Longitudinal course of clinical lung clearance index in children with cystic fibrosis

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The lung clearance index (LCI) is sensitive to assess lung disease progression in children with CF in routine clinical care. An increased change in LCI should prompt further diagnostic intervention to determine the underlying pathological process. https://bit.ly/3ae9Rhp


Abstract

Background Although the lung clearance index (LCI) is a sensitive marker of small airway disease in individuals with cystic fibrosis (CF), less is known about longitudinal changes in LCI during routine clinical surveillance. Here, our objectives were to describe the longitudinal course of LCI in children with CF during routine clinical surveillance and assess influencing factors.

Methods Children with CF aged 3–18 years performed LCI measurements every 3 months as part of routine clinical care between 2011 and 2018. We recorded clinical data at every visit. We used a multilevel mixed effect model to determine changes in LCI over time and identify clinical factors that influence LCI course.

Results We collected LCI measurements from 1204 visits (3603 trials) in 78 participants, of which 907 visits had acceptable LCI data. The average unadjusted increase in LCI for the entire population was 0.29 (95% CI 0.20–0.38) LCI units·year$^{-1}$. The increase in LCI was more pronounced in adolescence (0.41 (95% CI 0.27–0.54) LCI units·year$^{-1}$). Colonisation with either Pseudomonas aeruginosa or Aspergillus fumigatus, pulmonary exacerbations, CF-related diabetes and bronchopulmonary aspergillosis were associated with a higher increase in LCI over time. Adjusting for clinical risk factors reduced the increase in LCI over time to 0.24 (95% CI 0.16–0.33) LCI units·year$^{-1}$.

Conclusions LCI measured during routine clinical surveillance is associated with underlying disease progression in children with CF. An increased change in LCI over time should prompt further diagnostic intervention.

Introduction Lung disease in cystic fibrosis (CF) starts early in life with bacterial infection and pulmonary inflammation leading to structural abnormalities [1, 2]. Damage to the lung during sensitive periods of lung growth and development can influence the trajectory of lung disease [1–3]. Therefore, early and sensitive monitoring of lung disease progression is essential. Conventional surveillance strategies have several limitations. Lung function monitoring using conventional methods such as spirometry is less sensitive to assess small airway pathology [4, 5]. Computed tomography (CT) leads to radiation exposure [6], bronchoalveolar lavage (BAL) requires sedation and the invasive nature of both measures should limit their application to exigent clinical problems. Therefore, the multiple breath washout (MBW) technique has gained increasing interest as a noninvasive and sensitive tool to detect early CF lung disease [4, 5].

The lung clearance index (LCI) is a global measure of ventilation inhomogeneity from MBW that is sensitive to early, peripheral lung disease in children with CF [4, 5]. In healthy individuals, LCI ranges between 6 and 8; an increase in LCI above these limits indicates worsening lung function [7]. LCI correlates with
the extent of structural disease [8–10] and pulmonary inflammation [11] and is responsive to interventions [12, 13] in children with CF. Together, these data suggest that LCI is an appropriate clinical surveillance outcome in young children with CF.

However, before LCI can be used to guide clinical decisions, further knowledge of the longitudinal course of LCI during routine clinical surveillance is needed. To date, studies on longitudinal changes in LCI have rarely extended beyond 12 months [14, 15], were performed in research settings [16] or used equipment that is currently not available [17, 18]. At the Bern University Children’s Hospital (Bern, Switzerland), MBW measurements have been part of the 3-monthly routine clinical surveillance of paediatric participants with CF since 2011 using a commercially available MBW device. We have utilised this unique dataset of LCI measurements from early childhood to adolescence to 1) assess the longitudinal course of LCI in children with CF during routine clinical surveillance, 2) identify the clinical factors associated with changes in LCI over time, and 3) assess the different abilities of LCI and forced expiratory volume in 1 s (FEV1) to capture disease progression.

