children with CF living longer, studies that focus on antibiotic selection for PEx treatment are needed to improve clinical outcomes and minimize unnecessary antibiotic exposure that can lead to antibiotic toxicity and antibiotic resistance.

Reference

Pulmonary exacerbation antibiotic treatment for children with cystic fibrosis and polymicrobial infection

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Background: There is substantial variability in pulmonary exacerbation (PEx) management. Cystic Fibrosis Foundation PEx guidelines do not inform antibiotic selection in people with cystic fibrosis (PwCF) who culture multiple respiratory microorganisms. This study aimed to describe the number of in-hospital-treated PEx in PwCF who culture more than one CF-related bacteria, describe the proportion of these in-hospital-treated PEx who cultured more than one CF-related bacteria in the previous admission, (51% with complete coverage) in the group with incomplete antibiotic coverage on previous admission, (51% with complete coverage) in the group with incomplete antibiotic coverage on previous admission, 93% had complete antibiotic coverage for PEx. This was significantly lower (51% with complete coverage) in the group with incomplete antibiotic coverage on previous admission, p < 0.001 (Figure 1).

Methods: Retrospective cohort study using the Cystic Fibrosis Foundation Patient Registry—Pediatric Health Information System dataset. Children with CF aged 1 to 21 years with an in-hospital-treated PEx between 2006 and 2019 were included. Exclusion criteria included length of stay fewer than 4 days or more than 35 days, history of solid organ transplant or malignancy, history of nontuberculous mycobacteria in the prior 12 months, and ICU stay during the PEx. Antibacterial activity for each antibiotic was defined according to the Sanford Spectra of Activity Guide.

The presence of traditional bacteria (Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus (MRSA), methicillin-sensitive S. aureus (MSSA), Achromobacter xylosoxidans, Stenotrophomonas maltophilia, Haemophilus influenzae, and Burkholderia cepacia complex) was defined as any positive respiratory culture for that species in the 12 months before a study PEx.

Results: After applying eligibility criteria, 4,034 children with CF cultured more than one CF-related bacteria and contributed 20,214 PEx for analysis. Those who cultured one or fewer CF-related bacteria had mean baseline percentage predicted forced expiratory volume in 11 second of 78% (range 60–93%), compared with 74% (IQR 56–89%) in those who cultured more than one bacteria. Complete antibiotic coverage as defined was prescribed at admission in 68% of PEx in those who cultured more than one bacteria. The most common polymicrobial combinations were P. aeruginosa and MRSA (n = 2852 PEx); P. aeruginosa and MSSA (n = 2749); and P. aeruginosa, MRSA, and MSSA (n = 1465). Complete antibiotic coverage was prescribed in 82% of PEx when P. aeruginosa and MRSA were present; 81% when P. aeruginosa and MSSA were present; and 75% when P. aeruginosa, MRSA, and MSSA were present. Of those who cultured P. aeruginosa and MRSA and were prescribed complete antibiotic coverage on a prior admission for PEx, 93% had complete antibiotic coverage for PEx. This was significantly lower (51% with complete coverage) in the group with incomplete antibiotic coverage on previous admission, p < 0.001 (Figure 1).

Conclusions: Two-thirds of children with CF hospitalized for PEx treatment who cultured more than one CF-related bacteria in the previous

Table 1 (abstract 118):
Comparison of pre- and post-pulmonary exacerbation (PEx) treatment change in percentage predicted forced expiratory volume in 1 second (FEV1pp), return to ≥90% of baseline FEV1pp, and time to next PEx requiring intravenous (IV) antibiotics for PEx with and without an IV antibiotic change

<table>
<thead>
<tr>
<th>Outcome (reference: No)</th>
<th>Inverse Probability of Treatment Weighting Adjusted</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre- to Post-PEx ppFEV1 (Antibiotic Change: Yes)</td>
<td>0.8 - 1.23 (-1.77, -0.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Return to ≥90% of Baseline ppFEV1 (Antibiotic Change: Yes)</td>
<td>OR: 0.78 (0.72, 0.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to Next PEx Requiring IV Antibiotics within 12 Months (Antibiotic Change: Yes)</td>
<td>HR: 0.98 (0.88, 1.09)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Figure 1. Ten most common cystic fibrosis (CF)-related bacteria present on respiratory culture in children with CF receiving in-hospital treatment for pulmonary exacerbations (PEx).
12 months were prescribed antibiotics with complete antibiotic coverage. In children with CF who cultured *P. aeruginosa* and MRSA, a prior PE treatment with complete antibiotic coverage was associated with complete coverage during a future PE. Ongoing work is being done to compare outcomes of PE treated with partial antibiotic coverage with outcomes of PE treated with complete antibiotic coverage, which may help guide antibiotic selection to maximize clinical outcomes and minimize potentially unnecessary use.

