Antifungals in severe asthma

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Purpose of review
Despite guideline-based treatment, many patients with severe asthma continue to have uncontrolled disease. Fungal allergy is being increasingly recognized in the pathogenesis of severe asthma. Limited data exist on the approach to treatment of fungal asthma. This review summarizes existing evidence on the use of antifungal agents in allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS), and highlights needed areas of future investigation.

Recent findings
Recent studies evaluating oral triazole therapy in ABPA appear to support triazole use in a carefully considered clinical setting, whereas studies assessing triazole use in SAFS have yielded mixed results. Despite early encouraging findings that oral triazole use may improve asthma symptoms, stabilize lung function, decrease inhaled and systemic corticosteroid requirements, and alter serum biomarkers, overall data are limited. Appropriate patient selection, as well as choice of the optimal drug, dose, frequency, and duration of therapy, remains poorly defined.

Summary
The role of antifungal therapy in severe asthma remains unclear. Early studies have suggested a possible benefit of some antifungal agents, such as oral triazoles in ABPA and SAFS; however, routine clinical use of these agents in severe asthma without ABPA is not currently recommended. Further research is needed to better delineate the potential utility of antifungal medications in severe asthma and identify the asthma populations who benefit from such treatment.

Keywords
antifungals, azoles, fungal asthma, severe asthma, triazoles

INTRODUCTION

Asthma is an inflammatory disease of the airways that affects 8.2% of the population in the USA [1]. Up to 10% of patients with asthma suffer from severe disease [2]. Recent American Thoracic Society/European Respiratory Society guidelines define severe asthma as that which requires treatment with high doses of inhaled corticosteroids and a second controller medicine and/or systemic corticosteroids [3▪]. Severe asthma is associated with increased morbidity, mortality, and healthcare cost [4]. Despite guideline-based treatment, many patients with severe asthma continue to have uncontrolled disease, highlighting the need for additional effective therapeutic options.

Fungal exposure has been linked to clinical outcomes including worsening asthma control, decreased lung function, hospital admissions, ICU admissions, and asthma-related deaths [5–16]. Hypersensitivity to fungi has long been recognized as the driver of allergic bronchopulmonary aspergillosis (ABPA) [17,18▪]. ABPA is a clinical entity characterized by hypersensitivity to *Aspergillus fumigatus*. It is primarily seen in patients with asthma and cystic fibrosis, but can also occur in the absence of these conditions [19]. Clinical features are variable but can include uncontrolled asthma, recurrent pulmonary infiltrates, elevated total serum Immunoglobulin E (IgE) (>100 ng/ml), elevated *A. fumigates*-specific IgE or Immunoglobulin G (IgG), central bronchiectasis, eosinophilia, and mucous plugs [18▪,20▪▪,21].

More recent data showed an association between fungal sensitization and the development and persistence of severe asthma [14,20▪▪,22], with up to 65% of patients with refractory asthma

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KEY POINTS

- Fungal allergy is being increasingly recognized in the pathogenesis of severe asthma.
- Recent studies evaluating oral triazole therapy in ABPA appear to support this group of drug use in a carefully considered clinical setting.
- Routine clinical use of antifungal agents in severe asthma without ABPA is not currently recommended and needs further exploration.

demonstrating sensitization to fungi [23]. In 2006, Denning *et al.* [14] proposed the term severe asthma with fungal sensitization (SAFS) to describe patients with persistent severe asthma and evidence of fungal sensitization (by skin prick or antigen-specific serum IgE testing) who do not meet criteria for ABPA. Defining this asthma phenotype has allowed researchers to subsequently design clinical trials to evaluate the benefit of triazole antifungal therapy in patients with SAFS.

Despite increasing evidence strengthening the link between fungal sensitization and severe asthma, limited data exist on the approach to its treatment, particularly with the use of antifungal agents. As a result, the optimal treatment strategy for these patients remains unclear. This review aims to summarize existing evidence regarding the use of antifungal agents in ABPA and SAFS, and highlight the needed areas of future investigation related to the use of antifungal medications in patients with severe asthma.

ANTIFUNGAL AGENTS

Triazole antifungals have emerged as a first-line therapy for the treatment and prophylaxis of systemic mycoses. They have been employed in the treatment of ABPA, and there is an increased clinical and research interest for their potential utility in SAFS. Currently available triazoles include fluconazole, itraconazole, voriconazole, and posaconazole. They exert their antifungal effect by binding to and deactivating the cytochrome P450-mediated enzyme, 14-desmethylase, which is responsible for the conversion of lanesterol to erogosterol, a key component of the fungal membrane [24–26]. Triazoles are generally fungistatic; however, itraconazole and voriconazole are fungicidal against *Aspergillus* [26].