Methods

Study design

This study was a longitudinal, observational, single-centre study in children with CF aged 3–18 years attending 3-monthly outpatient clinical surveillance visits at the Bern University Children’s Hospital between January 1, 2011 and December 31, 2018. Clinical data were assessed retrospectively by structured chart review. Written informed consent was obtained from participants and caregivers at study entry, and the study was approved by the Local Ethics Committee in Bern.

Clinical data

Clinical data were collected at 3-monthly outpatient visits conducted by a paediatric pulmonologist using a standardised questionnaire. At each visit, symptom and treatment review of the past 3 months, clinical examination, microbiological sampling (throat swab or sputum), and lung function testing (MBW and spirometry) were performed. Pulmonary exacerbations were assessed at each visit and respiratory symptoms classified according to the modified Fuchs criteria (supplementary material) [19]. The influence of pro-inflammatory pathogens (Pseudomonas aeruginosa, Aspergillus fumigatus, Staphylococcus aureus, Haemophilus influenzae and Streptococcus pneumoniae [20]) on LCI was examined as an acute effect at every visit and by the overall colonisation status over the entire study period. Colonisation status was considered chronic if the pathogen was present in ≥50% of the samples and intermittent if present in <50% but at least once. This approach takes into account varying lengths of study participation [21]. Furthermore, we assessed the influence of new acquisition of a pathogen on the course of LCI. Severe exacerbations were defined if the modified Fuchs criteria were fulfilled with subsequent need for intravenous antibiotics and considered as number per year to avoid overestimation of this factor in participants with longer follow-up. CF-related diabetes was defined according to the International Society for Pediatric and Adolescent Diabetes guidelines (supplementary material) and assessed as acute effect by the time of clinical evidence [22]. Acute bronchopulmonary aspergillosis (ABPA) was defined as occurring at least once over the study period or never. For data analysis, only participants with at least three clinical visits and acceptable lung function data were included. A detailed summary of variable definitions is available in the supplementary material.

Lung function

Nitrogen MBW tests were performed using the Exhalyzer D MBW device and Spiroware software (Eco Medics, Duemten, Switzerland) with settings according to current consensus (supplementary material) [23]. Testing was performed using a mouthpiece and dead space adjusted according to the participant’s weight. As different software versions were used for data collection during the study period (versions 3.1.3, 3.1.6 and 3.2.1), MBW trials were reloaded into the latest Spiroware version 3.2.1 to ensure comparability. Quality control was performed according to current guidelines [23–26] and tests with at least two acceptable MBW trials were included in our analysis. Spirometry (Jaeger MasterScreen; CareFusion, Hochberg, Germany) was performed after MBW according to American Thoracic Society/European Respiratory Society guidelines [27–30]. Results for spirometry are expressed as z-score values calculated from the Global Lung Initiative reference equations [31].

Statistical analysis

We used a mixed effects linear regression model to assess the mean rate of change in LCI and spirometry indices with age included as linear term. We included a participant-specific random intercept and random slope to account for between-participant variability, different observation periods for each participant and unequal numbers of study visits [32]. The baseline model was adjusted for sex and body mass index.
(BMI). We then adjusted the final model for predefined clinically most relevant covariates. Next, we assessed all potentially influencing covariates on LCI course 1) in a univariate analysis and 2) in the fully adjusted model. We distinguished between time-invariant characteristics (sex, pathogen colonisation, severe exacerbations and ABPA) and time-varying characteristics that were visit-specific (acute pathogen sampling, acute exacerbations, CF-related diabetes and BMI). Time-invariant covariates were included as main effects and interaction terms with age to assess whether covariates were associated with a steeper slope in LCI over time. Visit-specific covariates were included as main effects only to assess the absolute differences in LCI associated with the presence of the characteristic at a given time-point. Nonparametric summaries are presented for skewed data; parametric summaries are used for normally distributed characteristics. Statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX, USA). Figures were created using Stata version 16.0 or Prism (GraphPad, San Diego, CA, USA).

