

REVIEW

Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic fibrosis: a systematic review

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Summary

Allergic bronchopulmonary aspergillosis (ABPA) is a rare disease that affects patients with asthma or cystic fibrosis. Its debilitating course has led to the search for new treatments, including antifungals and monoclonal antibodies. To evaluate the efficacy and safety of antifungal treatments in patients with ABPA and either asthma or cystic fibrosis, we performed a systematic review of the literature on the effects of antifungal agents in ABPA using three biomedical databases. Quality assessment was performed using the GRADE methodology and, where appropriate, studies with comparable outcomes were pooled for meta-analysis. Thirty-eight studies – four randomized controlled trials and 34 observational studies – met the eligibility criteria. 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. 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. Antifungal interventions in ABPA improved patient and disease outcomes in both asthma and cystic fibrosis. However, 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, especially in cystic fibrosis, to increase confidence in the effects of antifungal treatments in ABPA.

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Introduction

Aspergillus is a ubiquitous fungal species that causes opportunistic infections. The most frequent human pathogen of this species is *Aspergillus fumigatus* [1]. Aspergillosis may present as saprophytic, allergic or invasive disease [2, 3]. Of the allergic diseases induced by *Aspergillus* species, allergic bronchopulmonary aspergillosis (ABPA) is the archetype.

ABPA, which was first described in 1952 by Hinson et al. [4], affects patients with asthma or cystic fibrosis [5, 6]. Its clinical presentation is well established, with the earliest descriptions dating from 1971 [7]. It generally consists of an exacerbation of a pre-existing chronic respiratory disorder with the appearance of recurrent episodes of bronchial obstruction, fever, expectoration of brownish mucus plugs, peripheral blood eosinophilia and haemoptysis. Diagnosis is

dependent on the combination of clinical, radiological and serological criteria, all of which have evolved over time [8, 9]. Currently established criteria differ between asthma and cystic fibrosis patients. Diagnosis is challenging and requires awareness of the clinical progress of the patient; this is particularly important in cystic fibrosis due to the overlap of ABPA criteria with some common manifestations of the underlying disease [10]. Early diagnosis and treatment of ABPA ultimately results in better clinical outcomes. If left untreated, ABPA has a debilitating course associated with the persistent inflammatory cell influx that characterizes the pathogenesis of this disease [11].

ABPA is a hypersensitivity pulmonary disease; its mechanisms result in an early inflammatory reaction that activates the innate immune system, followed by a late inflammatory reaction, driven by a Th2-type immune response [12], which leads to an increase in

total IgE, specific IgE to *A. fumigatus* and eosinophil counts in the airways and peripheral blood. The immune-mediated mechanisms of this disease are further supported by recent evidence of a link to the major histocompatibility complex, with the HLA-DR 2 and DR5 being linked to increased susceptibility to ABPA and a protective role being attributed to HLA-DQ2 [12, 13]. As ABPA is a predominantly inflammatory disease, treatment is aimed at reducing inflammation or immunological activity as well as reducing the effects of fungal colonization through antifungal treatment [11].

The first recorded use of an antifungal treatment for ABPA was published in 1967 [14]. Since then, many different drugs, with varying antifungal properties, have been used. More recently, a consensus expert panel recommended the use of antifungals (itraconazole) in patients with slow or poor response to steroids, frequent relapses, steroid-dependent ABPA, or steroid toxicity [9]. Furthermore, two recent reviews by the Cochrane Collaboration concluded that, in ABPA, azole antifungals, principally itraconazole, may have some benefits in normalizing immunological parameters and lung function after 16 weeks of intervention [15]. In cystic fibrosis, however, there is not enough evidence to support the usefulness of antifungal treatment [16]. Moreover, in clinical practice, and especially in observational studies, different formulations and treatment regimens have been used [11, 17]. The benefits of antifungals in the treatment of ABPA in patients with asthma or cystic fibrosis are still not fully understood. Furthermore, safety issues arise, especially when antifungals are used in association with corticosteroid therapy [11, 15].

In this review, we assess the efficacy and safety of antifungal treatment in patients with ABPA and either asthma or cystic fibrosis through a systematic evidence-based review of the literature.

Methods

We selected published reports of randomized controlled trials (RCTs) and observational studies, including case series and case reports, that compared or assessed the effect of antifungal agents in patients of any age with a confirmed diagnosis of ABPA (accordingly to previously published diagnostic criteria [18]), and either asthma or cystic fibrosis, unrestricted of previous ABPA treatment. Patients with aspergilloma were excluded due to the association of an immunologically severe disease and higher risk of recurrent relapses [19]. Expert opinion articles, standard reviews, animal studies and studies of individuals exposed to intervention with drugs other than antifungals, immunocompromised patients and patients with *Aspergillus*-related disorders not fulfilling ABPA criteria were excluded.

Both primary and secondary outcomes were reviewed. The primary outcomes considered were symptoms, evaluated by the presence of respiratory symptoms and asthma control scores or quantitative measures of exercise tolerance; exacerbation frequency, measured by the number of episodes that required hospital admission and/or unscheduled visits to the doctor; and lung function, measured by forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), forced expiratory flow between 25% and 75% (FEF_{25–75}), residual volume and total lung capacity. Secondary outcomes included inflammatory biomarkers (peripheral blood eosinophils, serum total IgE, serum specific IgE and specific IgG to *A. fumigatus*), radiological findings (pulmonary infiltrates on chest X-ray and improvement in chest X-ray or computed tomography (CT) scan scores), steroid-sparing effects, quality of life scores and safety (evaluated by adverse effects reported with antifungal use).

