

Fungal colonization in Cystic Fibrosis (CF): Epidemiology and antifungal resistance in a French cohort of CF patients - Focused on *Aspergillus fumigatus* colonization

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Introduction:

Cystic fibrosis (CF) is the major genetic inherited disease in the European Caucasian population, with an average of 1 in 3000 living births in France. Prognostic depend essentially on the lung impairments. While considerable attention therefore has been paid over recent decades to prevent and treat bacterial respiratory infections, we observed emergence of fungi colonization in CF respiratory tract. In particular, *Aspergillus fumigatus* represents the most common causative agent colonizing the airways of CF patients; it can be responsible for Allergic Bronchopulmonary Aspergillosis (ABPA). Since oral corticosteroids and itraconazole represent the mainstay of ABPA treatment, long-term therapy may increase the risk of acquired resistance to azoles that is mainly associated with amino acid substitutions in the CYP51A gene of *A. fumigatus*.

Objective:

First, we managed to have exhaustive epidemiological data on species of filamentous fungi able to colonize the airway tract of 300 CF patients followed-up in our national prospective study ("MucoFong" study - PHRC1902). Second, CF patients being chronically exposed to azole (especially to itraconazole), our study aimed to evaluate the prevalence of azole resistance in isolates prospectively collected from CF patients followed-up in seven French hospitals involved in our national prospective study. Third, we focused on the most prevalent species: *Aspergillus fumigatus*, studying the azole resistance at molecular level. To our knowledge, it is the first multicenter study focused on azole resistance of *A. fumigatus* in CF.

Methods:

A total of 243 sputa were analyzed using the same protocol in each centre. The MICs of antifungal drugs were evaluated for each isolate using the E-test® strips. Focusing on *A. fumigatus*, a total of 87 isolates was collected in 85 patients. These isolates were characterized at the molecular level by targeting ITS, β -tubulin and MAT-A/ α genes. The CYP51A gene as well as its promoter was sequenced; a 3D Cyp51A protein homology model was built.

Results and discussion:

300 patients were enrolled in this study. At inclusion time, most of them were adults colonized with *A. fumigatus* (about 35% of the patients). *Scedosporium* was isolated in 5%, and *Exophiala* in about 2%. Regarding antifungal susceptibility, isolates of *Scedosporium* and *Exophiala* exhibited antifungal resistance comparable with published data. Regarding *A. fumigatus*, a majority of isolates (88.1%) were found sensitive to itraconazole (MIC \leq 2 μ g/ml), and 2 new mutations were identified and localized within 3-dimensional Cyp51A protein model. To obtain insight into azole resistance of *A. fumigatus*, the results are analyzed taking into account clinical data, itraconazole exposition, and the potential correlation between the identified CYP51A mutations and azole resistance is discussed based on the Cyp51A protein homology model.

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