Results

Study population

78 children (44 females) with CF aged between 3 and 18 years were monitored clinically and had MBW measurements performed between January 2011 and December 2018. Overall, 3603 MBW trials were reloaded and quality controlled in Spiroware version 3.2.1 and 1375 (38%) trials were excluded due to quality or technical issues (figure 1). Feasibility by age group is summarised in supplementary table E1. In total, 907 visits from 71 participants satisfied the inclusion criteria of at least three visits per participant with acceptable MBW data and matched clinical data. Patient demographics are summarised in table 1 and supplementary table E2.

LCI course over time without adjustments for risk factors

First, we studied the increase in LCI over time without adjusting for clinical risk factors. As shown in figure 2, LCI increased with age (mean slope 0.29 (95% CI 0.20–0.38) LCI units·year⁻¹; \( p<0.001 \)). LCI was stable during pre-school years (−0.40 (95% CI –1.10–0.33) LCI units·year⁻¹) and started to increase at school age (0.21 (95% CI 0.07–0.35) LCI units·year⁻¹). The highest increase in LCI was observed during adolescence (0.41 (0.27–0.54) LCI units·year⁻¹). There was a significant interaction between age and LCI slope \(( p_{\text{interaction}}=0.02 \) (table 2).

The pattern of the LCI slope was different between males and females (figure 2). Females displayed an earlier and more consistent increase in LCI over time than males, whereas males had a rapid increase in LCI between the ages of 10 and 14 years. Over the entire period there was no difference in the unadjusted increase in LCI between females (0.50 (95% CI 0.27–0.63) LCI units·year⁻¹) and males (0.42 (95% CI 0.21–0.64) LCI units·year⁻¹); \( p_{\text{interaction}}=0.86 \).

Covariates associated with an increase in LCI over the study period

The influence of clinical covariates on LCI course was first assessed in a univariate analysis and then in the fully adjusted model (table 3). We found that colonisation with any pro-inflammatory pathogen was associated with a steeper increase in LCI over time as indicated by the significant interaction with LCI slope (table 3). Aspergillus colonisation was individually associated with a steeper increase in LCI, with a higher LCI slope in those chronically colonised compared with never colonised (table 3 and figure 3). There was also a trend towards a higher LCI slope in those with chronic \( P. \) aeruginosa colonisation compared with never colonised, which was not statistically significant (figure 3). For \( S. \) aureus and \( H. \) influenzae colonisation we found no significant interaction with LCI slope. Furthermore, new acquisition of Aspergillus or \( P. \) aeruginosa was associated with a steeper increase in LCI slope compared with before colonisation (supplementary table E3). Severe exacerbations and experiencing ABPA during the study period were associated with a steeper increase in LCI over time. The increase in LCI over time was independent of baseline characteristics (baseline LCI, follow-up time, comorbidities and medication use) (supplementary table E4).

Covariates associated with acute changes in LCI

We also assessed visit-specific covariates that could result in acute changes in LCI (table 4). Acute exacerbations and clinical evidence of CF-related diabetes were associated with acute changes in LCI. A higher BMI was associated with a better (lower) LCI. Acute, visit-specific pathogen colonisation (any pro-inflammatory pathogen, Aspergillus, \( P. \) aeruginosa, \( S. \) aureus and \( H. \) influenzae) was not associated with acute LCI changes (supplementary table E4).

Increase in LCI over time with adjustments for risk factors

When adjusting our model for the predefined clinically most relevant covariates, i.e. sex, BMI, \( P. \) aeruginosa and Aspergillus colonisation, CF-related diabetes, and acute and severe exacerbations, the increase in
LCI over time diminished from 0.29 (95% CI 0.20–0.38) (figure 2) to 0.24 (95% CI 0.16–0.33) LCI units·year\(^{-1}\) (figure 4 and supplementary table E5). The change in LCI over time in the fully adjusted model indicates that also in the absence of risk factors (e.g. colonisation with \textit{P. aeruginosa}), LCI would still increase substantially over time.

After adjustment for clinical risk factors, the pattern of change in LCI at different ages was comparable to the unadjusted model; however, the overall increase in LCI was less pronounced (figure 4 and table 2). The steeper increase in LCI observed in females during adolescence was due to a combination of different prevalences of risk factors and different effect sizes of covariates between males and females (supplementary table E6). After adjusting for all covariates in the final model, the increase in LCI over time was similar between females and males (figure 4).