Search strategy

In October 2012, electronic searches were conducted in three large databases: Ebsco, Scopus and Pubmed. The following groups and associated terminology were used: allergic bronchopulmonary aspergillosis coupled with asthma or cystic fibrosis and antifungal agents (Table S1). *A priori* inclusion criteria limited retrieved articles to those assessing antifungals in individuals with ABPA and either asthma or cystic fibrosis. Subsequently, all articles retrieved were evaluated to assess if they met the entry criteria. No language restrictions were applied. Hand searches of the reference lists of pertinent studies were performed and relevant studies identified. Following both electronic and hand searches, two authors independently selected articles for full-text scrutiny based on the title and/or abstract and identified all studies that appeared to fit the inclusion criteria for full review. Afterwards, the two reviewers independently analysed the selected articles and agreed on a set of studies to be included in the systematic review for further analysis. The following data were extracted from each study: study design (randomization, blinding), participants (sample size, age range, presence of asthma or cystic fibrosis), antifungal treatment (type, dosage, treatment duration, associated therapy) and outcomes (type and analysis).

Grading system and meta-analysis

Evidence was classified according to the measured outcomes. The overall quality of evidence was assessed using the GRADE methodology, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions [20]. For each outcome, quality of evidence was classified using five criteria: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision and (5)

publication bias. Quality was considered as follows: high, if multiple RCTs with a low risk of bias had consistent, generalizable results for a particular outcome; moderate, if one of the criteria was not met; low, if two of the criteria were not met; and very low, if three of the criteria were not met. If just one study measuring an outcome existed, the data were considered sparse and the corresponding evidence classified as low [21–25]. GRADE profiler software (GRADEpro. [Computer program]. Version 3.6 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann [GRADE Working Group], Norway) was used for the analysis.

Quality of evidence reflects the extent to which the reviewers' confidence in an estimate of effect is adequate to support a particular recommendation. In the GRADE system, strength of recommendation is classified as strong or weak according to the quality of the supporting evidence and the balance between desirable and undesirable outcomes [21–25].

Studies with a similar design and comparable outcomes were selected for quantitative analysis and their results pooled using a random effect meta-analysis in Review Manager software (Review Manager (RevMan) [Computer program], Version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was evaluated by the I^2 test and risk of publication bias with funnel plot symmetry.

Results

After a systematic search of the literature, 38 studies were retrieved that met the entry criteria. Of these, four were RCTs and 34 were observational studies (21 case reports, 11 case series, one cohort study and one uncontrolled clinical trial). Figure 1 shows the flow chart of the study selection strategy. Table 1 describes the main characteristics of the studies included in the systematic review [14, 26–62]. Excluded studies and the reasons for exclusion are shown in Table S2.

The population in the evaluated studies included 197 asthmatics and 110 cystic fibrosis patients. All four RCTs pertained to adult asthmatic patients. The studies included participants with ages ranging from 6 to 76 years. Different interventions with antifungal agents and dosage protocols were used. Azoles were used in 29 of the studies. Itraconazole was used in two RCTs [56, 59] and reported as used in 19 of the observational studies [28–31, 33–35, 42, 43, 47–50, 52, 54, 55, 57, 58, 63]; voriconazole was used in seven observational studies [39, 41, 44, 45, 60–62], posaconazole in one observational study [60] and ketoconazole was used in one RCT [53] and one observational study [27]. Furthermore, nebulized treatment was also assessed with the use of amphotericin B [36] and nystatin [14] in one case report each and with nebulized natamycin in one RCT [32] and one observa-

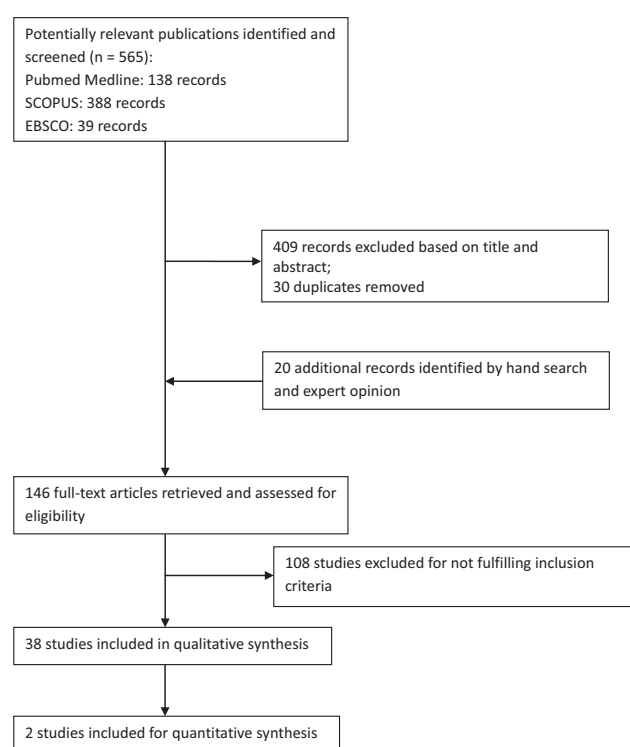


Fig. 1. Flowchart of the selection strategy.

tional study [38]. The combined use of antifungal agents was also reported. Two studies [36, 46] reported the use of different classes of antifungals (itraconazole and amphotericin B), while others [26, 60] reported mainly the change from itraconazole to voriconazole. The duration of antifungal treatment ranged from 6 weeks to 5 years.

Primary outcomes were addressed in all but nine of the studies [27, 31, 35, 36, 40, 41, 46, 51, 62]. Symptoms were reported in eight studies [14, 26, 28, 34, 38, 53, 57, 60] but only two used symptom scores [53, 60]; exacerbations were reported in 14 studies [14, 15, 26, 32, 35, 38, 42, 44, 45, 48, 52, 56–58] and lung function, measured by FEV₁, was assessed in 29 studies (Table 2). Inflammatory biomarkers were the most commonly reported outcome, described in all studies but five [34, 37, 41, 47, 51]. Radiological changes and steroid-sparing effects were assessed in 16 [14, 27, 28, 30, 31, 36, 38, 41, 42, 48, 53, 55–57, 60] and 22 studies [26, 28, 30–33, 35–37, 40, 41, 43, 44, 46, 47, 49–52, 55, 56, 58, 61], respectively. Safety issues were reported in 16 of the 38 studies included [26, 27, 32, 34, 35, 39, 44, 45, 47, 48, 54–56, 60–62]. In the majority of studies, patients were taking corticosteroids concomitantly, with the exception of two studies [29, 54], in which the use of itraconazole as monotherapy was assessed in 15 patients with cystic fibrosis.

