Summary

Background: Allergic bronchopulmonary aspergillosis (ABPA) is a complex condition that affects people with asthma and cystic fibrosis (CF). It results from exposure to the fungus Aspergillus fumigatus, which leads to worsening airway inflammation and progressive damage to the lungs. The aim of this review is to outline the pathogenesis of the disorder, diagnostic criteria and to discuss the use of anti-fungal agents in its treatment.

Methods: The Cochrane library of systematic reviews and the Cochrane database of controlled trials were searched for controlled trials on ABPA and its treatment in both asthma and CF. In addition, articles included within the reviews were examined separately, and a separate search carried out using Medline.

Results: A systematic review for the use of azole anti-fungal agents in ABPA was identified for their use in both CF and non-CF-related disease. The review of ABPA alone identified two randomized-controlled trials of itraconazole in chronic disease. These trials demonstrated improvements in symptoms and immune activation, but were short-term trials and failed to show a significant change in lung function. No trials were identified in CF.

Conclusions: The use of anti-fungal agents in ABPA seems to be a rational one, with short-term efficacy demonstrated for the use of itraconazole. Further investigations are required to identify individuals who will benefit most from treatment and to establish the correct dose and means of delivering treatment in ABPA. Longer-term studies are required to demonstrate that treatment modifies the progressive decline in lung function seen with the disease.

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Introduction

Aspergillus fumigatus (Af) is a spore-forming saprophytic fungus that is ubiquitous to the environment. It is responsible for a range of pulmonary diseases. These include severe life-threatening pneumonia in immunosuppressed people, subacute infections, such as the formation of aspergilloma in pulmonary cavities (a form of extrinsic allergic alveolitis) and hypersensitivity diseases. People with asthma or cystic fibrosis (CF) may become sensitized to Af after inhalation of spores. Once sensitized, this results in a type I, IgE-mediated reaction and a spectrum of clinical responses. These range from acute exacerbations of asthma to a more sustained and intense inflammatory response (demonstrating features of both type I and type III hypersensitivity), and leads to allergic bronchopulmonary aspergillosis (ABPA). 2

ABPA is a complex condition that was first described in the UK in 1952. 3 It has been estimated to occur in 1–2% of chronic asthmatics 4 and 2–15% of people with CF. 5 This review will focus on the pathogenesis of ABPA, with particular emphasis on the potential pathogenic role of Af and the rationale for the use of antifungal treatment. Secondly, I will review the evidence for the use of azole antifungal agents in the treatment of ABPA.

Immunopathogenesis of ABPA

Af is an effective pathogen in humans because intrinsic qualities of the organism have evolved, which enhance its ability to infect the lungs and cause disease. The spores of Af are 2–5 μm in size, with a hydrophobic coat that allows them to be inspired into the lungs. 6 Once respired, the conidia of Af are able to bind to surfactant molecules in the distal airway lumen, 7 as well as complement (C3) 8 and fibrinogen. 9 The conidia germinate within the airways and form hyphae; the mature organisms are capable of releasing allergens, virulence factors and proteases. 10–13 These factors contribute to (1) impaired mucociliary clearance; (2) impaired action of fungicidal proteins and complement in the airway lining fluid; (3) inhibition of phagocytosis and the killing capacity of phagocytic cells (macrophages and neutrophils). It is of particular relevance to asthma and the treatment of ABPA that neutrophil killing of Af is suppressed by corticosteroids. 14

As the organism is ubiquitous in the environment, sensitized individuals are likely to inhale spores regularly, and this will always represent a fresh source of antigenic stimulus. However, Af is unique, as an aeroallergen, and inhalation alone is insufficient to lead to ABPA. Persistence of viable Af within the airways seems to be an important factor in determining the development of ABPA. Viable Af has been found growing on and between bronchial epithelial cells, despite an intense inflammatory cell infiltrate, 15 whereas Af proteases lead to the release of pro-inflammatory mediators from epithelial cells. 13,16 These proteases also have the ability to detach epithelial cells from their basement membrane, 13 inevitably leading to a loss of epithelial integrity. Although other proteases, such as those derived from house dust mite allergen have been found to similarly detach epithelial cells, 17 the proteases released by Af are particularly potent, even with few organisms present. 18

This loss of epithelial integrity may lead to exposure of the underlying matrix, to which Af can also adhere, 19 with important implications to direct damage of the airways and the development of bronchiectasis. This intense recruitment of inflammatory cells to the airway lumen, and the development of progressive airway wall damage, is in keeping with airway inflammation found in patients with ABPA and the development of bronchiectasis. 20