**Lung function over time for spirometry indices**

For spirometry indices, \textit{i.e.} FEV\(_1\), forced vital capacity (FVC) and forced expiratory flow at 25–75% of FVC (FEF\(_{25–75}\%\)), the pattern of lung function decline for the entire cohort was comparable to LCI (supplementary figure E1). The unadjusted decrease was found to be \(-0.09\) (95% CI \(-0.14–\)

\(-0.05\)) FEV\(_1\) z-score·year\(^{-1}\), \(-0.03\) (95% CI \(-0.07–0.01\)) FVC z-score·year\(^{-1}\) and \(-0.09\) (95% CI \(-0.14–\)

\(-0.04\))
FEF25–75% z-score·year−1, with no differences in slope between pre-school age, school age and adolescence (supplementary table E7).

The association of time-invariant risk factors for spirometry indices was less pronounced than for LCI (supplementary tables E8 and E9). For time-dependent risk factors, only acute pulmonary exacerbation was associated with the rate of change of all spirometry indices (supplementary table E10). The decrease in lung function over time after adjusting for risk factors remained similar to the unadjusted model (−0.08 (95% CI −0.13 −−0.04) FEV1 z-score·year−1, −0.04 (95% CI −0.08 −0.01) FVC z-score·year−1 and −0.07 (95% CI −0.11 −0.03) FEF25–75% z-score·year−1).

Discussion

We found that LCI measured during routine clinical surveillance increased over time in children with CF, even after adjusting for clinical risk factors. LCI starts to increase at school age followed by a steeper
TABLE 3 Covariates associated with an increased change in lung clearance index (LCI) over time: influence of time-invariant clinical covariates on LCI course in the fully adjusted analysis

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Baseline model</th>
<th>Fully adjusted model</th>
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<tbody>
<tr>
<td></td>
<td>Slope# (95% CI)</td>
<td>p-value</td>
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<tr>
<td></td>
<td>LCI units·year⁻¹</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male (n=27)</td>
<td>0.21 (0.07–0.34)</td>
<td>0.56</td>
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<tr>
<td>Female (n=44)</td>
<td>0.27 (0.15–0.36)</td>
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<tr>
<td>Any pro-inflammatory pathogen¶</td>
<td></td>
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<tr>
<td>Intermittent (n=9)</td>
<td>0.21 (0.06–0.37)*</td>
<td></td>
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<tr>
<td>Chronic (n=62)</td>
<td>0.24 (0.15–0.32)*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Aspergillus fumigatus colonisation</td>
<td></td>
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<tr>
<td>Never colonised (n=40)</td>
<td>0.15 (0.03–0.26)*</td>
<td></td>
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<tr>
<td>Intermittent (n=26)</td>
<td>0.31 (0.18–0.43)*</td>
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<tr>
<td>Chronic (n=5)</td>
<td>0.48 (0.21–0.73)*</td>
<td>0.04*</td>
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<tr>
<td>Pseudomonas aeruginosa colonisation</td>
<td></td>
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<tr>
<td>Never colonised (n=31)</td>
<td>0.18 (0.04–0.31)</td>
<td></td>
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<tr>
<td>Intermittent (n=29)</td>
<td>0.23 (0.11–0.35)</td>
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<tr>
<td>Chronic (n=11)</td>
<td>0.40 (0.20–0.60)</td>
<td>0.2</td>
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<tr>
<td>Haemophilus influenzae colonisation</td>
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<tr>
<td>Never colonised (n=18)</td>
<td>0.41 (0.25–0.56)</td>
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<tr>
<td>Intermittent (n=50)</td>
<td>0.19 (0.09–0.28)</td>
<td></td>
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<tr>
<td>Chronic (n=3)</td>
<td>0.24 (−0.17–0.66)</td>
<td>0.07</td>
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<tr>
<td>Staphylococcus aureus colonisation</td>
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<tr>
<td>Never colonised (n=5)</td>
<td>0.23 (−0.08–0.54)</td>
<td></td>
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<tr>
<td>Intermittent (n=17)</td>
<td>0.07 (−0.10–0.24)</td>
<td></td>
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<tr>
<td>Chronic (n=49)</td>
<td>0.29 (0.19–0.39)</td>
<td>0.09</td>
</tr>
<tr>
<td>Severe exacerbations per year</td>
<td></td>
<td></td>
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<tr>
<td>0 (n=62)</td>
<td>0.12 (−0.01–0.24)*</td>
<td></td>
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<tr>
<td>≥1 (n=35)</td>
<td>0.34 (0.23–0.45)*</td>
<td>0.01*</td>
</tr>
<tr>
<td>Acute bronchopulmonary aspergillosis during study period</td>
<td></td>
<td></td>
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<tr>
<td>0 (n=62)</td>
<td>0.20 (0.11–0.28)*</td>
<td></td>
</tr>
<tr>
<td>≥1 (n=9)</td>
<td>0.40 (0.26–0.54)*</td>
<td>0.01*</td>
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</table>