According to the GRADE approach, all the studies included in this review had a low or very low quality of evidence (Tables 2 and 3).

Table 1. Studies included in the systematic review

Reference	Study design and participants	Intervention	Outcome measure	Results
Chishimba et al. [60]	Case series, 21 asthma patients, mean age 60 year	Voriconazole (300–600 mg/day) – 19 courses, mean duration 16.7 months Posaconazole (800 mg/day) – 9 courses, mean duration 16.3 months (All performed previously itraconazole)	Symptoms Lung function Biomarkers Radiology Adverse effects Quality of life	Improvement of symptoms by 69% with voriconazole and 78% with posiconazole No significant changes in FEV ₁ or FVC Decrease Median total IgE by 27.3% and specific IgE by 24% Improvement radiological infiltrates in 57% with voriconazole and 50% posaconazole Adverse effects occurred in 40% with voriconazole and 22% posaconazole Improvement of quality of life by 58% and 78%, respectively, to voriconazole and posaconazole
Godet et al. [36]	Case report, 1 asthma patient, 67 year	Nebulized amphotericin B and oral corticosteroids for 6 months	Biomarkers Radiology Steroid-sparing effect	Decrease in eosinophil counts, total IgE and specific IgE and precipitating antibodies to Af Improvement in CT consolidations Oral corticosteroid discontinuation in 2 months
Markantonis et al. [62]	Case series, 8 CF patients, median age 15 year	Voriconazole for 6–12 months	Adverse effects	Adverse effects: liver dysfunction (3); photosensitivity (6); optical disturbance (2); headaches (1) and tremor (1)
Kirschner et al. [41]	Case report, 1 asthma patient, 25 year	Voriconazole 300 mg bid and oral and inhaled corticosteroids, for 6 months	Radiology	Decrease in CT infiltrates
Hayes et al. [37]	Case report, 1 CF patient, 14 year	Itraconazole 200 mg bid for 2 months, followed by nebulized amphotericin B 10 mg bid for 6 months	Symptoms Lung function Biomarkers Steroid-sparing effect	Improvement in cough and dyspnoea Improvement in FEV ₁ and FVC Decrease in total IgE and specific IgE to Af Prednisone was weaned after 6 months of amphotericin B
Mulliez et al. [45]	Case report, 2 asthma patients, 47 and 37 year	Voriconazole 200 mg bid, for 4 months	Exacerbations Lung function Biomarkers Adverse effects	Both patients had exacerbations Increase in FEV ₁ Decrease in eosinophils and total IgE Adverse effects: abdominal pain, visual

(continued)

Table 1. (continued)

Reference	Study design and participants	Intervention	Outcome measure	Results
Proesmans et al. [51]	Case series, 7 CF patients, mean age 15 year	Multiple antifungal treatments (amphotericin B, itraconazole, voriconazole, posaconazole)	Steroid-sparing effect	alterations, and photosensitivity reactions 5/7 patients weaned off systemic steroids for at least 12 months
Tang et al. [57]	Case report, 1 asthma patient, 47 year	Itraconazole 400 mg daily for 5 months and oral corticosteroids	Symptoms Exacerbations Lung function Biomarkers Radiology	Symptoms (sputum plugs, purulent sputum, increased coughing) relieved and decrease in number of exacerbations No changes in pulmonary function tests Total serum IgE decreased by 36.8%, slight increase in specific IgE No radiological improvement
Glackin et al. [61]	Case series, 10 CF patients, median age 14 year	Voriconazole 100 to 200 mg bid, for 6 weeks to 3 months	Lung function Biomarkers Steroid-sparing effect Adverse effects	No significant increase FEV ₁ Decrease of total serum IgE ($P < 0.005$) Decrease oral corticosteroid 7.5 mg/day ($P < 0.06$) Adverse effects: photosensitivity (1); optical disturbance (1)
Pasqualotto et al. [50]	Case series, 33 asthma patients (11 with ABPA), median age 52 year	Itraconazole for at least 6 months, median dose 300 mg/day	Lung function Biomarkers Steroid-sparing effect	FEV ₁ improvement of 12% ($P = 0.08$) Decrease of total IgE ($P = 0.005$) and eosinophilia ($P = 0.40$) Reduction of steroid dosage by 43% ($P = 0.109$)
Gimeno et al. [26]	Case report, 1 asthma patient, 54 year	Itraconazole for intermittent periods (4 months in total), voriconazole (intermittent periods for 18 months in total) – total 6 periods of treatment	Symptoms Biomarkers	Improvement in respiratory symptoms in 4 periods of treatment Decrease in total IgE
Cakir et al. [28]	1 case report, CF patient, 7 year	Two separate courses of itraconazole 200 mg daily for 6 month in association with oral corticosteroid	Symptoms Biomarkers Radiology	Improvement in cough and shortness of breath Reduction in serum IgE Resolution of pulmonary infiltrates
Julio Maggiolo et al. [42]	Case series, 6 patients (2 with CF, 4 with asthma), 5 with ABPA, mean age 13 year	Itraconazole 2–5 mg/kg/day for 5 months and oral corticosteroids	Exacerbations Lung function Biomarkers Radiology	Exacerbations increased in 2 patients, 1 of whom died Improvement in FEV ₁ and PEF in all patients Decrease in serum eosinophils in 2 patients Improvement in radiographic lung infiltrates in all patients
Mulliez et al. [44]	1 case report, 1 asthma patient, 47 year	Voriconazole 200 mg bid for 2 periods (9 and 5 months) and oral corticosteroids	Lung function Biomarkers Steroid-sparing effects Adverse effects	Improvement in FEV ₁ in both periods Decrease in eosinophils, total IgE and precipitating

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Table 1. (continued)

