

Bronchopulmonary complications therapy

Allergic bronchopulmonary aspergillosis (abpa) in cystic fibrosis

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Background

Aspergilli are saprophytic, spore-forming, filamentous fungi found ubiquitously in the environment. Aspergillus fumigatus (AF) is the most prevalent fungal species isolated from the respiratory secretions of CF patients.

AF presents a clinical challenge in pwCF, with some people seemingly unaffected while others potentially experiencing substantial morbidity from ABPA or fungal bronchitis (Poore ST et al. 2023). Several factors may contribute as risk factors for AF colonization. Recently data derived from the German CF Registry correlated them to lung function, chronic PA infection and treatment for CF lung disease. Age represented an independent risk factor for persistent AF colonisation. Prevalence was low in children less than ten years, highest in the middle age and getting lower in higher age (? 50 years). Continuous antibiotic lung treatment was significantly associated with AF prevalence in all age groups. CF patients with chronic PA infection had a lower lung function (FEV1%predicted). However, AF colonisation without chronic PA infection was significantly associated with a lower function, too. AF might be associated with decrease of lung function if not disguised by chronic PA infection (Duesberg U et al. 2020).

Pseudomonas aeruginosa (PA) and AF are the most common bacterial and fungal species present in CF airways and coinfection results in a worse disease phenotype. Recently a review examined the mechanisms of interaction evaluating the clinical and inflammatory impacts of this co-infection. Cross-sectional data indicate a worsened disease state in co-infected patients where both mutually antagonistic and cooperative factors may contribute to disease progression (Keown K et al. 2020). Another review outlined predominantly mutual antagonistic factors of PA and AF on lung damage based on published data derived from animal models, while a few data described synergistic interactions (Beswick E et al. 2020).

AF is thought to promote lung function decline in CF patients by phagocytes iperactivation. As CFTR modulators have been shown to reduce *A. fumigatus* colonization *in vivo*, while other treatments including azithromycin and acebilustat may dampen *Aspergillus*-induced inflammation due to their immunomodulatory properties, a study (<u>Currie AJ et al. 2020</u>) was conducted in order to determine the effects of these new therapies on ROS production and fungal killing. Isolated peripheral blood mononuclear cells (PBMCs) and polymorphonuclear cells (PMNs) from ten adult voluntary CF patients with a median age of 26 years with acute or chronic infection by AF and healthy volunteers were challenged with different strains of *A. fumigatus* following pre-treatment with CFTR modulators, azithromycin or acebilustat. Ivacaftor/lumacaftor treated CF PMNs resulted in a significant reduction (p < 0.05) in *Aspergillus*-induced ROS compared to control group. For CF PBMC, *Aspergillus*-induced ROS was significant reduction compared to control subject PBMC (p < 0.05). Azithromycin and acebilustat had no effect on ROS production by CF or control subject phagocytes. CFTR modulators may impact on *Aspergillus*-induced inflammation in CF. It is still not clear the exact mechanism of action (<u>Poore ST et al, 2023</u>).

Generally several distinct clinical phenotypes are observed in CF (King J et al, 2016):

- 1. Aspergillus can persist without respiratory decline (Aspergillus colonization);
- 2. Aspergillus may develop a localized infection, associated to mucosal inflammation and worsening respiratory disease without allergic responses (Aspergillus bronchitis);
- 3. Aspergillus may trigger an IgE-mediated hypersensitivity response either with or without respiratory exacerbation, airway inflammation, and the development of bronchiectasis and fibrosis (Aspergillus sensitization and ABPA respectively).

Allergic Broncho-Pulmonary Aspergillosis (ABPA) is the result of a Th2-mediated hypersensitivity response to colonisation with the fungus AF (Janahi IA et al. 2017). ABPA usually occurs in susceptible individuals suffering from bronchial asthma and in people with CF and is generally associated with an accelerated decline in lung function. Comparable ABPA prevalences in paediatric and adult CF patients range from 1 up to 20%, although huge variations are observed between countries. Prevalence of ABPA in children with CF and the potential predisposing factors to Aspergillus infection (AI) and ABPA (<u>Walicka-Serzysko K et al. 2015</u>) have been evaluated in a care CF centre.