Covariates assessed are time invariant and considered in the model as stated over the entire study period in the fully adjusted analysis. The slope coefficients are derived from a multilevel mixed effects model adjusted for the main effects of final selected covariates (fully adjusted model summarised in supplementary table E5). A positive coefficient indicates a worsening LCI (higher LCI), whereas a negative coefficient indicates an improving LCI (lower LCI). #: slope represents the increase in LCI over time compared within the group characteristic (95% confidence interval represents the comparison with zero increase in LCI for each subgroup separately); ¶: pro-inflammatory pathogens were considered S. aureus, P. aeruginosa, H. influenzae, Streptococcus pneumoniae and Aspergillus; p-values are derived from the interaction within the group characteristic and LCI slope. *: statistically different from zero at p<0.05 significance level.
increase during adolescence. LCI course was primarily influenced by pulmonary exacerbations, pathogen colonisation, CF-related diabetes and ABPA.

Comparison with literature
We report an increase in LCI over time of between 0.24 and 0.29 LCI units·year$^{-1}$, depending on which risk factors were adjusted for in the model. Only a few studies have assessed the course of LCI over $\geq$12 months, and have reported increases between 0.18 and 0.61 LCI units·year$^{-1}$ [14–18]. However, comparability of absolute LCI values may be limited due to the different methodologies and study designs.

In our cohort, LCI remained stable during pre-school years (age 3–5 years) and did not significantly increase until school age and adolescence. This is contrary to the findings of STANOJEVIC et al. [16], who reported an increase in LCI of 0.4 LCI units·year$^{-1}$ over a 2-year follow-up of pre-school children with CF aged 2.5–5.9 years. The cause of these divergent findings is unclear but likely to be influenced by 1) cohort characteristics (mostly newborn screened CF patients in the STANOJEVIC et al. [16] study versus mostly clinically diagnosed in our cohort) and 2) study design differences (research setting with standardised enrolment and follow-up compared with a clinical surveillance setting with different periods of enrolment and follow-up). Furthermore, one major difference in our study was that the clinicians in our centre

<table>
<thead>
<tr>
<th>TABLE 4 Covariates associated with acute changes in lung clearance index (LCI): influence of visit-specific clinical covariates on acute LCI changes in the fully adjusted analysis</th>
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<tbody>
<tr>
<td>Covariate</td>
</tr>
<tr>
<td>Acute exacerbations (n=586/907)</td>
</tr>
<tr>
<td>Cystic fibrosis-related diabetes (n=84/907)*</td>
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<tr>
<td>Body mass index z-score</td>
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</table>

Coefficients represent the increase (with 95% confidence intervals) in LCI at a given time-point compared with those without the characteristic and are derived from a multilevel mixed effects model adjusted for the main effects of final selected covariates (fully adjusted model summarised in supplementary table E5). A positive coefficient indicates a worsening LCI (higher LCI), whereas a negative coefficient indicates an improving LCI (lower LCI). *: six patients developed diabetes during the study period, two patients had diabetes at study entry; in total contributing to 84 visits with diabetes. **: statistically different from zero at p<0.05 significance level.
were not blinded to LCI. Therefore, pre-school children with elevated LCI might have received more intensive treatment at a period where lung disease is still modifiable.