In addition to the direct effect Af has on the airway epithelium, it seems to be able to elicit a powerful TH2-immune response. The presence of Af infection in mice induces a Th2-lymphocyte response. 21,22 The extracts from Af, when co-cultured with B cells, elicit the release of IgE 23 and people with ABPA develop a specific Th2 CD4+ in response to exposure. 24

Clearly, only a minority of people with asthma or CF develop ABPA. A genetic predisposition is suggested by reports of a familial occurrence of ABPA. 25,26 In the case of CF, the presence of atopy seems to be important, suggesting that an allergic-type response to the pathogen impairs the ability to clear it, whereas the pre-existing airway inflammation and impaired mucociliary clearance may provide a favourable environment for Af to exist. In the case of patients with asthma and ABPA, two small studies have shown a higher carriage rate of at least one mutation of the CF transmembrane regulator (CFTR) gene in people with ABPA, compared with people with positive skin tests to Af and with asthma alone. 27,28 The alleles HLA-DR2 and DR5 have been linked to severity of disease in ABPA. 24,29 Most recently, a polymorphism of surfactant proteins has been shown to be associated with increased serum IgE and blood eosinophilia in patients with ABPA. 30 These findings suggest there may be a link between ABPA and an inability to
clear the organism effectively in a group whose immune response is likely to be one of hypersensitivity.

In summary, we have seen the development of a model for the pathogenesis of ABPA in recent years, in which the susceptible individual acquires Af in their lungs where it is able to germinate and persist. Consequently, it attaches to the epithelial cells, resulting in release of pro-inflammatory mediators and an influx of granulocytes. Viable Af releases proteases, which damage the epithelial layer. These exacerbate inflammation and expose the immune system to Af-associated allergens, which elicit an intense Th2-type immune response. A combination of these components is likely to account for the development of progressive fibrosis and bronchiectasis. Although traditional treatment has focused on suppressing the immune reaction to these phenomena, with high-dose corticosteroids, the presence of viable organisms driving this process makes the option of antifungal chemotherapy an attractive adjunct.

Diagnosis and clinical course of the disease

The criteria for diagnosis were standardized in 1977 by Patterson et al. They require the patient to fulfill the following criteria: (1) a pre-existing diagnosis of asthma (or CF); (2) immediate-type skin reactivity to Af; and (3) peripheral blood eosinophilia, precipitating antibodies to Af antigen, elevated serum IgE, elevated serum IgE and IgG antibodies against Af (at least during exacerbations or in the absence of treatment). Radiological evidence of proximal bronchiectasis is a frequent accompaniment of ABPA, but is not now felt to be a prerequisite for diagnosis. However, the presence of bronchiectasis along with skin-test reactivity and eosinophilia is quite specific for ABPA.

The disease has been subdivided into five stages. Stage one is the initial acute presentation, with eosinophilia, immediate-type skin reactivity to Af, total serum IgE greater than 2500 ng/ml and pulmonary infiltrates on a chest radiograph. Stage two is the disease in remission, where there is persistent immediate-type skin reactivity and precipitating antibodies to Af antigens. In stage three, symptoms exacerbate, with all the characteristics of stage one, a two-fold rise in serum IgE and new pulmonary infiltrates. Stage four patients have asthma, and control of symptoms is dependent on chronic use of high-dose corticosteroids. In stage five, chronic disease has progressed to predominately fixed airflow obstruction, with extensive bronchiectasis and fibrosis.

There may be a wide spectrum of disease activity in ABPA, and diagnosis is made more easily in those with severe disease; however, diagnosis and treatment of people with mild disease may prevent progressive disease. In milder disease, a high index of suspicion is required, with the criteria fulfilled only during an exacerbation or when off parenteral corticosteroids.

Skin-prick testing is a useful screening test to identify people with potential ABPA. It is highly sensitive but not specific. Consequently, a negative skin-prick test to Af can rule out ABPA, whereas a positive test warrants further investigation, particularly in the case of asthmatic people with frequent exacerbations or corticosteroid dependence. Patients with a positive skin test should be evaluated with serology, including measurement of total serum IgE, specific IgG and IgE antibodies to Af and precipitins. The presence of peripheral blood eosinophilia and cultures of Af from sputum is not mandatory but is corroborative. Patients with an IgE of over 1000 ng/ml (400 IU/ml) and positive IgE Af and IgG Af are likely to have ABPA, and warrant further investigation with a high resolution computed tomography of the chest to determine the presence of bronchiectasis. Patients with central bronchiectasis then are classed as ABPA-CB (ABPA with central bronchiectasis), those without, ABPA-S (ABPA serology). Those who do not have immunological evidence of ABPA when tested will need to be reviewed.