ABPA manifests clinically with respiratory exacerbations, especially wheeze, positive antibodies against Aspergillus and characteristic radiological abnormalities. Since the clinical features of this condition overlap significantly with that of CF, ABPA remains underdiagnosed in a lot of patients. Diagnosis of ABPA in CF patients should be sought in those with evidence of clinical and radiologic deterioration that is not attributable to another etiology, a markedly elevated total serum IgE level (while off-steroid therapy) and evidence of AF sensitization.

A consensus statement for diagnosis and management of ABPA in current practice is still debating, thus accounting for the ongoing variation in reported prevalence.

In a recent review, immunopathogenesis, clinical features, diagnosis, and current treatment modalities have been summarized based on published data in the pediatric and more less in the adult age including asthmatic patients (<u>Sunman B et al. 2020</u>).

The use of multiple recombinant antigens may improve the diagnostic accuracy in CF complicated with ABPA or AB. Asp f1 reactivity may relate to the presence of actively growing Aspergillus spp., which might be a useful marker for guiding antifungal therapy in ABPA (<u>Alghamdi Ns et al. 2019</u>).

In the past several Authors (Aqarwal R et al. 2015) have been evaluated the performance of serum galactomannan (GM) in patients



with ABPA as a diagnostic criteria. The results of this study suggested that serum GM estimation has a limited role in the diagnostic workup of patients with ABPA. New commercially available tools (<u>Barrera C et al. 2016</u>) might accelerate diagnosis of ABPA in patients with CF. A recent papers reviews biomarkers that can be included in diagnostic criteria and novel research biomarkers that may be used in the diagnosis and treatment follow-up of ABPA in CF (<u>Steels S et al. 2023</u>).

It is still debated what is the ideal antifungal therapy for ABPA and other fungi. High doses of corticosteroids as oral prednisolone are suggested as the treatment of choice for ABPA (<u>Smith AR et al., 2014</u>). However, their long-term benefits are unclear, while their side effects are well documented.

More data are in favour of treatment with antifungal therapy.

In general a diagnosis of ABPA should be considered for people with CF who are symptomatic and not responding to antibiotic therapy (<u>Burgel PR et al. 2024</u>). *Aspergillus* bronchitis, *Aspergillus* sensitization, allergic bronchopulmonary aspergillosis (ABPA), and rarely, aspergilloma represent disease variability. Diagnostic criteria exist for ABPA (<u>Tracy MC and Boss RB, 2018</u>). Mycological diagnosis, including a *Scedosporium*-selective culture medium, are recommended for detection of fungi in CF, fungal culture of sputum or BAL fluid should be considered in cases of clinical deterioration. When present ABPA is characterised by cough, wheezing, chest X-ray or CT changes and increased sputum production. Diagnosis of ABPA relies on elevated total IgE (usually greater than 1000 IU/mL) and also includes allergy skin testing, detection of Aspergillus-specific serum IgE and IgG antibodies, and CT scan. Annual total serum IgE screening is recommended to monitor baseline levels. ABPA is treated with oral corticosteroids with or without antifungal therapy, as there is no established evidence for the use of antifungal therapy. Triazoles interact with CFTR modulator therapy, requiring dose adjustment of the modulator. There is an increasing evidence base to support the use of anti-IgE therapy (omalizumab and other biologics) to treat ABPA in CF and reduce steroid use (<u>Burgel PR et al. 2024</u>).

Issues

- 1. To assess the optimal type, duration and dose of antifungal therapy;
- 2. to test the hypotheses whether antifungal therapy:
- may improve clinical status compared to placebo or standard therapy;
- is devoid of any unacceptable adverse effect;
- maay reduce corticosteroids treatment choice.