Interestingly, follow-up data of the STANOJEVIC et al. [16] cohort revealed that LCI flattened during school age years, which the authors hypothesised was due to intense periods of treatment during pre-school years [33]. Substantial therapeutic changes in the last few years with the availability of CF transmembrane conductance regulator (CFTR) modulators may be an additional explanation of the different LCI trajectories between these two cohorts. Our findings are similar to the reported increase in LCI of 0.18 LCI units·year−1 from pre-school to adolescence in patients with CF in the study of DAVIES et al. [18]. While there are methodological differences to our study, the cohort assessed is clinically the most comparable currently available. The different patterns of LCI increase between males and females during adolescence only observed in our study are most probably attributable to the different prevalences of risk factors between males and females.

Associations between LCI and disease markers have mostly been reported in cross-sectional or short-term longitudinal studies. A range of clinical factors, such as pulmonary inflammation, infection and exacerbations, have been shown to influence LCI [8, 11, 13, 34, 35]. We confirmed that these clinical variables also influence the long-term course of LCI. A novel finding was the strong association between Aspergillus colonisation and increase in LCI independent of other risk factors and occurrence of ABPA. While associations between Aspergillus infection and clinical outcomes have been reported previously, the impact of Aspergillus infection, especially in the absence of ABPA diagnosis, on lung disease progression is unclear [36–38]. Interestingly, detection of Aspergillus in BAL samples from children with CF was associated with progression of structural lung disease on chest CT over time [34]. We also found that colonisation with any pro-inflammatory pathogen and new acquisition of P. aeruginosa were associated with an increased LCI slope [20]. The detrimental effect of pulmonary exacerbations on long-term lung function decline has been reported previously for spirometry [39]. In our study, we could show that severe and acute pulmonary exacerbations were associated with acute and long-term effects on LCI course [13].

While spirometry indices FEV₁ and FEF₂₅₋₇₅% showed comparable patterns of lung function decline to LCI, the association with age was less pronounced. Except for acute exacerbations, none of the risk factors assessed were consistently associated with spirometry outcomes. While direct comparison between spirometry outcomes and LCI was not the objective of our study, our findings suggest that LCI is more sensitive to detect underlying clinical manifestations of lung disease in children with CF compared with spirometry [4, 17].

![Graph showing lung clearance index (LCI) increase over time with adjustments for risk factors.](https://doi.org/10.1183/13993003.02686-2020)
**Strengths and limitations**

One of the main strengths of the present study is the use of a longitudinal dataset of routinely measured LCI in a clinical cohort of children with CF. Despite an increasing number of studies using LCI as an endpoint, data on the long-term course of LCI are still limited. We used a commercially available MBW device and analysed all data in the currently available software version to obtain high-quality MBW data. We performed rigorous quality control according to the latest guidelines [23, 24, 26]. This approach led to a relatively high exclusion rate of MBW tests (24%). While these numbers appear high for an experienced centre in MBW testing, it is important to note that MBW testing at our centre started in 2011 before current quality control standards were available. Furthermore, feasibility was lowest at pre-school age, which is not unexpected and comparable to other studies (supplementary table E1) [40]. Thus, we believe our dataset is representative of LCI in the clinical setting as it incorporates all challenges associated with the use of LCI measurements in routine testing: limited measuring time, the broad age range of participants with varying disease severities, staff with different levels of testing experience and varying intervals between measurements. The definition of pathogen colonisation status and the sensitivity of different sampling methods likely influenced the interpretation of pathogen data in our study. However, there is no clear consensus on how to define colonisation in the clinical setting and recent omics-based monitoring further questions our understanding of culture-based pathogen detection [41]. In general, one of the major limitations of observational studies is to disentangle the direct effects of exposure variables from potential confounding characteristics of the participants. This issue could have been minimised with a healthy control population, which was not available for our cohort.