The proposed mechanism of action of triazole antifungals in ABPA and SAFS is based on their ability to reduce airway fungal burden resulting in decreased allergic response; however, there may be other mechanisms by which these drugs work. Itraconazole, a potent inhibitor of CP3A4, is also known to increase glucocorticoid levels and therefore may potentiate corticosteroid effect [27–30]. The interaction between corticosteroids, and voriconazole and posaconazole is thought to be less profound. Triazoles have also been shown to have significant in-vitro immunologic properties that may add to their activity in allergic fungal disease [31–36].

Itraconazole, voriconazole, and posaconazole have all been studied in ABPA or SAFS. Each drug has its own pharmacokinetic properties, side-effect profile, and drug–drug interactions. Itraconazole is water-soluble and has variable bioavailability following oral ingestion. It is metabolized by the liver and is a strong inhibitor of CP3A4. Itraconazole can cause nausea and vomiting, transaminase elevation, hypokalemia, rash, and congestive heart failure [37,38]. Voriconazole has 96% oral bioavailability and is also metabolized by the liver. It is usually well tolerated, though visual disturbances can occur in over 20% of patients [39]. Posaconazole is available as an oral suspension and has increased absorption when taken with food. It is also a moderate inhibitor of CP3A4. Posaconazole appears to have a more favorable safety profile than voriconazole or itraconazole, with gastrointestinal complaints being the most common [40,41]. Calcineurin inhibitors, calcium channel blockers, benzodiazepines, warfarin, statins, and corticosteroids are some of the drugs that commonly interact with triazoles [42].

Beyond triazoles, limited data exist for the use of other antifungal agents in ABPA or SAFS. Ketoconazole and inhaled natamycin have been tried in ABPA with minimal success [43,44], whereas neither drug has been studied in SAFS. The use of nebulized amphotericin B has also not been studied in great detail in either ABPA or SAFS.

ANTIFUNGAL THERAPY IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Treatment of ABPA has focused on the suppression of eosinophilic inflammation with inhaled and systemic corticosteroids, and more recently, with concomitant reduction in fungal allergen burden through treatment with triazole antifungals. Multiple studies have evaluated the efficacy of oral triazole therapy in ABPA, including two randomized clinical trials, and the results are summarized in Table 1. In a study by Stevens *et al.* [46], 55 patients were randomized to receive itraconazole 200 mg twice daily vs. placebo for 16 weeks. The second phase of the study involved treating all patients with itraconazole 200 mg daily for an additional 16 weeks to evaluate long-term use. In the double-blind

Table 1. Summary of studies evaluating triazoles in ABPA and SAFS

Reference	Study design	Patients (*n*)	Intervention	Results
ABPA				
Salez *et al.* [45]	Uncontrolled clinical trial	14	Itraconazole 200 mg/day for 12 months	Decrease of 50% in blood eosinophils
				Decrease of 50% in total IgE
				Decrease of 70% in precipitating antibodies
				Increase in FEV1
				Decrease in corticosteroid use
				Decrease in mean exacerbations 2.4 vs. 1.9 per year ($P<0.01$)
				No adverse effects
Stevens *et al.* [46]	Double-blind, placebo-controlled RCT	55	Itraconazole 200 mg b.i.d. for 16 weeks followed by itraconazole 200 mg/day for 16 weeks	Overall response rate with treatment of 46 vs. 19% with placebo ($P=0.04$)
				No significant difference in adverse events
Wark *et al.* [47]	Double-blind, placebo-controlled RCT	29	Itraconazole 400 mg/day for 16 weeks	Decrease in sputum eosinophils ($P<0.01$)
				Decrease in total IgE ($P<0.01$)
				Decrease in IgG to *Aspergillus fumigatus*
				Fewer exacerbations requiring oral corticosteroids ($P=0.03$)
				No significant difference in lung function
Chishimba *et al.* [48]	Retrospective case review	25	Voriconazole 300–600 mg/day	Improvement of symptoms in ≥70%
			Or	No change in lung function
			Posaconazole 800 mg/day	Reduction in total IgE by 27% and specific IgE by 24%
			All previously received itraconazole	Improvement in radiological infiltrates in ≥50%
				Improvement in quality of life in >55%
				Adverse events in 40% with voriconazole and 22% with posaconazole
SAFS				
Denning *et al.* [30]	Double-blind, placebo-controlled RCT	58	Itraconazole 200 mg b.i.d. for 32 weeks	Improvement in AQLQ score compared with placebo (+0.85 vs. −0.01; $P=0.014$)
				Improved rhinitis score
				Improved morning peak flow (20.8 l/min; $P=0.028$)
				Decrease in total serum IgE
				No severe adverse events
Pasqualotto *et al.* [49]	Retrospective cohort study	33 SAFS ($n=22$); ABPA ($n=11$)	Itraconazole 100–450 mg/day	Decrease in total IgE and serum specific IgE ($P=0.04$)
				Decrease in blood eosinophils ($P=0.037$)
				Reduction in oral corticosteroid dose ($P=0.043$)
				Reduction in courses of systemic steroids ($P=0.041$)
				Improved lung function ($P=0.016$)