Reference	Study design and participants	Intervention	Outcome measure	Results
Casaulta et al. [29]	Case series, CF patients, 23 had ABPA, median age 19 year (6–45)	6 patients with itraconazole and oral corticosteroid, 3 with itraconazole monotherapy	Lung function Biomarkers	antibodies Decrease in oral corticosteroid dose Photosensitivity reaction No significant changes in FEV ₁ or FVC No significant changes in total serum IgE or specific IgE levels to recombinant Asp f 3,4,6
Hilliard et al. [39]	Case series, CF patients, 13 had ABPA, median age 12.5 year	Voriconazole, median dose 100 mg/day for 24 weeks (1–50 weeks); 9 in association with oral corticosteroid, 2 with immunomodulatory therapy, and 2 as monotherapy	Lung function Biomarkers Adverse effects	Significant increases in FEV ₁ and FVC Significant decrease in total IgE Adverse effects: nausea (<i>n</i> = 2), photosensitivity (<i>n</i> = 1), liver dysfunction (<i>n</i> = 1)
Skowronski et al. [55]	Case report, 1 CF patient, 8 year	Itraconazole 100 mg bid and oral corticosteroids for 4 months	Lung function Biomarkers Radiology Steroid-sparing effect Adverse effects	Improvement in FEV ₁ Decrease in total IgE Radiological improvement Decrease in prednisone dose over 3.5 months Cushing syndrome
Van Hoorn et al. [58]	Case report, 2 CF patients, 14 and 16 year	Itraconazole and oral corticosteroids	Lung function Biomarkers Steroid-sparing effect	In 1 patient, improvement in FEV ₁ , decrease in IgE, and reduction in corticosteroid dose
Christopher Coop et al. [31]	Case report, 1 asthma patient, 13 year	Itraconazole and oral corticosteroids for 6 months	Biomarkers Radiology	Decrease in total IgE by 79% Radiological improvement in infiltrates
Ferrari et al. [34]	Case report, 1 asthma patient, 46 year	Itraconazole 200 mg bid and oral corticosteroid	Lung function Adverse effects	Improvement in FEV ₁ and FVC of 90% and 69%, respectively Adverse effects: renal failure and rhabdomyolysis
Wark et al. [59]	Double-blind placebo RCT, 29 asthma patients, mean age 56 year	Itraconazole 400 mg/day	Exacerbations Lung function Biomarkers Adverse effects	Median number of exacerbations requiring prednisone: 0 with itraconazole and 1.5 with placebo (1.5), (<i>P</i> = 0.03) No significant differences in FEV ₁ or FEF Significant decrease in median total serum IgE (<i>P</i> < 0.01) and in sputum eosinophils (<i>P</i> < 0.01) and eosinophil cationic protein levels Decrease in specific IgG to Af Nausea in 1 patient

(continued)

Table 1. (continued)

Reference	Study design and participants	Intervention	Outcome measure	Results
Skov et al. [54]	Case series, 21 CF patients, median age 13 year (8–30)	9 treated with itraconazole 200–600 mg/day and oral corticosteroids 12 with itraconazole	Lung function Biomarkers Adverse effects	Significant increase in FEV ₁ and FVC only in combination therapy with corticosteroid Decrease in total IgE and precipitating antibodies ($P < 0.05$), and decrease in specific IgE in 6 patients Hepatic cytolysis in 11 patients
Coltey et al. [30]	Case report, 1 CF patient, 24 year	Itraconazole 5 mg/kg/day and oral corticosteroid and antibiotic treatment	Lung function Biomarkers Radiology	Improvement in FEV ₁ Decrease in specific IgE and IgG to Af Resolution of lung infiltrates
Khan et al. [40]	Case report, 1 CF patient, 8 year	Itraconazole 100 mg/day with oral corticosteroids for 4 weeks	Biomarkers Steroid-sparing effects	Decrease in total IgE, specific IgE, specific IgG and blood eosinophil counts Reduction in oral corticosteroid dosage
Mussaffi et al. [46]	Case report, 1 CF patient, 5 year	Itraconazole 100 mg bid and oral corticosteroid for 16 months	Biomarkers	Decrease in total IgE and eosinophil count
Stevens et al. [56]	Double-blind placebo-controlled RCT, 55 non-CF individuals, followed by open label trial with 50 individuals	Itraconazole 200 mg bid for 16 weeks, followed by itraconazole 200 mg/day for 16 weeks	Quality of life Lung function Biomarkers Radiology Steroid-sparing effect Adverse effects	No differences in SF-36 scores or exercise tolerance Improvement in FEV ₁ , FEF _{25–75} , and FVC Decrease in total IgE No differences seen for radiological improvement Decrease in need for corticosteroids in comparison with placebo Adverse effects in 25 of 28 patients in itraconazole group and in 23 of 27 of patients in placebo group
Nepomuceno et al. [47]	Case series, CF patients, 16 of whom had ABPA, median age 22.5 year	Itraconazole and oral and inhaled corticosteroids (12 individuals)	Exacerbations Lung function Steroid-sparing effect Adverse effects	Reduction in number of exacerbations ($P = 0.0009$) No decrease in FEV ₁ Reduction of 47% in daily steroid dose ($P = 0.05$) Transient changes in liver function tests in 3 patients
Salez et al. [52]	Uncontrolled clinical trial, 14 asthma patients, mean age 44 year	Oral itraconazole 200 mg/day for 12 months	Exacerbations Lung function Biomarkers Steroid-sparing effect Adverse effects	Decrease in mean (SD) number of exacerbations from 2.4 (0. 2)/year to 0.9 (0.4)/year ($P < 0.01$) For 1-year treatment: Increase in FEV ₁ and FEF _{25–75} ($P < 0.005$) Decrease of 50% in eosinophils and total serum IgE and of 70% in precipitating antibodies

(continued)

Table 1. (continued)

