Therapy for lung infection by agent other that bacteria

Fungi in cystic fibrosis

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Background

Opportunistic fungal infections are life-threatening especially in acute and chronic compromised patients. Early and accurate diagnosis is very important for the prompt onset of treatment and to reduce unnecessary use of antifungal drugs. Fungi are frequently recovered from lower airway samples of people with CF, yet the role of fungi in the progression of lung disease is debated. In a recent paper (Cuthbertson L et al, 2021) next generation sequencing of the ITS2 region was used to examine fungal community composition involving 42 cases of non-CF bronchiectasis and 134 patients with CF. Main results show the presence of *Aspergillus* in CF patients more frequently than in non bronchiectasis CF as expected, however other dominant members of the fungal airway microbiome as Candida have been documented, whose clinical effect is not still clear. Culture methods alone do not seem adequate for the clinical management of fungal disease.

In a recente review (Poore TS et al, 2021) it has been suggested that worsening of clinical outcomes may be associated with airway fungal detection, although most studies to date are retrospective or observational. Fungi can elicit a T helper cell type 2 (Th-2) mediated inflammatory reaction, known as allergic bronchopulmonary aspergillosis (ABPA), particularly in those with a genetic atopic predisposition. In this review risk factors, the spectrum of fungal disease presentations, clinical outcomes after isolation of fungi from airway samples, the role of airway co-infections and the association between fungi and airway inflammation have been highlighted.

A combined clinical-genomic approach, including global analysis of the fungal microbiome from CF sputum samples, identified a genetic basis of pathogen adaptation associated to loss of function of transcriptional repressor Nrg1(Kim SH et al, 2015).

In general, the most common fungi in respiratory samples of patients with CF are *Aspergillus fumigatus*, *Aspergillus terreus* and *Scedosporium* species for filamentous fungi, and yeasts such as *Candida albicans* and *Candida glabrata* (Schwarz C et al, 2018).

Efforts providing more rapid and more sensitive diagnosis of invasive fungal infections have been developed. Real-time polymerase chain reaction (RT-PCR), galactomannan (GM) and 1,3-ß-D-Glucan (BG) tests performed both in sera and in BAL samples might aid to the early diagnosis and treatment of patients when invasive fungal infections are suspected in compromised patients (Sav H et al, 2012).

Recently a review evaluated proteomics-based information as potential tools for diagnostic and therapeutical targets, including secreted and cell wall proteins derived from the most common filamentous fungi in CF, i.e., Aspergillus and Scedosporium/Lomentospora species. Secreted allergens were identified in secretomes of Aspergillus Fumigatus and other Aspergillus species associated with CF as Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, and Aspergillus terreus. Cell wall proteins, cytochrome P450 and eEF-3 were also proposed as diagnostic targets, while other proteins were suggested as protective vaccines in A. fumigatus. On the other hand, the heat shock protein Hsp70 was identified for Scedosporium/Lomentospora species as the most significant secreted and cell wall antigen candidated for developing diagnostic and therapeutic tools for fungal infections in CF patients (Ramirez-Garcia A et al, 2018).

Therapeutic strategies depend on the detected fungus and the underlying clinical status of the patient. The antifungal therapy can range from a simple monotherapy up to a combination of three different drugs based on different clinical involvement (Russo A et al, 2020). The following table synthesizes treatment of pulmonary aspergillosis entities.

***Aspergillus* lung disease**	**First-line treatment**	**Duration of therapy**	**Alternative treatment**	**Comments**
ABPA	Prednisolone 0.5 mg/kg/day for 4 weeks followed by 0.25 mg/kg/day for 4 weeks followed by 0.125 mg/kg/day for 4 weeks Itraconazole 200 mg twice daily	3–5 months	Oral voriconazole Posaconazole	Glucocorticoids are the first-line treatment for exacerbations Antifungal therapy has a corticosteroid-sparing effect and could be considered in patients who fail to show improvement after steroid treatment
Aspergilloma	No therapy Surgical resection when appropriate	–	Itraconazole Voriconazole Bronchial artery embolization	Anti-fungal therapy may be considered in cases of lung invasion or when there is the possibility of peri-operatively dissemination
CPA	Itraconazole 200 mg twice daily Voriconazole 6 mg/Kg po/IVq12 h?×?1 day followed by 4 mg/Kg po/IV q12 h	6 months	Posaconazole Liposomal Amphotericin B Caspofungin Micafungin	Prolonged treatment may be necessary Surgery has a limited role and may be associated with complications Anti-fibrinolytic agent or bronchial artery embolization could be considered for management of hemoptysis
IPA	Voriconazole 6 mg/Kg po/IVq12 h?×?1 day followed by 4 mg/Kg po/IV q12 h Isavuconazole 372 mg po/IV q8 h?×?6 doses followed by 372 mg po/IV daily	6–12 weeks	Liposomal Amphotericin B Caspofungin	Combination therapy is not routinely recommended, but may be considered in selected refractory cases Surgical resection is considered in selected situations Empiric treatment could be considered in critically-ill patients with severe liver cirrhosis and/or end-stage chronic obstructive pulmonary disease and/or clinical worsening despite broad-spectrum antibiotics

A recent study including updated standard of care (Burgel PR et al, 2024) pointed out the most relevant aspects of *Aspergillus* -related lung disease. *Aspergillus* bronchitis, *Aspergillus* sensitization, allergic bronchopulmonary aspergillosis (ABPA), and rarely, aspergilloma represent disease variability.

