Changes in lung clearance index in newborns who screened positive for cystic fibrosis with an inconclusive diagnosis

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Background: Routine follow-up of newborns who screened positive for cystic fibrosis (CF) with an inconclusive diagnosis (CFSPID) is considered standard of care to observe for indications of clinical features of disease [1]. Standard measures of lung function may not be sensitive enough to pick up early signs of disease. The lung clearance index (LCI), as measured by multiple-breath washout (MBW), has been found to be a sensitive measure of early lung disease and progression in cystic fibrosis and could be a useful tool for tracking the CFSPID population over time. Our previous analysis of this cohort was limited primarily to preschool-aged children [2]; with the availability of school-aged data in this group, this study aims to describe changes in LCI over time in CFSPID individuals.

Methods: Children identified as CFSPID were prospectively followed annually with routine sweat chloride testing and clinical assessments, as outlined previously [1]. A subset of performed MBW during their annual visits, using the Exhalyzer D (Eco Medics AG, Switzerland) with nitrogen as a tracer gas, and results were generated out of Spiroware v3.3.1 (Eco Medics AG). Visits were classified as stable or symptomatic if the individual had respiratory symptoms at the time of testing based on physician assessment. Spirometry and sweat chloride results were collected for each visit.

Results: Fifty-eight MBW measurements were collected in 20 children (55% female). CFSPID children had a median of 3 (interquartile range 2–5) MBW measurements. Mean ± SD age at first MBW measurement was 5.1 ± 1.6. Overall, the mean ± SD LCI for all visits was 6.34 ± 0.67. The LCI was 1.05 units higher for school-aged (6–12) than preschool-aged (<6) children (95% CI, −0.83 to −0.12; p = 0.009). The LCI was 1.05 units higher for symptomatic visits than for stable visits (95% CI, 0.60–1.51; p < 0.001), with six of the seven symptomatic visits occurring in children younger than 7, reflecting the higher incidence of viral infections in younger children. All school-aged children with previously high LCI for whom repeated measures were available demonstrated decline (improvement) in LCI on follow-up, and LCI remained within the range defined for healthy children (Figure 1) [3].

Conclusions: Our current analysis suggests that children with CFSPID have normal lung function measured according to LCI during early school age. Follow-up measurements in children with previously high LCI may be useful to ensure that the initial measurement is not interpreted as evidence of significant lung disease.

References


Clinical improvement 2 years after starting exacaftor/tezacaftor/ivacaftor in patients with advanced lung disease

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Background: With the introduction of new cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy (exacaftor/tezacaftor/ivacaftor), people with CF experiencing severe lung disease can experience significant improvements in clinical symptoms.

Methods: This single-center institutional review board–approved retrospective chart review identified patients with advanced lung disease who met criteria for a compassionate use or expanded access program because of high risk of death or transplant need within 2 years. Clinical data collection for all patients began at baseline, 2 to 4 weeks after therapy initiation, and continued every 3 months for 2 years. Data were collected on demographic characteristics, clinical progress notes, clinical labs, forced expiratory volume in 1 minute (FEV1), weight, body mass index, respiratory colonization, and hospitalizations after drug initiation. Patients also completed sinus and chest computed tomography (CT) to track clinical changes.

Results: Eighteen people with CF (aged 15–49, 56% male) from a large midwestern CF center who initiated drug therapy between July and September 2019 in an inpatient hospital or clinic setting were identified. Clinical markers (Table 1) indicated that modulator therapy was well tolerated and not discontinued by any participant; safety lab values did not indicate medical concern or discontinuation. There were 90 admissions for the group in the 2 years before therapy and 17 admissions during the 2 years after, although seven of the posttherapy admissions were for nonrespiratory indications. Monitoring results indicated the safety of modulator therapy because there were no adverse clinical occurrences or laboratory events, and all patients presented with universal stabilization. There have been no deaths and no transplants. Unlike lumacaftor/ivacaftor, there were no increases with chest tightness or any difficulty with troublesome increases in expectoration burden or choking during initiation of therapy. Most had significant reduction in or loss of spontaneous cough and sputum production. The impact on microbial colonization is unclear, because even in this severe group, inability to produce sputum on command led to considerable missing data in follow-up, leaving colonization status at follow-up unclear.

