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Cystic Fibrosis: Frequently Asked Questions

Question 11: How should Allergic Bronchopulmonary Aspergillosis [ABPA] be managed in Cystic Fibrosis?

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Aspergillus fumigatus is a ubiquitous, filamentous and spore-bearing fungus which usually grows at 37 degrees Celsius. It can be an opportunistic pathogen and can induce an inflammatory response in the airways through the production of various toxic and allergenic exoproducts. As a consequence, the clinical presentation may take a number of forms: Allergic bronchopulmonary aspergillosis (ABPA), aspergillus bronchitis, invasive pulmonary aspergillosis and an aspergilloma. ABPA occurs almost exclusively in asthma or cystic fibrosis (CF) patients [1].

ABPA is a T-helper cell (Th2) type-2 mediated hypersensitivity reaction to the presence of Aspergillus fumigatus [2]. Clinically, it is characterized by pulmonary infiltrates with impaired mucociliary clearance leading to mucoid impaction and airway obstruction. In CF lungs, the presentation can vary from simple colonisation which does not need treatment, to ABPA, which can be a cause of an acute deterioration in pulmonary function.

A positive Aspergillus fumigatus culture from sputum does not necessarily correlate with ABPA as various Aspergillus species are frequently isolated from CF patients (reported range of 30 – 57%) [2]. Only a fraction of these individuals develop ABPA [3]. The prevalence of ABPA in CF ranges from 2% – 15% [4]. The clinical impact of Aspergillus sensitization on disease progression is not clearly understood. However, studies have shown that there is an association between poor lung function and aspergillus sensitization [5,6]. Therefore, a high level of clinical suspicion is necessary for the early recognition and treatment of ABPA to prevent the potential contribution to progressive lung damage.

CLINICAL SIGNS AND SYMPTOMS OF ABPA

Patients may be initially asymptomatic or minimally symptomatic with everyday subtle symptoms consistent with established CF lung disease such as slight cough, increased sputum and exercise related dyspnoea. Alternatively, the onset may be more obvious, and rarely fulminant [7]. Suspicion should be raised if there is no clinical response to conventional nebulised or intravenous antibiotic therapy. Symptoms may include increased wheezing, fever, malaise and thick sputum with brown or black bronchial casts.

DIAGNOSIS OF ABPA

The diagnosis of ABPA is based on the presence of a combination of clinical, laboratory, and radiological findings (Figure 1) [8]. In the context of CF, the diagnosis can be difficult as most of the diagnostic criteria can be positive in the absence of ABPA. The Cystic Fibrosis Foundation Consensus Conference has established diagnostic and screening criteria for ABPA (Table 1) [7,8]. Staging of ABPA is not often applied in CF with ABPA, although a staging system has been used for patients with asthma and ABPA [8].

CURRENT THERAPEUTIC OPTIONS

Successful management of ABPA requires an early diagnosis and prompt intervention. There are three important therapeutic considerations: Treatment of ABPA, treatment of the underlying CF lung disease and environmental control.

Systemic corticosteroids

The current mainstay of treatment of ABPA is with systemic corticosteroids. Expert opinions recommend the use of systemic

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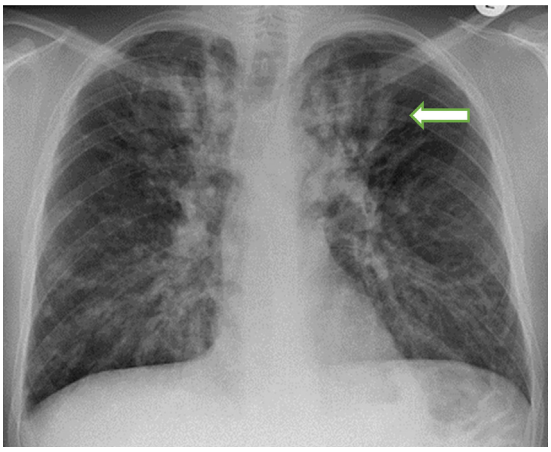

Figure 1. Chest radiograph of a CF patient with ABPA. The image demonstrates bilateral bronchiectasis and mucoid impaction with classic finger-in-glove opacities [arrow].

corticosteroids for all exacerbations of ABPA in CF unless there is a contraindication (e.g. pre-existing osteoporosis or worsening of diabetes) [8]. Recent guidelines have suggested oral prednisolone as the treatment of choice for ABPA [9].

Systemic corticosteroids reduce the inflammatory response triggered by Aspergillus. Various dosage regimens have been proposed. Some further guidance may be found with treatment regimens for ABPA complicating asthma in adults, where a "medium dose" approach beginning at 0.5 mg/kg of prednisone was compared with a "high dose" strategy beginning with 0.75 mg/kg and showed equivalent outcomes at 2 years in terms of ABPA exacerbations and corticosteroid dependency at 1 and 2 years [10]. Currently, no consensus exists regarding the precise doses of systemic corticosteroids and suggested treatment regimens differ among countries [8,11].