Reference	Study design and participants	Intervention	Outcome measure	Results
				to Af ($P < 0.05$) Increase in specific IgE Decrease in corticosteroid use No adverse effects
Nikaido et al. [48]	Case report, 1 asthma patient, 23 year	Itraconazole 100 mg/day monotherapy	Exacerbations Biomarkers Radiology	No exacerbations at 20 months of treatment Decrease in total serum IgE and eosinophil counts Improvement in radiological pulmonary infiltrates
Germaud [35]	Cohort study of 12 asthma patients, mean age 44 year (17–70)	Oral itraconazole 200 mg/day for at least 6 months, associated with oral corticosteroids in 6 cases	Biomarkers Steroid-sparing effect Adverse effects	Decrease in eosinophil count, total IgE, and precipitating antibodies Decrease in corticosteroid use in half of the patients No adverse clinical or biological effects
Mannes et al. [43]	Case report, 2 CF patients (twins), 18 year	Itraconazole 200 mg bid and oral corticosteroid taken sequentially by the twins, with a 5-month interval	Lung function Biomarkers Steroid-sparing effects	Improvement in FVC Reduction in total serum IgE and specific IgG to Af with antifungal treatment; no reduction in specific IgE Tapering of steroid use began earlier in the twin who started itraconazole earlier
Pacheco et al. [49]	Case report, underlying disease not specified, 36 year	Itraconazole 200 mg/day for 4 months	Lung function Biomarkers	Increase in FEV ₁ and FVC of 19% and 18%, respectively IgG to Af fell by 66.7%
Denning et al. [33]	Case series, 3 CF patients and 3 patients with severe asthma, age range 14–49 year (1 HIV ⁺ patient)	Itraconazole 200 mg bid for (1–6 months)	Lung function Biomarkers Steroid-sparing effect Adverse effect	Improvement in FEV ₁ and FEV _{25–75} ($P < 0.05$) Decrease in total IgE ($P < 0.05$) Reduction in need for prednisone by 19 mg (14;52), ($P < 0.01$) Decrease in libido
Borghi et al. [27]	Case report, 1 asthma patient, 23 year	Ketoconazole 200 mg bid and oral corticosteroids for 3 months	Biomarkers Radiology	Decrease in total serum IgE of 3% Disappearance of radiological infiltrates
Currie et al. [32]	Double-blind placebo-controlled RCT, 24 asthma patients	Nebulized natamycin 5 mg bid for 50 weeks and oral corticosteroids	Exacerbations Lung function Biomarkers Steroid-sparing effect Adverse effects	No differences in antibiotic use for exacerbations or hospital admissions No difference in FEV ₁ Decrease in total IgE Corticosteroid use: natamycin – median decrease 2.25 mg vs. placebo – median decrease

(continued)

Table 1. (continued)

Reference	Study design and participants	Intervention	Outcome measure	Results
Shale et al. [53]	Double-blind placebo-controlled RCT, 10 asthma patients, mean age 48 year	Oral ketoconazole 400 mg/day for 12 months	Symptoms Lung function Biomarkers Radiology	2.5 mg Two patients had adverse drug effects and withdrew Reduction in symptom scores ($P < 0.001$) No improvement in FEV ₁ or FVC Significant improvement in total IgE, IgG, and specific IgE ($P < 0.05$) No radiological improvement
Henderson et al. [38]	Case report, 3 asthma patients, 33, 37 and 40 year	Nebulized natamycin, for at least 18 months	Symptoms Exacerbations Biomarkers Radiology	No improvement in respiratory symptoms in 1 patient No decrease in number of exacerbations Reduction of blood eosinophilia in 1 patient Radiological aggravation in 1 case
Stark et al. [14]	Case report, 1 asthma patient, 46 year	Nebulized nystatin, 100 000 units, 10 days	Symptoms Biomarkers Radiology	Resolution of fever and asthma symptoms Decrease in eosinophil counts Improvement in pulmonary infiltrates
Summary	38 studies – 4 RCTs, 34 observational studies (21 case reports, 11 case series, 1 cohort study, and 1 uncontrolled clinical trial)	Antifungal agents to treat ABPA	Symptoms Quality of life Exacerbations Lung function Biomarkers Radiology Steroid-sparing effect Adverse effects	Decrease in symptoms in 8/9 studies; 1/2 revealed improvement of quality of life scores Increased number of exacerbations in 3/15 studies Improvement in lung function (FEV ₁) in 19/25 studies Evaluation of serum biomarkers (total and specific IgE, specific IgG, and eosinophils) in 30 studies, 26 of which showed a decrease in total IgE Improvement in radiological infiltrates in 12/15 studies Steroid-sparing effect in 20/23 studies Adverse effects in 14/16 studies

Af, *Aspergillus fumigatus*; APBA, allergic bronchopulmonary aspergillosis; bid, twice daily; CF, cystic fibrosis; CT, computerized tomography; FEF_{25–75}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; RCT, randomized controlled trial; SF-36, 36-item Medical Outcome Study Short-Form General Health Survey).

Table 2. GRADE evidence profile assessing the question: Should antifungal agents be used to treat allergic bronchopulmonary aspergillosis?