Conclusions: This study focused on people with CF who qualified for modulator therapy based on advanced lung disease. Initiation of modulator therapy was deemed safe and resulted in objective positive changes in nutrition; cough; FEV1; and subjective reports of clinical status, level of activity, and reduction in burden of treatment. No evidence was found of difficulty managing the increased expectoration during initial therapy. Limitations were noted in missing data during the COVID-19 pandemic, small sample size, and delayed follow-up for drug monitoring.

Figure 1. Longitudinal measurements of the lung clearance index (LCI) over time for newborns who screened positive for cystic fibrosis with an inconclusive diagnosis. X = physician-determined symptomatic visits.
Physical activity has been shown to have a positive impact on cystic fibrosis (CF) symptoms and slows decline in lung function. Additionally, moderate-intensity activities have been shown to improve sputum expectoration and oxygen saturation in children with CF, improving symptoms [1]. This study assessed whether using fitness trackers and providing a daily step goal would increase physical activity in hospitalized children with CF.

**Methods:** This pre-post pilot study included participants aged 6 to 21 who were admitted to the hospital for a pulmonary exacerbation of CF between October 2020 and November 2021. Garmin vivosmart 4 wrist-based activity trackers were issued, and baseline data were tracked and analyzed for the first 2 study days. Pre-goal number of steps was defined as average number of steps taken on those 2 days. On study day 3, a step goal and menu of activities designed to increase physical activity were shared with the participants. Steps after goal setting were defined as average number of steps taken on study day 3 and beyond while hospitalized, excluding day of discharge. Data collected from the medical record and the activity tracker were analyzed for only the first week after discharge because of poor adherence to wearing the device.

**Results:** Eight participants aged 6 to 18 completed the study. Hospital length of stay ranged from 4 to 14 days. Participants took an average of 1508 ± 1078 steps before goal setting, which increased to an average of 3704 ± 1555 steps after the intervention. Step goals were met 56% of the time, although this was highly variable. Two patients met their goal 100% of the time (9-year-old boy, 7-year-old girl), two met it 0% of the time (18-year-old boy, 17-year-old girl), one met it 44% of the time (6-year-old boy), and the remaining three met it 67% of the time (10-year-old girl, 17-year-old girl, 14-year-old boy).

**Conclusions:** This intervention shows promise, with daily number of steps doubling from baseline during the intervention period. There was great variability among participants, suggesting that the approach helps some more than others. Enrollment was initially planned for 20 patients, but the SARS-CoV-2 pandemic and changes to CF therapy reduced hospitalizations during the study period. Outpatient data were analyzed for only the first week after discharge because of poor adherence to wearing the device. Although our results show a positive impact, further research is needed to determine the effect such an intervention would have on a larger scale. Future directions of research include determining potential clinical benefit from increased activity during hospitalization and prolonged follow-up to assess long-term benefits of intervention.

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**Reference**


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**Table 1 (abstract 123):**

<table>
<thead>
<tr>
<th>Clinical indicators before and after modulator therapy</th>
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<tr>
<td><strong>Prior to Therapy</strong></td>
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<tr>
<td>First of two sweat chlorides</td>
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<tr>
<td>ppFEV1 (baseline vs six-months)</td>
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<tr>
<td>Weight (baseline vs six-months)</td>
</tr>
<tr>
<td>BMI (baseline vs six-months)</td>
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<tr>
<td>Hospital admissions</td>
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</tbody>
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*Completed post-drug initiation (earlier than 12 months), **24 months before and after therapy initiation*