Initial daily dosages of 1–2 mg/kg prednisolone for 2 weeks have been shown to be adequate followed by weaning over two to three months guided by clinical response, spirometry, radiology and total IgE levels. In children, where the growth implications of systemic corticosteroids are important and treatment adherence may falter for a myriad of reasons in busy families.

We suggest the following treatment regime for consideration:

Weeks 0-2:	Prednisolone 1 mg/kg daily (Maximum daily dose 50 mg)
Weeks 2-4:	Prednisolone 0.5 mg/kg daily
Weeks 4-6:	Prednisolone 0.5 mg/kg 3 times weekly [Monday, Wednesday, Friday]
Weeks 6-8:	Prednisolone 0.25 mg/kg 3 times weekly [Monday, Wednesday, Friday]
Weeks 8-10:	Prednisolone 0.1 mg/kg 3 times weekly [Monday, Wednesday, Friday].

Table 1
Recommendations of US Cystic Fibrosis Foundation for the diagnosis and screening of allergic bronchopulmonary aspergillosis. (Adapted from reference [8]).

Classical diagnostic criteria
Acute or subacute clinical deterioration
Immediate cutaneous reactivity to Aspergillus species > 3 mm or positive RAST
Elevated total serum IgE (> 1000 IU/ml)
Positive A. fumigatus precipitins or presence of anti-A. fumigatus IgG
New or recent changes on chest X-ray or CT
Guidelines for annual screening
Maintain high level of a clinical suspicion
Measure total serum IgE annually
If Serum IgE > 500 IU/ml, perform immediate skin test or RAST

A resolution of symptoms, return of respiratory function to previous levels, resolution of chest radiograph (CXR) changes and a fall of total IgE is indicative of remission [Figure 1]. A 30–50% reduction of total IgE level is expected after commencement of therapy [12]. Recurrence is common within 2-3 years of the first episode, and often high doses of steroids are needed for a prolonged period. The CXR should be repeated as steroids are weaned to exclude evidence of relapse. Monitoring of serum total IgE levels is a useful parameter of disease response with steroid therapy.

Corticosteroids are not without substantial toxicity. This is especially true for CF patients who are already predisposed to diabetes, bone demineralization, growth failure and increased risk of non-tuberculous mycobacterial infection [13]. Therefore, it is important to monitor and treat the adverse effects [Table 2].

Antifungal agents

Antifungal therapy has been used as an adjunct in the treatment of ABPA to prevent exacerbations. It decreases the burden of fungal organisms and antigenic stimulation [14].

It is often commenced with steroids and continued for a minimum of 6 weeks, and possibly for the duration of the steroid course. A recent Cochrane review concluded that there were no randomized controlled trials to evaluate the use of antifungal therapies for the treatment of ABPA in CF [15]. However, itraconazole add-on therapy has been reported to be clinically beneficial in several uncontrolled studies of ABPA in CF patients [1]. It was suggested that it could improve the clinical outcome and can be used as a steroid sparing agent [8].

The Cystic Fibrosis Foundation Consensus Conference on ABPA in patients with CF recommended that itraconazole should be added to oral steroids in patients with slow or poor response to oral steroids, relapse of ABPA, steroid toxicity or steroid-dependence [1,8]. The recommended dosage and frequency ranged considerably in published reports [11,16]. However, in general, 200–400 mg of itraconazole can be given daily in 1 or 2 divided doses for 1–2 weeks and then gradually tapered over several months. The duration of therapy varies, but may be of the order of 3–6 months.

The starting dose for itraconazole is 5 mg/kg/day to a maximum of 400 mg/day. It is usually given once daily if dose is < 200 mg/day. If the once daily dose exceeds 200 mg/day, a twice daily regimen should be followed [11]. There is evidence that oral itraconazole is poorly absorbed by CF children. Suspension seems to be more effective than capsules and it should be taken on an empty stomach with an acidic drink [17]. Serum itraconazole trough (pre-dose) level should be measured on 7 to 10 days from starting therapy. The trough level is usually aimed at 500 to 1000 microgram/L. However, the association between serum levels and clinical outcome is not clearly defined [11].

Table 2
Suggested patient monitoring while on and after corticosteroid treatment

1. Total serum IgE levels at every 3 to 6 months for 1 year.
2. Chest radiograph even in an asymptomatic patient if IgE level doubles [12].
3. Spirometry should be obtained at least 3 to 6 monthly. An unexpected decline of 15% in functional vital capacity (FVC) might be an indication of ABPA exacerbation [8].
4. Side effects of prolonged corticosteroid therapy including adrenal suppression. A short synathen test for suspected adrenal insufficiency may be required.
5. Explore the possibility of mould exposure in the patient's environment, especially for refractory cases [8].