http://orcid.org/0000-0002-5576-9517
Nicola Ullmann http://orcid.org/0000-0003-1111-5690
Frederik Buchvald http://orcid.org/0000-0003-4196-3893
Matthias Kappler http://orcid.org/0000-0003-3889-9552
Matthias Griese http://orcid.org/0000-0003-0113-912X

REFERENCES

1 Kurland G, Deterding RR, Hagood JS, *et al*. An official American thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med* 2013;188:376–94.
2 Griese M, Irnstetter A, Hengst M, *et al*. Categorizing diffuse parenchymal lung disease in children. *Orphanet J Rare Dis* 2015;10:1–6.
3 Griese M, Haug M, Brasch F, *et al*. Incidence and classification of pediatric diffuse parenchymal lung diseases in Germany. *Orphanet J Rare Dis* 2009;4:26.
4 de Benedictis FM, Attanasi M. Asthma in childhood. *Eur Respir Rev* 2016;25:41–7.
5 Kapur N, Masters IB, Morris PS, *et al*. Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. *Pediatr Pulmonol* 2012;47:68–75.
6 Sanders DB, Bittner RCL, Rosenfeld M, *et al*. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med* 2010;182:627–32.
7 Sunther M, Bush A, Hogg C, *et al*. Recovery of baseline lung function after pulmonary exacerbation in children with primary ciliary dyskinesia. *Pediatr Pulmonol* 2016;51:1362–6.
8 Oelsner EC, Loehr LR, Henderson AG, *et al*. Classifying chronic lower respiratory disease events in epidemiologic cohort studies. *Ann Am Thorac Soc* 2016;13:1057–66.
9 Mayer-Hamblett N, Rosenfeld M, Emerson J, *et al*. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *Am J Respir Crit Care Med* 2002;166:1550–5.
10 Lieu TA, Ray GT, Farmer G, *et al*. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics* 1999;103:e72.
11 Britto MT, Kotagal UR, Hornung RW, *et al*. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002;121:64–72.
12 Konstan MW, Morgan WJ, Butler SM, *et al*. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr* 2007;151:134–9.
13 Kim DS, Park JH, Park BK, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006;27:143–50.
14 Song JW, Hong S-B, Lim C-M, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011;37:356–63.
15 Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. *Can Respir J* 2004;11:117–22.
16 Usui Y, Kaga A, Sakai F, *et al*. A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia. *BMJ Open* 2013;3:e002971.
17 Tachikawa R, Tomii K, Ueda H, *et al*. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases-related versus idiopathic. *Respiration* 2012;83:20–7.
18 Tomioka H, Sakurai T, Hashimoto K, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis: role of Chlamydophila pneumoniae infection. *Respirology* 2007;12:700–6.
19 Ushiki A, Yamazaki Y, Hama M, *et al*. Viral infections in patients with an acute exacerbation of idiopathic interstitial pneumonia. *Respir Investig* 2014;52:65–70.
20 Wootton SC, Kim DS, Kondoh Y, *et al*. Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:1698–702.
21 Collard HR, Yow E, Richeldi L, *et al*. Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respir Res* 2013;14:73.
22 Raghu G, Collard HR, Egan JJ, *et al*. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
23 Miyazaki Y, Tateishi T, Akashi T, *et al*. Clinical predictors and histologic appearance of acute exacerbations in chronic hypersensitivity pneumonitis. *Chest* 2008;134:1265–70.
24 Park I-N, Kim DS, Shim TS, *et al*. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. *Chest* 2007;132:214–20.
25 Houin PR, Deterding RR, Young LR. Exacerbations in neuroendocrine cell hyperplasia of infancy are characterized by increased air trapping. *Pediatr Pulmonol* 2016;51:E9–12.
26 Clement A, de Blic J, Epaud R, *et al*. Management of children with interstitial lung diseases: the difficult issue of acute exacerbations. *Eur Respir J* 2016;48:1559–63.
27 Griese M, Seidl E, Hengst M, *et al*. International management platform for children's interstitial lung disease (chILD-EU). *Thorax* 2018;73:231–9.
28 Fan LL, Kozinetz CA. Factors influencing survival in children with chronic interstitial lung disease. *Am J Respir Crit Care Med* 1997;156:939–42.
29 Fan LL, Langston C. Chronic interstitial lung disease in children. *Pediatr Pulmonol* 1993;16:184–96.
30 Quanjer PH, Brazzale DJ, Boros PW, *et al*. Implications of adopting the global lungs initiative 2012 all-age reference equations for spirometry. *Eur Respir J* 2013;42:1046–54.
31 Niemitz M, Schwerk N, Goldbeck L, *et al*. Development and validation of a health-related quality of life questionnaire for pediatric patients with interstitial lung disease. *Pediatr Pulmonol* 2018;53:954–63.
32 Gozal D, Bailey SL, Keens TG. Evolution of pulmonary function during an acute exacerbation in hospitalized patients with cystic fibrosis. *Pediatr Pulmonol* 1993;16:347–53.
33 Cunningham S, McColm JR, Mallinson A, *et al*. Duration of effect of intravenous antibiotics on spirometry and sputum cytokines in children with cystic fibrosis. *Pediatr Pulmonol* 2003;36:43–8.
34 Kurosu K, Takiguchi Y, Okada O, *et al*. Identification of annexin 1 as a novel autoantigen in acute exacerbation of idiopathic pulmonary fibrosis. *J Immunol* 2008;181:756–67.
35 Ravens-Sieberer U, Bullinger M. Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results. *Qual Life Res* 1998;7:399–407.
36 Hammer J, Eber E. Paediatric pulmonary function testing. *Respiratory Care* 2005;51:77.
37 Davis SD, Rosenfeld M, Kerby GS, *et al*. Multicenter evaluation of infant lung function tests as cystic fibrosis clinical trial endpoints. *Am J Respir Crit Care Med* 2010;182:1387–97.
38 Jaeschke R, Guyatt GH, Keller J, *et al*. Interpreting changes in quality-of-life score in N of 1 randomized trials. *Control Clin Trials* 1991;12:S226–33.
39 Coclite D, Napoletano A, Gianola S, *et al*. Face mask use in the community for reducing the spread of COVID-19: a systematic review. *Front Med* 2020;7:594269.
40 The Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, Azathioprine, and *N* -Acetylcysteine for Pulmonary Fibrosis. *N Engl J Med Overseas Ed* 2012;366:1968–77.