Quality assessment			No. of patients				Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antifungals	Control	Absolute	Quality	Importance
Exacerbations (need of rescue treatment, corticosteroid or hospital admission)											
3 ¹	Randomized trials	No serious risk of bias	Serious ^{1,2}	Serious ²	Serious ³	None	0/37 (0%) ⁴	0/29 (0%)	Not pooled	⊕ very low	Critical
12 ⁵	Observational studies ⁶	Serious ^{2,5,6}	Serious ^{2,5}	Serious ²	Serious ^{3,8}	Reporting bias ⁷	28/55 (50.9%) ⁸	-	-	⊕ very low	Critical
Lung Function (FEV1 improvement)											
4 ⁹	Randomized trials	No serious risk of bias	Serious ⁹	Serious ¹⁰	No serious imprecision	None	20/53 (37.7%)	13/51 (25.5%)	Not pooled	⊕⊕ low	Critical
21 ¹¹	Observational studies ⁶	Serious ²⁰	Serious ^{6,10}	Serious ¹⁰	Serious ^{3,6}	Reporting bias ⁷	61/143 (42.7%) ¹²	-	-	⊕ very low	Critical
Total IgE (Total IgE decrease)											
4 ⁹	Randomized trials	No serious risk of bias	Serious ⁹	No serious indirectness	Serious ³	None	22/54 (40.7%) ¹³	11/52 (21.2%)	Not pooled	⊕⊕ low	Important
22 ¹⁴	Observational studies ⁶	Serious ⁶	Serious ¹²	Serious ¹⁰	Serious ¹⁰	None	83/122 (68.0%) ¹²	-	-	⊕ very low	Important
Specific IgE to <i>Aspergillus fumigatus</i> (Specific IgE reduction)											
1 ¹⁵	Randomized trial	Serious ^{16,17}	No serious inconsistency	Serious ¹⁷	Serious ^{3,16}	None	4	3	Mean 5.9, decrease from 7.7 before the intervention (4.4 to 7.3)	⊕ very low	Important
6 ¹⁸	Observational studies ⁶	Serious ⁶	Serious ¹⁸	No serious indirectness	Serious ^{3,6}	None	35/76 (46.1%)	-	-	⊕ very low	Important
Specific IgG to <i>Aspergillus fumigatus</i> (Precipitating antibodies and IgGs to <i>Aspergillus fumigatus</i> decrease)											
6 ¹⁹	Observational studies ⁶	Serious ⁶	Serious ¹⁹	No serious indirectness	Serious ³	None	31/50 (62%) ¹²	-	-	⊕ very low	Important
Eosinophils (peripheral blood eosinophils' decrease)											
14 ²⁰	Observational studies ⁶	Serious ⁶	Serious ²⁰	No serious indirectness	Serious ^{3,6}	None	31/72 (43.1%) ¹²	-	-	⊕ very low	Important
Radiological findings (Improvement or resolution of pulmonary infiltrates)											
2 ²¹	Randomized trials	No serious risk of bias	Serious ²¹	No serious indirectness	Serious ³	None	18/26 (69.2%)	18/26 (69.2%)	Not pooled	⊕ low	Important
13 ²²	Observational studies ⁶	Serious ⁶	Serious ²²	Serious ²³	Serious ^{3,6}	Reporting bias ⁷	22/30 (73.3%)	-	-	⊕ very low	Important
Steroid-sparing effect (corticosteroid dose reduction, with eventual weaning)											
2 ²⁴	Randomized trials	Serious ¹²	Serious ²⁴	Serious ²	Serious ³	None	17/32 (53.1%) ²⁵	14/35 (40%)	Not pooled	⊕ very low	Important
21 ²⁶		Serious ⁶	Serious ²⁶	Serious ²	Serious ^{3,6}		-	-	-	⊕ very low	Important

(continued)

Table 2. (continued)

Quality assessment							No. of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antifungals	Control	Absolute	Quality	Importance
Observational studies ⁶							70/86 (81%)				
Safety (adverse events reported during treatment)							Reporting bias ⁷				
2 ²⁴	Randomized trials	No serious risk of bias	Serious ²⁴	Serious ²	Serious ²	None	26/38 (68.4%)	24/37 (64.9%)	Not pooled	⊕ very low	Important
14 ²⁷	Observational studies ⁶	Serious ⁶	Serious ²⁷	No serious indirectness	Serious ^{2,3,6,27}	None	45/110 (41%)	-	-	⊕ very low	Important

¹Different antifungal interventions: itraconazole [56, 59] and natamycin [32].²Differed in the definition of the outcome.³Small sample size.⁴The number of events per patient was provided only by Stevens *et al.* [56]; the other studies only reported median number of exacerbations [32, 59].⁵Different interventions: itraconazole [35, 42, 47, 48, 52, 57, 58], voriconazole [44, 45], natamycin [38], nystatin [14] and itraconazole in association with voriconazole [26].⁶All case reports and case series, with no control groups.⁷Risk of bias as a preference for publication of positive outcomes with antifungal treatment.⁸Number of patients with event were provided by all studies except for that by Nepomuceno [47], where no events per patient were included.⁹Different antifungal interventions: itraconazole [56, 59], natamycin [32] and ketoconazole [53].¹⁰The studies provided only a statement of improvement in outcome; no specific data for the measured outcome were reported in some of the studies.¹¹Different antifungal interventions: itraconazole [29, 30, 33, 34, 42, 47, 49, 50, 52, 54, 55, 57, 58], voriconazole [39, 44, 45, 60, 61], posaconazole [60], natamycin [38], amphotericin B [51] and amphotericin B in association with itraconazole [37].¹²Number of patients with event was provided by all studies except for that by Salez and Glackin [52, 61], where no values per patient were provided.¹³Number of patients with event was provided by all papers except those by Shale and Currie [32, 53].¹⁴Different antifungal interventions: itraconazole [28, 30, 31, 33, 35, 40, 43, 48, 50, 52, 54, 55, 57], voriconazole [39, 44, 45], ketoconazole [27] and itraconazole in association with amphotericin B [36, 46] or voriconazole [26].¹⁵Only one study reported using ketoconazole [53].¹⁶Selection bias, single-center study.¹⁷No comparison was performed between intervention and placebo (pre- and post-treatment comparison only).¹⁸Different antifungal interventions: itraconazole [29, 50, 52, 54], voriconazole and posaconazole [60] and amphotericin B in association with itraconazole [36].¹⁹Different antifungal interventions: itraconazole [35, 49, 52, 54], voriconazole [44] and itraconazole in association with amphotericin B [36].²⁰Different interventions: itraconazole [35, 40, 42, 48, 50, 52, 54, 58], voriconazole [44, 45, 60, 61], posaconazole [60], natamycin [38], nystatin [14] and amphotericin in association with itraconazole [36, 46].²¹Different antifungal interventions: itraconazole [56] and ketoconazole [53].²²Different antifungal treatments: itraconazole [28, 30, 31, 42, 48, 55, 57], ketoconazole [27], voriconazole [41, 60, 61], posaconazole [60], nystatin [14], natamycin [38] and itraconazole in association with amphotericin B [36].²³Evaluation of radiological findings based on interpretation, with a lack of standardization between studies.²⁴Different antifungal interventions: itraconazole [56] and natamycin [32].²⁵Number of patients with event in the intervention group not included by Currie [32] as individual outcome results were not reported per patient.²⁶Different antifungal interventions: itraconazole [28, 31, 33, 35, 40, 43, 47, 49, 50, 52, 55, 58], voriconazole [41, 44, 61], amphotericin B [11, 51], itraconazole followed by voriconazole [26] or amphotericin B [36, 37] and amphotericin B followed by itraconazole [46].²⁷Different adverse effects reported and different antifungal treatments used: itraconazole [33–35, 47, 48, 54, 55], voriconazole [39, 44, 45, 60–62], posaconazole [60] and itraconazole followed by voriconazole [26].