What is known

1 CDSR (<u>Francis NZ, 2022</u>) on antifungal therapies for ABPA in people with CF concluded that at present, there are no randomised controlled trials that evaluate the use of antifungal therapies for the treatment of ABPA in people with CF, although one trial is currently ongoing which could be eligible for a future update. These conclusions were already judged in a previous CDSR (<u>Elphick HE et al, 2016</u>) that was performed with the aim to compare antifungal treatments to either placebo or no treatment.

2 CDSRs (Jat Kana R. 2021)(Jat Kana R et al. 2018) investigated anti-IgE therapy compared to placebo or other therapies for ABPA in CF people with CF. ABPA was diagnosed using the Rosenberg-Patterson criteria, Nelson's criteria, Greenberger's criteria or the Cystic Fibrosis Foundation Consensus Criteria. All doses of anti-IgE therapy in this review and no limit of age or disease severity for participants were included. Only 1 double?blind study including 14 pts was eligible for inclusion in the review comparing a daily dose of 600 mg omalizumab or placebo along with twice daily itraconazole and oral corticosteroids, with a maximum daily dose of 400 mg. Treatment lasted 6 months but the study was terminated prematurely due to the inability to recruit participants into the study despite all reasonable attempts; complete data were not available. One or more serious side effects were encountered in six out of nine (66.67%) and one out of five (20%) participants in omalizumab group and placebo group respectively. In conclusion there is lack of evidence for the efficacy and safety of anti?IgE (omalizumab) therapy in CF people with ABPA. There is a need for large prospective randomized controlled studies in this field.

Azoles compounds have been proposed as an alternative treatment to corticosteroids for ABPA, as they are endowed with activity against AF. Itraconazole is the most active one, whereas a few data are available on the efficacy of voriconazole. Posaconazole has been recently proposed for AF treatment in CF. Amphotericin B has been employed in aerosolized form to treat invasive infection with A fumigatus. A recent review summarizes evidence of pharmacokinetic /pharmacodynamic, tolerability, and efficacy studies of drugs, including corticosteroids, amphotericin B, azole antifungals (isavuconazole, itraconazole, posaconazole, and voriconazole), and a monoclonal antibody omalizumab in the treatment of ABPA (Epps QJ et al. 2020).

In a a retrospective analysis of 32 patients Aspergillus-specific IgE was evaluated as an outcome for the use of tiazoles. Main results showed that there was a significant reduction in Aspergillus IgE with posaconazole but not with other triazoles (P?=?0.026). Aspergillus IgE levels were inversely correlated with the therapeutic drug level of posaconazole, suggesting that posaconazole is better than comparator azoles at decreasing serological response to Aspergillus and that this response was better with therapeutic levels of posaconazole (PeriseIneris J et al. 2019)

Previously (<u>Nové-Josserand R et al. 2017</u>) 32 cases (11 children and 21 adults) from a retrospective multicenter observational French study were evaluated in the context of ABPA. One year of omalizumab therapy did not show any significant difference regarding lung function, BMI, or the number of patients receiving oral corticosteroids. Five patients were able to discontinue corticosteroids during follow-up and nine patients were able to reduce their daily dose.

A DARE review on the effects of antifungal agents in ABPA (Moreira AS et al. 2014) evaluated thirty-eight studies - four randomized



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controlled trials and 34 observational studies. The antifungal interventions described were itraconazole, voriconazole, posaconazole, ketoconazole, natamycin, nystatin and amphotericin B. An improvement in symptoms, frequency of exacerbations and lung function was reported in most of the studies and was more common with oral azoles. Antifungals also had a positive impact on biomarkers and radiological pulmonary infiltrates, but adverse effects were also common. However, the quality of the evidence supporting these results was low or very low due to a shortage of controlled studies, heterogeneity between studies and potential bias.

Clinical trials

A retrospective study (Lehman S, 2014) of six patients with CF and ABPA treated with omalizumab within an observation period of 7.5 years showed that Omalizumab has the potential to be an additional and solitary treatment option in patients with CF and ABPA. Early onset treatment may be beneficial and patients with early stage of lung disease seem to benefit more.

