

Increased frequency of non-aeruginosa *Pseudomonas* species isolation from the airways of people with cystic fibrosis after initiating Elexacaftor/Tezacaftor/Ivacaftor treatment

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Abstract

The introduction of elexacaftor/tezacaftor/ivacaftor (ETI) has significantly improved outcomes in people with cystic fibrosis (pwCF), although its impact on non-aeruginosa *Pseudomonas* species (NAPs) remains poorly understood. We retrospectively analysed respiratory cultures from 417 pwCF attending three Italian CF centres before and after ETI initiation. Twenty patients (4.8%) had at least one NAPs-positive culture after ETI, compared with one patient before treatment ($p < 0.001$). Fifteen different species were identified, mainly belonging to the *Pseudomonas fluorescens* and *P. putida* groups. ETI may alter the airway microbiota, increasing NAPs detection. Further studies are needed to determine their clinical significance and guide management.

Introduction

The introduction of elexacaftor/tezacaftor/ivacaftor (ETI) CFTR modulator therapy has had a remarkable impact on clinical outcomes and quality of life in people with cystic fibrosis (pwCF). Although the effects of ETI on the major CF pathogens have been extensively described, limited data are available regarding its impact on other bacterial species [1]. The aim of this retrospective study was to evaluate the incidence of non-aeruginosa *Pseudomonas* species (NAPs) during the year before and the year after initiation of ETI therapy, which has been licensed in Italy since July 2021 for pwCF carrying at least one *F508del* allele.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee for Paediatric Clinical Trials in Florence (Approval No. 47/2024). Written informed consent was obtained from all participants or from the parents/legal guardians of minors. Microbiological data from routine respiratory cultures collected from pwCF attending three Italian CF centres between 2022 and 2024 were retrospectively analysed. Clinical data were extracted from the medical records at each participating centre. All microbiological analyses were performed at the Microbiology Laboratory of the Florence CF Centre according to national and international CF microbiology guidelines. Bacterial isolates were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) [2].

Results

Twenty of 417 pwCF (4.79%; 12 males and 8 females; median age 15.08 years, IQR 18.5) had at least one respiratory sample positive for NAPs within one year after starting ETI therapy. A total of 74 respiratory samples (48 oropharyngeal swabs and 26 sputum specimens; mean 3.7 samples/patient/year) were analysed during the post-ETI period. Retrospective analysis of samples collected during the year before ETI initiation identified only one patient with a positive NAPs culture among 62 respiratory samples (35 oropharyngeal swabs and 27 sputum specimens; mean 2.6

samples/patient/year). This increase was statistically significant ($p < 0.001$ Fisher's exact test). The mean time to first detection of a NAPs species after ETI initiation was 5 months (IQR 9). Fifteen different species were identified. Members of the *Pseudomonas fluorescens* group and *Pseudomonas putida* group accounted for the majority of isolates (Table). In two samples, two different NAPs species were isolated simultaneously.

organism	number of isolates
P. fluorescens group	
P. fluorescens	5
P. koreensis	2
P. tolaasii	2
P. gessardi	2
P. mucidolens	1
P. proteolitica	1
P. rhodesiae	1
P. azotoformans	1
P. libanensis	1
P. putida group	
P. monteilii	3
P. putida	2
P. orizihabitans	2
P. plecoglossicida	1
P. chlororaphis group	
P. chlororaphis	1
P. aeruginosa group	
P. alcaligenes	1

Table: different species of NAPS isolated in the described cohort

Conclusions

Our findings indicate that NAPs, which were rarely and only transiently isolated from CF airways in the pre-modulator era [3–5], are now detected more frequently following ETI therapy. This increased detection may reflect substantial changes in the airway microenvironment induced by CFTR modulation, resulting in alterations of the airway microbial community. Although some species, including *P. fluorescens*, *P. putida*, *P. oryzae*, and *P. alcaligenes*, have previously been reported in pwCF [3–5], this is, to our knowledge, the first description of several of the other identified species in this population. As the clinical significance of these isolates remains unclear and no specific management recommendations currently exist for NAPs, further studies are needed to determine their clinical relevance. Careful longitudinal monitoring of both microbiological findings and clinical status will be essential to avoid unnecessary antibiotic treatment in clinically stable pwCF. To our knowledge, this is the largest case series describing the emergence of non-aeruginosa *Pseudomonas* species after ETI therapy.

Declarations

Author Contribution

SC collected and analyzed the data and wrote the manuscript. DD contributed to the microbiological analyses. RC contributed to data collection. VT, MCL, and PM collected clinical data from patients at the three different treatment centers. All authors reviewed the manuscript.

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