### 120 Sleep disturbances after initiation of elexacaftor/tezacaftor/ivacaftor therapy

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**Background:** The U.S. Food and Drug Administration approved the cystic fibrosis transmembrane conductance regulator (CFTR) modulator elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in October 2019 for patients with cystic fibrosis (CF) and at least one F508del mutation [1]. Phase 3 trials indicated that it is generally well tolerated, and patients participating in the trials did not report any sleep disturbances [2], but sleep disturbances related to CF can occur, and poor sleep can affect health outcomes [3]. In addition, although no sleep disturbances were reported in trials, one case study reported sleep paralysis with hypnopompic hallucinations, depression, and anxiety after initiation of ELX/TEZ/IVA, so it is important to assess for sleep disturbances after initiation of this modulator as a routine part of CF care. The goal of this study was to examine self-reported sleep disturbances in people with CF after initiation of ELX/TEZ/IVA.

**Methods:** A retrospective chart review was conducted of adults with CF (N = 127) receiving care at an adult CF clinic in an academic health center in the southeastern United States from January 2015 to February 2022. Data collected included demographic data, percentage predicted forced expiratory volume in 1 second (predicted for age, gender, and height) at each visit, consistency and timeline of ELX/TEZ/IVA use, and self-reported sleep disturbances.

**Results:** One hundred twenty-seven people were screened for study eligibility, and 100 were included. Twenty-three percent reported new-onset or ongoing sleep disturbances after initiation of ELX/TEZ/IVA. Two discontinued the modulator after reporting significant insomnia, anxiety, and depression.

**Conclusions:** More than half of the participants reported new-onset or ongoing sleep disturbances after initiation of ELX/TEZ/IVA that contributed to two patients discontinuing the modulator. It is important to screen for and treat sleep disturbances as a routine part of CF care.

**References**


### 121 Evaluation of lung disease progression after introduction of lumacaftor/ivacaftor in young children

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**Background:** The introduction of cystic fibrosis (CF) transmembrane conductance regulator modulator therapy has ushered in a new era in CF treatment. Because progressive lung damage is the most prominent cause of morbidity and mortality in CF, the possibility of preventing this progression is a major argument for starting modulator therapy in young patients, but evaluating the effect of modulators on pulmonary disease in preschool-aged children is challenging. Although neutrophil influx and structural damage to the lungs have been shown to occur in the first years of life, improvement in respiratory symptoms can be difficult to identify in early disease stages, and objective parameters such as spirometry are difficult to reliably obtain in children under the age of 5. The goal was to compare two objective measures of pulmonary disease—chest computed tomography (CT) and neutrophil count in bronchoalveolar lavage fluid (BALF)—in a cohort of young children before and after start of lumacaftor/ivacaftor (LUM/IVA) therapy and to compare the children with untreated peers.

**Methods:** As part of our monitoring program, children with CF undergo a bronchoscopy and chest CT at ages 1, 3, and 5 (I-BALL cohort). LUM/IVA was introduced in the Netherlands in 2019 in children aged 2 to 5 with dF/dF mutations. Paired samples were collected from 25 patients in total (aged 1–3, n = 14; aged 3–5, n = 11) of whom nine started LUM/IVA between visits (aged 1–3, n = 4; aged 3–5, n = 5), and 17 did not. Data at ages 1 and 3 or 3 and 5 were included for post hoc analysis, with varying treatment duration. Cell count from BALF was collected, and the amount of neutrophilic inflammation was expressed as percentage neutrophils of total BALF cells (%Neu). CF lung disease was assessed on chest CT using the Perth-Rotterdam Annotated Grid Morphometric Analysis for CF score, measuring percentages of bronchiectasis (%BE) and total airway disease (%Dis = %BE, mucus plugging, abnormal airway wall thickening). Pearson correlation, one-way analysis of variance and Student t-tests were used for statistical analysis.

**Results:** Overall, mean %Neu was 15.8% at age 1, 25.3% at age 3, and 38% at age 5, showing an increase with age (p = 0.02). %BE increased from 0.16% at age 1 to 0.75% at age 5 (p = 0.003). %Dis was 0.99% at age 1, 1.76% at age 3, and 2.89% at age 5 (p = 0.001). %Dis was positively correlated with %Neu (r = 0.59, p = 0.001). When comparing visits 1 and 2 from paired samples of control subjects (age 1–3 or 3–5), a mean increase in %Dis of 1.05% was found, compared with a mean increase of 0.47% in LUM/IVA–treated subjects (p = 0.62). In control subjects, mean %Neu increase was 8.9% between visits, compared with 3.9% in LUM/IVA–treated (p = 0.55).

**Conclusions:** In our cohort of young children with CF, increases in neutrophilic inflammation and structural lung disease were observed with age. We found a slightly lower increase in %Neu or %Dis in children treated with LUM/IVA than in untreated children, but this was not a significant difference. Differences in lung disease progression might become more pronounced with longer follow-up or larger sample size. Still, these findings suggest that progression of CF lung disease continues despite LUM/IVA therapy in young children and that more-effective CFTR modulators are needed. Our findings also highlight the need for objective monitoring tools in young children in whom functional tests are not yet feasible.

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