Practice points

Diagnosis in classic ABPA
- Immediate skin-prick test positive to Af.
- Total serum IgE greater than 1000 ng/ml (400 IU/ml).
- Serum-specific IgG and IgE antibodies to Af (or positive precipitins).
- Presence of bronchiectasis
  - Yes, ABPA-CB.
  - No, ABPA-S.

Diagnosis in CF is more difficult, and is complicated by the presence of a disorder that independently leads to bronchiectasis and fibrosis. These criteria have recently been reviewed and standardized by a consensus conference. The consensus statement suggests the diagnosis be made in the presence of (1) an acute or subacute deterioration in clinical symptoms (cough, wheeze, exercise
capacity, change in pulmonary function or increase in sputum) not attributable to another cause; (2) a total serum IgE greater than 400 IU/ml; and (3) immediate skin-test reactivity to \( A f \) along with one of the following: precipitins to \( A f \) or specific IgG to \( A f \), new or recent infiltrates, mucus plugging or proximal bronchiectasis on either chest radiograph or computed tomography. A multiple-regression analysis of over 14,000 individuals with CF determined that wheezing, a diagnosis of bronchial asthma and colonization with \( P. \) Aeruginosa, were independent risk factors for ABPA. As is the case with asthma, the development of ABPA in someone with CF heralds a more complicated clinical course and is associated with more bacterial colonization, lower lung function and an increase in pulmonary complications.

**Practice points**

**Diagnosis in CF**
- Acute or subacute deterioration in respiratory symptoms or lung function.
- Total serum IgE greater than 400 IU/ml.
- Skin-prick test positive to \( A f \), together with either
  - Positive Aspergillus precipitins
  - Radiographic features consistent with ABPA.

**Management of ABPA with azole antifungal agents**

Up until recently, corticosteroids have been the cornerstone for management of ABPA, and a more detailed review of their use is provided elsewhere. Prednisolone is highly effective in treating acute exacerbations of disease, but patients require relatively high doses to suppress acute exacerbations, and it is unclear how much they prevent the progression of lung disease. The considerable side-effects of long-term corticosteroids make alternative therapies worthwhile investigating.

The currently available antifungal agents with known efficacy against \( A f \) are amphotericin B and the azoles (ketoconazole, itraconazole and voriconazole). Treatment of Aspergillus infection with amphotericin is effective, and has even been used as a nebulized preparation for chemoprophylaxis in at-risk immunosuppressed people. However, its use has been limited by its toxicity and cost. Azoles are effective, easy to administer and have favourable side-effect and cost profiles. They inhibit ergosterol synthesis in the fungal cell membrane, and thereby inhibit fungal growth.

**Ketoconazole**

Shale et al. studied 10 patients with mild, stable ABPA who were on maintenance-inhaled corticosteroids, and reported that ketoconazole significantly reduced specific IgG antibody to \( A f \), total IgE and \( A f \)-specific IgE after 12 months \( (P < 0.05) \). There was also a significant improvement in symptom scores, which correlated with the change in the IgG levels, but no significant changes in lung function. In contrast to these findings, Fournier et al. previously failed to show a benefit from ketoconazole 400 mg daily in nine uncontrolled cases, all of which were also on 10–15 mg of prednisone daily.

Long-term ketoconazole use would, however, be complicated by its side-effects. It is a rare cause of severe hepatic disease (1 in 10,000) and, in a dose-dependent manner, it is associated with sexual dysfunction inhibition of testosterone and adrenocortical function.

**Itraconazole in ABPA**

Itraconazole has fewer side-effects and a wider spectrum of activity than ketoconazole. The main side-effects are dose-related nausea and vomiting. Itraconazole is effective for invasive aspergillosis, and the outcome for pulmonary disease is better than for other sites. Several retrospective trials or case series have looked at the use of itraconazole in ABPA or have included patients with ABPA and other forms of aspergillus-related pulmonary disease (Table 1). All but two of these studies have been uncontrolled, and most have had small numbers. Despite this, they have consistently shown positive results.