In a review study (<u>Tanou K. 2014</u>) including eight case reports, 13 children with CF and ABPA received anti-IgE therapy resulting in improved FEV1, fewer respiratory symptoms and decreased corticosteroid use.

An open-label phase I observational trial showed that daily Vitamin D3 supplementation over a 24-week period was associated with reduced *Aspergillus* induced IL-13 responses from periphera, CD4+ T cells and *Aspergillus*-specific IgE levels, as well as increased serum vitamin D levels (<u>Nguyen NL et al. 2015</u>).

In a small population of 6 CF patients omalizumab treatment decreased IgE levels, and improved respiratory symptoms, suggesting that omalizumab may be an alternative therapy for ABPA in CF patients who fail to respond to systemic corticosteroids or have serious adverse effects (<u>Emiralioglu N. 2016</u>).

A multicenter RCT study (<u>NCT00787917</u>) regarding the efficacy of Omalizumab (subcutaneous injections of maximum 600mg daily dose) in severe ABPA versus conventional therapy as itraconazole (twice daily with a maximum daily dose of 400 mg) and oral corticosteroids has been terminated prematurely for side effects and difficulty to enroll patients. No published results are available.

Recently a prospective cohort study (Lanfranchi C et al. 2025) including 16 pwCF who initiated ETI therapy and had received antifungal treatment in the preceding five years due to ABPA group or 47 AF-related clinical manifestations (AF group) to evaluate the effects of modulators on changes from baseline to 12 months in spirometry measures and lung clearance index (LCI_{2.5}), as well as respiratory colonization by AF, compared to 45 controls with no prior respiratory cultures positive for AF. Annual fold changes in the geometric mean of immunological markers were estimated using generalized estimating equations with a piecewise linear spline model, fitted to data collected from three years before to one-year post-ETI. Spirometry and LCI_{2.5} improvements were comparable across groups. Positive respiratory cultures decreased from 43.8 to 18.8% in the ABPA group (p = 0.30), and from 78.7 to 23.4% in the AF group (p < 0.001). Total IgE and IgG anti-AF decreased in both the ABPA and the AF groups, with annual reductions of 20-42%. No ABPA episodes occurred during ETI therapy. Main results show that during ETI therapy, pulmonary outcomes improved, AF colonization and sensitization decreased, and no episodes of ABPA were observed in pwCF with a clinical history of AF infection.

Unresolved questions

The review on antifungal therapy of ABPA did not find any completed RCT on this topic.

Screening for early detection of Aspergillus colonization in the annual assessment of CF patients who are over 6 years old is suggested. Due to the small sample size and retrospective design of available studies, the identification of risk factors of ABPA in CF requires further prospective studies.

While data are already available from studies regarding people with ABPA but without CF, diagnosis of ABPA is quite difficult in CF, as many of their findings overlap with common manifestations of the lung disease. No RCT data support the evidence of patients responsiveness to corticosteroid therapy on disease evolution. An improvement in symptoms associated to decrease of exacerbations, and increase of lung function has been reported in more studies and was more common with oral azoles. Antifungals also had a positive impact on biomarkers and radiological pulmonary infiltrates, but adverse effects were also common.

Data supporting the use of Omalizumab are still inconclusive, however its indication is only for selected cases. The quality of evidence supporting these results was low or very low due to a shortage of controlled studies, heterogeneity between studies, and potential bias. The recommendation for their use is weak and clinicians should therefore weigh up desirable and undesirable effects on a case-by-case basis. More studies with a better methodology are needed to increase confidence in the effects of antifungal treatments in ABPA.

The last CDSR review concluded that there is a need for large prospective randomized controlled studies of anti-IgE therapy in people with CF and ABPA with both clinical and laboratory outcome measures such as steroid requirement, number of allergic bronchopulmonary aspergillosis exacerbations and lung function profile.

The era of HEMT could impact also on this severe comorbidity modulating inflammatory response.

Keywords

Allergic Bronchopulmonary Aspergillosis -ABPA-; Aspergillus;