Table 1 (*Continued*)

Reference	Study design	Patients (*n*)	Intervention	Results
Agbetile *et al.* [50▪▪]	Double-blind, placebo-controlled RCT	65	Voriconazole 200 mg b.i.d. for 3 months	No significant difference in severe exacerbations
				No significant difference in AQLQ or any other secondary measures

ABPA, allergic bronchopulmonary aspergillosis; AQLQ, Asthma Quality of Life Questionnaire; b.i.d., twice daily; d, day; FEV1, forced expiratory volume in 1 s; RCT, randomized clinical trial; SAFS, severe asthma with fungal sensitization.

phase of the trial, the rate of response to therapy was significantly higher in the itraconazole group vs. placebo (46 vs. 19%; $P = 0.04$). Patients treated in the itraconazole arm demonstrated a decrease in corticosteroid dose and serum total IgE, and an improvement in exercise tolerance and pulmonary function. No changes were seen in pulmonary infiltrates between the groups. The rate of adverse events was similar in both the treatment groups. In the open-label phase of the study ($n = 50$), 12 of the 33 patients who did not respond in the double-blind phase of the study experienced an improvement in symptoms, and none of the patients who responded in the initial phase of the study had a relapse.

In a more recent study, Wark *et al.* [47] randomized 29 patients to receive either itraconazole 400 mg daily or matched placebo for 16 weeks. Patients in the itraconazole treatment group experienced a 35% per week reduction in sputum eosinophils compared to no change in the placebo group ($P < 0.01$). Treatment with itraconazole decreased the serum IgE ($P < 0.01$) and serum IgG levels to *A. fumigatus* ($P = 0.03$). Furthermore, there were fewer exacerbations requiring oral corticosteroids in the itraconazole group ($P = 0.03$). No significant difference in change of lung function was observed between the groups.

Other studies have retrospectively evaluated the use of oral triazoles in ABPA. Salez *et al.* [45] followed 14 patients with ABPA who were initially treated with inhaled corticosteroids for 2 years, although the majority also required treatment with oral prednisolone. Patients subsequently received itraconazole 200 mg daily for 1 year in addition to their corticosteroids. Addition of itraconazole resulted in improved lung function and a decrease in blood eosinophilia, serum IgE levels, and antibodies against *A. fumigatus* antigen. All patients decreased oral corticosteroid dose with complete withdrawal in seven of the 14 patients. Chishimba *et al.* [48] retrospectively evaluated 25 patients with ABPA ($n = 25$) or SAFS ($n = 5$) to assess the benefit of voriconazole and posaconazole in patients who failed therapy ($n = 14$) or developed adverse events ($n = 11$) on itraconazole. Response rates to voriconazole and posaconazole were above 70% at 3, 6, 9, and 12 months. Asthma severity was downgraded in 38% of the patients. Seventy-five percent of patients were able to discontinue corticosteroids. Short-acting beta agonist use, healthcare utilization related to asthma, overall health status, and immunologic markers also improved with treatment.

In order to evaluate the efficacy and safety of antifungal use in ABPA, Moreira *et al.* [51▪▪] recently performed a detailed systematic review including 38 studies. Most of these studies were observational in nature and the quality of evidence was graded low or very low. Despite the limitations of the existing data, antifungal therapy appeared to have a positive impact on symptoms, frequency of exacerbation, steroid-sparing effect, and lung function in patients with ABPA. Biomarkers and radiologic findings also appear to improve with treatment. The effects were most consistent in oral triazole treatment.

The overall evidence for oral triazole therapy in ABPA appears to support triazole use in a carefully considered clinical setting. However, the data remain limited. Appropriate patient selection, as well as choice of the optimal drug, dose, frequency, and duration of therapy, remains poorly defined. The potential for antifungal monotherapy is currently being evaluated in a randomized controlled trial with itraconazole being compared to oral prednisolone (MIPA study; clinicaltrials.gov; NCT01321827). Additional randomized controlled clinical trials may be of benefit in better clarifying the role of oral triazoles in ABPA.