A systematic review assessing the evidence for the use of azoles in ABPA without CF has been carried out. The review identified only two randomized-controlled trials. The RCT by Stevens et al. was a parallel, randomized, double-blind, placebo-controlled trial of itraconazole 200 mg twice daily for 16 weeks. Inclusion criteria were an FEV1/FVC ratio of less than 0.7, immediate skin test positive to Aspergillus, an elevated total serum IgE, IgG antibodies to Aspergillus, a history of pulmonary infiltrates and dependence on oral corticosteroids. Participants
with CF were not excluded, although none were recruited. The study recruited 55 participants from 13 centres on at least 10 mg of prednisone daily, and randomized them to itraconazole or placebo. The itraconazole arm received 200 mg twice daily initially for 16 weeks. Steroid reduction was attempted. The study was then unblinded, and all received 200 mg daily for a further 16 weeks. In the treatment group, 46% of participants achieved an improvement in one of the following outcome parameters: a 50% or more reduction in oral corticosteroid dose, a 25% or greater fall in IgE, or a 25% increase in pulmonary function tests (FEV1, FVC, diffusion of carbon dioxide across the lung [DLCO], FEF and peak flow) or exercise tolerance. Only 19% of the placebo group met one of these criteria for improvement (Fisher’s exact test: \( P = 0.04 \)). Although the difference between the groups was significant in terms of overall response, it failed to reach statistical significance for each of these outcomes when examined separately. Adverse events were similar in both groups. Quality-of-life scores were not significantly different.

Wark et al.\(^{46}\) conducted a parallel-group, randomized, double-blind, placebo-controlled trial of itraconazole 400 mg daily for 16 weeks with 29 participants. Inclusion criteria were as follows: asthma with evidence of variable airflow obstruction, immediate skin sensitivity to \( Af \), positive serum IgE and IgG antibodies to \( Af \), a serum total IgE of over 1000 ng/ml. The primary outcomes were markers of airway inflammation measured using induced sputum. Participants who received itraconazole had a 35% reduction (95% CI 20–48% reduction) in sputum eosinophils, which was sustained throughout the trial, whereas the placebo arm showed no change (the 95% CI included a 19% fall and a 12% increase). There was a similar fall in sputum eosinophil cationic protein, a marker of eosinophil degranulation and airway inflammation. The itraconazole group showed a 42% fall (95% CI 19, 58% reduction), the placebo group had a 23% fall (the 95% CI included a 66% fall and a 30% increase). There was a similar fall in systemic immune activation. Participants taking itraconazole had a median fall in serum IgE of 310 IU/ml compared with a rise in the placebo group of 18 IU/ml (\( P = 0.001 \)). These data from the two trials were pooled and analysed.\(^{47}\) The proportion of participants with a decline in serum IgE of at least 25% was significantly greater with itraconazole than with placebo (odds ratio 3.26 [1.30 to 8.15]) (Fig. 1).\(^{47}\) Wark et al.\(^{46}\) also showed that participants taking itraconazole had less exacerbations of their chest disease requiring the use of oral corticosteroids during the period of the trial, with a mean number of exacerbations per participants of 0.4 (standard deviation [SD] 0.5) compared with placebo 1.3 (SD 1.2); \( P = 0.03 \). They did not demonstrate any statistically significant change in lung function, although the itraconazole arm recorded an increase

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### Table 1 The use of itraconazole in the treatment of ABPA.

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<tr>
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*Results: I=improvement (\( P<0.05 \)) in \( Af \) serology and immunology tests; P=improvement (\( P<0.05 \)) in pulmonary function tests; S=improvement (\( P<0.05 \)) in symptoms.

\(^1\)Includes people with cystic fibrosis.
in FEV₁ of 7.9% and the placebo arm a fall of 1.9% (P = 0.5). The proportion who had an increase in FEV₁ of 25% or more was pooled with data from Stevens et al.⁴⁵ for participants who had an improvement in lung-function parameters.⁴⁷ Participants taking itraconazole did not show an improvement in lung function (OR 2.15 [0.85 – 5.46]) (Fig. 2).

One participant withdrew from the trial by Wark et al.⁴⁶ because of nausea related to itraconazole use, but there were no other serious adverse events.

The evidence from these two trials demonstrates that itraconazole reduces the inflammation associated with ABPA and improves clinical outcomes over 16 weeks. As both the intensity of the inflammatory response and acute exacerbations of the disease are felt to lead to progressive lung disease, the ability of itraconazole to modify both of these factors in the short term may have important implications for the chronic management of the disease.

Itraconazole in treatment of ABPA in patients with cystic fibrosis

Neither randomized trials of itraconazole included participants with CF. Three case series have been published,⁴⁸–⁵⁰ which have included participants with CF (n = 18). All demonstrated small improvements in lung function, symptoms or a reduction in corticosteroid usage (Table 1). Skov et al.⁵¹ reported a patient with CF who developed Cushing’s syndrome while using inhaled corticosteroids and itraconazole. They then went on to show that, in participants with CF, co-existent use of inhaled budesonide and itraconazole led to suppression of adrenal glucocorticoid synthesis in 11 out of 25 participants. This is potentially an important adverse event, and its occurrence should be considered when planning future trials in all people with ABPA.