Issues

- To evaluate frequency of fungi beyond Aspergillus Fumigatus (AF) in CF
- to define potential risks factors
- to identify the role of more accurate diagnostic tools
- to inidicate the most efficacy treatment for uncommon fungi

What is known

1 CDSR (Francis NZ, 2022) on antifungal therapies for allergic bronchopulmonary aspergillosis in pwCF concluded that at present, there are no randomised controlled trials that strenghten the use of antifungal therapies for the treatment of ABPA in pwCF, although one trial is currently ongoing which can be eligible for a future update.

No CDSR is available on fungi spp beyond Aspergillus Fumigatus.

A Dutch epidemiological prospective study analyzed respiratory samples of CF patients during a 3-year period, using a uniform fungal culture protocol, focusing on filamentous fungi and azole resistance in AF. Filamentous fungi were recovered from 699 patients from at least one respiratory sample, corresponding with 3787 cultured fungal species. 107 different fungal species were identified, with 39 Penicillium species and 15 Aspergillus species (Engel TGP et al, 2019). A. fumigatus was cultured most often with a mean prevalence of 31.7%, followed by Penicillium species (12.6%), non-fumigatus Aspergillus species (5.6%), Scedosporium species (4.5%) and Exophiala dermatitidis and Cladosporium species (1.1% each).

In order to determine the association between the presence of *Af* and respiratory outcomes in individuals with CF a prospective

longitudinal cohort study of 206 adults and adolescents (age 14 yr and older) with CF (O'Dea AL et al. 2023) was conducted, collecting sputum for selective fungus culture. Clinical outcome measurements, including patient-reported outcomes (measured by the Cystic Fibrosis Questionnaire-Revised), spirometry, and number of pulmonary exacerbations (PEx) were assessed for a 1-year period. Mixed-effects linear models were used to determine the association between positive *Af* culture results, defined as *Af* detection in sputum culture at the study visit, with both respiratory domain score and FEV_1 pp, adjusted for confounders. Mixed-effects Poisson regression models were employed to examine the association between positive *Af* culture results and PEx events, as well as the association between *Af* history, defined as *Af* detection at baseline or within 2 years of enrollment, and respiratory outcomes. *Af* prevalence was 10.3% (95% confidence interval [CI], 6.8, 15.7) at baseline. Forty-eight (23.3%; 95% CI, 17.7, 29.7) participants had at least one *Af*-positive culture result during the study period. Positive *Af* culture result was not associated with lower respiratory domain score. However, *Af* history was associated with a 6.48-point lower respiratory domain score, related to worse respiratory quality of life (95% CI, -11.96, -0.99; $P = 0.02$). Positive *Af* culture result was associated with a 2.54% lower FEV_1 pp (95% CI, -4.64, -0.44; $P = 0.02$) and a 1.71-fold increase in severe PEx incidence (95% CI, 1.05, 2.76; $P = 0.03$). These data show that positive *Af* culture was not associated with lower patient-reported, respiratory-related quality of life. Positive *Af* culture result was associated with both lower FEV_1 pp and increased frequency of severe PEx warranting intravenous antibiotics in adolescents and adults with CF.

A review (Staerck C, et al. 2017) outlined the potential role of antioxidant detoxifying enzymes against reactive oxygen species (ROS) and reactive nitrogen species (RNS) released by phagocytic cells during the colonization process of these emerging species, paving the way for future investigations on the role of these enzymes as new therapeutic targets.

The association between chronic inhaled antibiotics and Scedosporium isolation has been suggested (Hong G et al. 2019), including data from a retrospective cohort study of 19023 subjects followed in the CF Foundation Patient Registry between 2010 and 2012, where the prevalence of Scedosporium spp was 615 (3.2%).

In a multicentre study, including 12 centres from January 2008 to December 2014 (Schwarz C et al. 2019) 31 patients with a lung infection caused by moulds of the genus *Scedosporium/Lomentospora* were treated with 36 courses of antifungal treatment, *Scedosporium*

Diagnostic algorithms, radiological score and treatment options have been recently reported in a review as current approach of ABPA in children with CF (Sunman B et al. 2020).

Many years ago a report indicated that colistin may exhibit *in vitro* antifungal activity against filamentous ascomycetes occurring in CF patients either as single agent and in combination with other antifungals offering a novel therapeutic option (Schemuth H. 2012). No further data confirmed this result.

Unresolved questions

An ongoing phase2/phase 3 trial (NCT04966234) is recruiting CF children and adolescents (age range: 8-17 years) with Aspergillus infection to determine the dosing regimen of Posaconazole at 100mg vs 40 mg. The recruiting status is unknown.

A randomized, double-blind, placebo-controlled, 3-part, single-ascending dose Phase 1a study in healthy volunteers (Part A) and multiple-ascending dose Phase 1b study in healthy volunteers (Part B), and a Phase 2a study in subjects with CF (Part C) (NCT05802264) is actively recruiting CF adolescents and adults (age = 16 years and older) and healthy volunteers to assess the safety, tolerability, PK, and preliminary efficacy of Amphotericin B cystetic for inhalation (ABCI) doses. Approximately 72 subjects total will be randomized to 9 cohorts (48 subjects in 6 cohorts in Part A, 24 subjects in 3 cohorts in Part B) and an additional 26 subjects will receive one of 2 dose/regimens in Part C.

Development and validation of biomarkers characteristic of different fungal clinical phenotypes, and controlled clinical trials of antifungal agents in well-characterized target populations remain goals to be achieved, as well as the need of more epidemiological studies on prevalence and clinical characteristics of fungi colonization out of AF in CF.

Keywords

Aspergillus; Candida albicans; Fungi; Antifungal Agents;