ANTIFUNGAL THERAPY IN SEVERE ASTHMA WITH FUNGAL SENSITIZATION

The first randomized control trial of oral antifungal treatment in SAFS was performed by Denning *et al.* [30]. The Fungal Asthma Sensitization Trial (FAST) randomized 58 patients with severe asthma and sensitization to at least one of the seven fungi to receive either oral itraconazole 200 mg twice daily or matched placebo for 32 weeks. The primary endpoint was change in Asthma Quality of Life Questionnaire (AQLQ) [52]. In all, 60% of the patients

treated with itraconazole showed substantial improvement in their AQLQ score compared with the placebo group (+0.85 vs. −0.01; $P = 0.014$). This improvement in AQLQ was larger than the minimally important difference of 0.5 [53]. Secondary endpoints showed an improvement in rhinitis score and serum IgE level in the treatment group. At 4-month follow-up, after discontinuation of therapy, AQLQ scores had returned to near prestudy values. Whereas no severe adverse events were observed, adverse events led to discontinuation in five patients in the antifungal group and two patients in the placebo group.

In a subsequent retrospective study, Pasqualotto *et al.* [49] evaluated the effects of antifungal therapy on SAFS ($n = 22$) and ABPA ($n = 11$). Patients receiving 6 months of itraconazole therapy had improved lung function, decreased serum total IgE and *A. fumigates*-specific IgE, and reduced blood eosinophils when compared to the pretreatment levels. There was also a reduction in both total oral corticosteroid dosage and courses of systemic corticosteroids. Three patients were switched to oral voriconazole due to adverse effects, low itraconazole levels, or clinical deterioration. Interestingly, the benefit of antifungal therapy was less profound after 12 months of treatment, but only 17 patients were evaluated for 12-month endpoints, making statistically significant differences difficult to show.

The recently published randomized controlled effectiveness of voriconazole in the treatment of Aspergillus fumigatus–associated asthma (EVITA3) study sought to evaluate the effectiveness of voriconazole in the treatment of *A. fumigatus*-associated asthma [50▪▪]. Sixty-five patients with asthma who were IgE-sensitized to *A. fumigatus* and had a history of at least two severe asthma exacerbations in the prior 12 months were randomized to receive oral voriconazole 200 mg twice daily or placebo for 3 months, followed by observation for 9 months. Patients were using an equivalent of 2000 μg of inhaled beclomethasone per day and about 30% were on maintenance oral prednisolone. Treatment with voriconazole did not result in a reduction in the number of severe exacerbations per patient per year compared with placebo. Additionally, no improvement in quality of life, measure by AQLQ, was seen. The negative results of this trial contrast the results seen in the FAST trial. Direct comparisons may be difficult as the duration of treatment was significantly shorter in the EVITA3 study compared to the FAST trial (12 vs. 32 weeks, respectively). It is also possible that compared to voriconazole, itraconazole may have a stronger effect on increasing corticosteroid levels [54,55] or may have more potent immunosuppressive properties [34].

Whereas early data have shown some promise, there is still insufficient evidence to support the routine use of triazole antifungals in the treatment of SAFS. This is reflected in recent European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines on severe asthma that do not recommend the use of antifungal agents in severe asthma without ABPA irrespective of sensitization to fungi [3▪]. Additional investigation is warranted prior to routine clinical use of antifungal agents for SAFS.

FUTURE DIRECTIONS

Despite increasing evidence regarding the use of antifungal agents in ABPA and SAFS, a significant deficit in knowledge remains. A better clarification on the mechanism of action of antifungals in fungal allergy-driven asthma is needed. Further, it remains unclear whether the potential benefit seen with the triazole antifungals is related to a decrease in fungal burden with subsequent decrease in fungal allergy, or if the beneficial effects are related to increased bioavailability of corticosteroids or inherent anti-inflammatory properties of triazoles. There needs to be further evaluation of triazole treatment, including newer drugs such as posaconazole, with additional randomized control trials. Evaluation of inhaled agents, such as nebulized amphotericin B, may provide better insight into whether beneficial effects are related to a decrease in fungal burden or an increase in corticosteroid bioavailability. Additionally, inhaled therapies may provide the added benefit of decreasing systemic side-effects and limiting drug interactions that are sometimes seen with oral triazoles. Beyond the selection of adequate agents, little is known about the appropriate dose, duration of therapy, or impact of chronic use. In order to answer these questions, larger-scale, multicenter randomized clinical trials are needed.

CONCLUSION

Fungal allergy is being increasingly recognized in the pathogenesis and clinical course of asthma. Clinical descriptions, including phenotyping and endotyping in conjunction with immunological markers of ABPA and SAFS, continue to be refined. Although the role of fungi in severe asthma is becoming more apparent, the role of antifungal therapy remains unclear. Early studies have suggested a possible benefit of oral triazole therapy in ABPA and SAFS. Further research is needed to better delineate the potential utility of antifungal medications in severe asthma.

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Conflicts of interest

None of the authors disclose any conflict of interest.

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