**Clinical relevance**

We found that LCI increases over time in children with CF even in the absence of risk factors, indicating that LCI is sensitive to assess disease progression without overt clinical symptoms. A wide spectrum of different clinical factors, including microbiology, pulmonary and endocrinological complications, was associated with increasing LCI, which suggests that LCI is useful to monitor disease pathology in CF. An increased LCI in individual children with CF should prompt further diagnostic tests. Overall, our results highlight the clinical validity of LCI for several reasons: 1) known clinical risk factors of disease progression influenced LCI course over time, 2) LCI increases also in the absence of risk factors, and 3) adjusting for risk factors minimised differences in LCI course between female and male participants.

**Outlook**

Two main questions remain to be addressed before LCI can be recommended for widespread clinical use. 1) Is LCI responsive to detect and monitor treatment changes in clinical practice? 2) Would LCI-guided therapy improve outcomes in children with CF? To answer these questions, randomised trials of LCI-guided therapies [42] where clinicians are blinded to LCI results are needed. To better interpret and understand changes in LCI from a pathophysiological point of view, prospective longitudinal studies that compare LCI results with structural and/or functional imaging methods [10, 43] and direct comparisons of conventional lung function parameters are required. Future longitudinal studies in cohorts of participants diagnosed by newborn screening and/or receiving novel CFTR-modulating treatments are needed to define the impact of these substantial diagnostic and therapeutic changes on LCI course.

**Conclusions**

These novel data from longitudinal clinical measurements provide further evidence that LCI is a sensitive measure to assess lung disease progression over time. An increased change in LCI should prompt further diagnostic intervention to determine the underlying pathological processes even in the absence of overt clinical signs and symptoms.

Acknowledgements: The authors thank all our patients and families for allowing their MBW data to be used for research. The authors also thank all our lab technicians for collecting daily MBW measurements, especially Sandra Lüscher, Bettina Vessaz, Sharon Krattinger and Gisela Wirz; special thanks are granted to physicians from our department taking care of our patients: Carmen Casaulta, Florian Singer, Elizabeth Kieninger and Chiara Abbas; furthermore, we thank Daniel Sirtes for his support in data management and Florian Wyler for software engineering, both employees of our research team (Inselspital, Bern, Switzerland).

Data availability: Individual participant data that underlie the results reported in this article could be shared after de-identification. The study protocol and analytic code will be shared beginning 3 months and ending 36 months following article publication with investigators whose proposed use of the data has been approved by an independent review. Proposals should be directed to the corresponding author. Requestors will need to sign a data access agreement.
Author contributions: B.S. Frauchiger, K.A. Ramsey, S. Yammine and P. Latzin were responsible for the conception and design of this study. Data acquisition was conducted by B.S. Frauchiger, S. Binggeli, L. Krüger and S. Yammine. B.S. Frauchiger, K.A. Ramsey, P. Latzin and B. Spycher were responsible for data interpretation. B. Spycher supported the statistical analysis which was conducted by B.S. Frauchiger. B.S. Frauchiger, K.A. Ramsey and P. Latzin drafted the manuscript, and all authors revised and approved the manuscript for intellectual content before submission.

Conflict of interest: B.S. Frauchiger has nothing to disclose. S. Binggeli has nothing to disclose. S. Yammine reports grants from Swiss National Science Foundation, outside the submitted work. B. Spycher reports grants from Swiss National Science Foundation and Swiss Cancer League, outside the submitted work. L. Krüger has nothing to disclose. K.A. Ramsey reports grants from Swiss National Science Foundation, outside the submitted work. P. Latzin reports grants from Vertex, during the conduct of the study; personal fees from Vertex, Novartis, Roche, Polyphor, Vifor, Gilead, Schwabe, Zambon and Santhera, grants from Vertex, outside the submitted work.

Support statement: This project was funded by the Swiss National Science Foundation (grant numbers 182719 (P. Latzin), 168173 (K.A. Ramsey) and 179905 (S. Yammine)) and Vertex (IIS-2017-106193). Funding information for this article has been deposited with the Crossref Funder Registry.

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