Practice point

Treatment with itraconazole

- Itraconazole therapy reduces immune activation in ABPA.
- Itraconazole improves short-term symptoms and reduces the frequency of exacerbations that require the use of oral corticosteroids.
- Short-term use of itraconazole has not shown an improvement in lung function.
- Itraconazole may exacerbate the adrenal suppression seen with regular corticosteroid use.

Voriconazole

Voriconazole is the newest of the azole antifungal agents, and has been effective in the treatment of invasive pulmonary aspergillosis in
immunosuppressed people. So far, its use has not been reported in the treatment of ABPA.

Conclusions and future directions

Allergic bronchopulmonary aspergillosis remains an important complication of both asthma and cystic fibrosis. It contributes to worsened morbidity and progressive deterioration in lung function. Af is well adapted to survive in the human airway, and persistence of the organism is a constant source of antigenic stimulus. Evidence shows that it can release virulence factors and proteases, contributing to a more heterogenous inflammatory response that is likely to play a central role in the development of bronchiectasis and progressive lung damage.

The drive to find novel therapeutic interventions in ABPA is with the aim of preventing progressive decline in lung function and consequent worsening respiratory impairment, while minimising the use of systemic corticosteroids. The use of antifungal therapy, therefore, seems to be a rational one in association with more traditional anti-inflammatory therapy. Both the randomized-controlled trials of itraconazole demonstrated improvements in symptoms and immune activation, but were short-term trials and failed to show a significant change in lung function.

Important questions remain unanswered. Lower doses of itraconazole may be effective, particularly for maintaining disease. Alternatively, administration by nebulization should be explored, given the previous success with amphotericin. This could be used in a similar way to nebulized antibiotics in CF, with the potential of delivering an effective dose to the lungs but minimising systemic side-effects. It also remains unclear which patients will benefit most from treatment. Individuals with a high pathogen burden may stand to benefit most; however, at this time there is no reliable way to determine this. Mechanistic studies relating endobronchial biopsy findings that attempt to quantify Af from bronchoalveolar lavage or its presence in the sputum, and correlating this to airway inflammation and clinical disease, would help answer this. Susceptibility of Af to treatment with itraconazole may also affect efficacy as was identified by Stevens et al. It would be prudent that future trials assess in-vitro sensitivity in individuals at the start and during long-term treatment trials, and determine if this relates to efficacy. The current studies show that serum IgE or sputum inflammatory markers can be used to assess response in short-term efficacy studies, and many of these issues could be determined, therefore, by smaller single-centre studies. However, the most important outstanding questions remain whether treatment will modify disease progression and for how long that treatment should be. As most patients with ABPA have long-standing lung disease, with a component of irreversible airflow obstruction, larger numbers of participants with longer follow-up will be required to detect a difference, such as
impairing the decline in lung function with treatment over time. In addition, adverse events such as adrenal suppression may only be evident over time and with associated use of corticosteroids. Realistically, to achieve an estimate of these events, trial periods of 2–5 years may be required. As the minimum number of participants required would need to be similar to the number recruited by Stevens et al.,, this could only be achieved by a multicentre collaborative trial.

These results cannot be automatically extrapolated to CF, and there is a need to assess the efficacy of itraconazole specifically in ABPA associated with CF, particularly in the context of the regular use of antibiotics and agents to increase mucociliary clearance. In addition, diagnosis in CF remains problematic, and a clearer understanding of the pathogenesis of ABPA in CF is required along with the ability to detect the disease more reliably and at an early stage.

Therefore, antifungal therapy with itraconazole seems, at least in the short term, to modify the immune activation seen with ABPA and improve symptoms. Longer-term trials are likely to be needed to demonstrate an improvement in lung function. Questions also remain as to what the correct dose should be, when itraconazole should be commenced and for what period of time? A consideration of these issues needs to be made before the widespread regular use of itraconazole is adopted.

Research directions
- Longer-term trials are required to assess the impact of itraconazole on lung function and disease course in ABPA.
- Smaller short-term trials are needed to determine the dosing schedule and the most effective means of delivering treatment.
- In-vitro sensitivity testing of Af to antifungal treatment should be considered in future trials.
- The additive effect of itraconazole on adrenal suppression associated with corticosteroid use needs to be closely observed with long-term use and its effect on bone-mineral density considered in all future trials of long-term therapy.
- The role of antifungal agents in acute exacerbations of the disease needs to be determined.
- The role of antifungal agents to treat ABPA in CF needs to be addressed in separate clinical trials both in terms of efficacy and adverse events.

References