Table 3. GRADE – Summary of findings: use of antifungals for allergic bronchopulmonary aspergillosis treatment

Outcomes	Study design	No. of participants (studies)	Quality of evidence (GRADE)	Comments
Exacerbations	Randomized controlled trial	66 (3 studies ¹)	⊕⊕⊕⊕ very low ^{1,2,3,4}	
Need for rescue treatment, corticosteroids or hospital admission	Observational studies	55 (12 studies ^{5,6})	⊕⊕⊕⊕ very low ^{2,3,4,5,6,7}	Case series and case reports; 28 events
Lung function	Randomized Controlled Trials	104 (4 studies ⁸)	⊕⊕⊕⊕ low ^{8,9}	
Improvement in FEV ₁	Observational Studies	143 (21 studies ^{6,10})	⊕⊕⊕⊕ very low ^{3,4,6,7,9,10}	Case series and case reports; 61 events
Total IgE	Randomized Controlled Trials	106 (4 studies ⁹)	⊕⊕⊕⊕ low ^{3,8}	
Decrease in IgE	Observational Studies	122 (22 studies ^{6,11})	⊕⊕⊕⊕ very low ^{4,6,9,11}	Case series and case reports; 83 events
Specific IgE to <i>Aspergillus fumigatus</i>	Randomized Controlled Trials	7 (one study ¹²)	⊕⊕⊕⊕ very low ^{3,12,13,14}	
Reduction in specific IgE	Observational Studies	76 (six studies ^{6,15})	⊕⊕⊕⊕ very low ^{2,6,15}	Case series and case reports; 35 events
Specific IgG to <i>Aspergillus fumigatus</i>	Observational Studies	50 (six studies ^{6,16})	⊕⊕⊕⊕ very low ^{3,4,6,16}	Case series and case reports; 31 events
Decrease in precipitating antibodies and IgGs to <i>Aspergillus fumigatus</i>				
Eosinophils	Observational Studies	72 (14 studies ^{6,17})	⊕⊕⊕⊕ very low ^{2,4,6,17}	Case series and case reports; 31 events
Decrease in peripheral blood eosinophils				
Radiology	Randomized Controlled Trials	52 (2 studies ¹⁹)	⊕⊕⊕⊕ low ^{3,18}	
Improvement in or resolution of pulmonary infiltrates	Observational Studies	30 (13 studies ^{6,19})	⊕⊕⊕⊕ very low ^{3,6,7,19,20}	Case series and case reports; 22 events
Steroid-sparing effect	Randomized Controlled Trials	67 (2 studies ²¹)	⊕⊕⊕⊕ very low ^{2,3,4,21}	
Reduction in corticosteroid dose, with eventual weaning	Observational Studies	86 (21 studies ^{6,22})	⊕⊕⊕⊕ very low ^{2,3,6,7,22}	Case series and case reports; 70 events
Safety	Randomized Controlled Trials	75 (2 studies ²¹)	⊕⊕⊕⊕ low ^{2,21}	
Adverse effects reported during treatment ²³	Observational Studies	110 (14 studies ^{6,24})	⊕⊕⊕⊕ very low ^{2,3,6,24}	Case series and case reports; 45 events

GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

¹Different antifungal interventions: itraconazole [56, 59] and natamycin [32].

²Differed in the outcome definition.

³Small sample size.

⁴The number of events per patient was not provided by all studies.

⁵Different interventions; itraconazole [35, 42, 47, 48, 52, 57, 58], voriconazole [44, 45], natamycin [38], nystatin [14] and itraconazole in association with voriconazole [26].

⁶All case reports and case series.

⁷Risk of publication bias, over-reported positive outcomes.

⁸Different antifungal interventions: itraconazole [56, 59], natamycin [32] and ketoconazole [53].

⁹The studies provided only a statement of improvement of the outcome, no quantitative data of the measured outcome was provided in some of the studies.

¹⁰Different antifungal interventions: itraconazole [29, 30, 33, 34, 42, 47, 49, 50, 52, 54, 55, 57, 58], voriconazole [39, 44, 45, 60, 61], posaconazole [60], natamycin [38], amphotericin B [51] and amphotericin B in association with itraconazole [37].

¹¹Different antifungal interventions: itraconazole [28, 30, 31, 33, 35, 40, 43, 48, 50, 52, 54, 55, 57], voriconazole [39, 44, 45, 60, 61], posaconazole [60], ketoconazole [27] and itraconazole in association with amphotericin B [36, 46] or voriconazole [26].

¹²Only one study reported using ketoconazole [53].

¹³Selection bias, single-centre in association with e study.

¹⁴No comparison between intervention and placebo (pre- and post-treatment comparison only).

¹⁵Different antifungal interventions: itraconazole [29, 50, 52, 54], voriconazole and posaconazole [60] and amphotericin B in association with itraconazole [36].

¹⁶Different antifungal interventions: itraconazole [35, 49, 52, 54], voriconazole [44] and itraconazole in association with amphotericin B [36].

¹⁷Different interventions: itraconazole [35, 40, 42, 48, 50, 52, 54, 58], voriconazole [44, 45], natamycin [38], nystatin [14] and amphotericin in association with itraconazole [36, 46].

¹⁸Different antifungal interventions: itraconazole [56] and ketoconazole [53].

¹⁹Different antifungal treatments: itraconazole [28, 30, 31, 42, 48, 55, 57], ketoconazole [27], voriconazole [41, 60], posaconazole [60], nystatin [14], natamycin [38] and itraconazole in association with amphotericin B [36].

²⁰Evaluation of the radiological findings was based on interpretation, with lack of standardization between studies.

²¹Different antifungal interventions: itraconazole [56] and natamycin [32].

²²Different antifungal interventions: itraconazole [28, 30, 31, 33, 35, 40, 43, 47, 49, 50, 52, 55, 58], voriconazole [41, 44, 61], amphotericin B [51], itraconazole followed by voriconazole [26] or amphotericin B [36, 37] and amphotericin B followed by itraconazole [46].

²³Reported adverse effects varied from increase in dyspnoea, haemoptysis, transient liver function changes and photosensitivity to renal insufficiency, Cushing syndrome and rhabdomyolysis.

²⁴Reported different adverse effects and performed different antifungal treatments: itraconazole [33–35, 47, 48, 54, 55], voriconazole [39, 44, 45, 60–62], posaconazole [60] and itraconazole in association with voriconazole [26].

Symptoms and quality of life

Nine studies addressed symptoms and quality of life; four analysed itraconazole [26, 28, 34, 57] and the others analysed voriconazole [60], posaconazole [60], ketoconazole [53], nebulized nystatin [14] and natamycin [38]. All performed a qualitative symptom description, except for one that used an author-established respiratory symptoms score [53] and another that scored each respiratory symptom by severity and frequency [60]. Improvement, evaluated qualitatively, was reported in eight of the nine studies. No improvement was seen with nebulized natamycin in one of the three case reports presented. Symptoms were evenly reported between asthma and cystic fibrosis patients. However, as no validated respiratory symptoms or control scores were used, this outcome was not considered in the GRADE assessment. Quality of life scores and improvement in exercise tolerance were reported in one RCT [56], which used the SF-36 (36-item Medical Outcome Study Short-Form General Health Survey) and in one observational study that assessed quality of life as patient's perceptions of symptoms, but did not state a specific measure [60]. No differences were observed between the intervention and the placebo groups and improvement in exercise tolerance had no defined measure in the RCT trial [56].

Exacerbations

Exacerbations were reported in 14 studies [14, 26, 32, 35, 38, 42, 44, 45, 48, 52, 56–59], three of which were RCTs [32, 56, 59] and multiple antifungal interventions were assessed (Table 1). The definition of an exacerbation episode differed among studies, ranging from an acute episode or relapse after the tapering of corticosteroids, to the need for prednisone or antibiotics, or hospital admission. All of the studies except two [42, 47] were performed in asthmatic patients. Two of the RCTs assessed itraconazole efficacy and showed a reduction in the number of exacerbations in comparison with placebo [56, 59]. The third trial [32], which analysed nebulized natamycin, reported no differences between the study and placebo groups in terms of the number of exacerbations. Half (50.9%) of the patients in the observational studies had an exacerbation while on antifungal therapy.

Lung function

Lung function results were assessed by FEV₁, as this was the most commonly reported parameter (Table 2). Twenty one observational studies [29, 30, 33, 34, 37–39, 42, 44, 45, 47, 49–52, 54, 55, 57, 58, 60, 61] and four RCTs [32, 53, 56, 59] assessed FEV₁. FEV₁ was

mainly reported as the percentage of improvement in comparison with baseline measures [59]. However, the study by Salez et al. [52] provided median lung function values for all treated patients, while some of the observational studies reported the result of the intervention in qualitative terms. The studies were evenly distributed between cystic fibrosis and asthma patients. All of the RCTs involved asthma patients [32, 53, 56, 59] and only one of these [56] reported that FEV₁ improvement was more pronounced in patients in the intervention group. All the case reports and case series reported improvements in FEV₁, except for two studies that evaluated itraconazole in cystic fibrosis patients [29, 47] and two studies that assessed voriconazole, one that evaluated patients with asthma [60] and the other patients with cystic fibrosis [61].

We attempted a quantitative analysis for FEV₁ using data from Wark et al. [59] and Stevens et al. [56], who performed the same intervention (itraconazole 400 mg/day) and used a similar design. A funnel plot of the pooled data is shown in Figure S1. While it shows possible asymmetry, the heterogeneity assessed with the *I*² test was 0%. A meta-analysis was precluded due to the small sample size and risk of potential bias.

Biomarkers

Several measures were used in the assessment of inflammatory biomarkers, namely, total serum IgE, specific IgE and specific IgG to *A. fumigatus*, eosinophil counts and specific IgE to recombinant *A. fumigatus* Asp f3, 4 and 6 in one study [42]. The most frequently described biomarker was total IgE, reported in four RCTs [32, 53, 56, 59] and 22 observational studies [26–28, 30, 31, 33, 35, 36, 39, 40, 43–46, 48, 50, 52, 54, 55, 57, 60, 61]. In the RCTs, although total IgE decreased significantly after the intervention, no comparison was made with placebo.

Due to the similarity of the studies and the measured outcome, data from the trials of Wark et al. [59] and Stevens et al. [56] was pooled for total IgE. The resulting funnel plot shows asymmetry (Figure S1). Moreover, heterogeneity evaluated by *I*² was 62%, suggesting the presence of substantial heterogeneity for this outcome.

All the observational studies reporting total IgE showed a similar result to the RCTs, except for one case series of patients with cystic fibrosis [29], where no differences were seen with itraconazole. Similarly, this study reported no differences when specific IgE to *A. fumigatus* was assessed; all the other studies showed a decrease in this biomarker [29, 50, 52–54, 60].

Specific IgG to *A. fumigatus* was described in six observational studies [35, 36, 44, 49, 52, 54] and in all a decrease was seen after treatment. With the exception of one case series of patients with cystic fibrosis [54],

all the studies evaluated asthmatic patients. Peripheral blood eosinophil count decreased in all 14 observational studies in which they were reported [14, 35, 36, 38, 40, 42–46, 48, 50, 52, 54, 58], irrespective of antifungal intervention or primary disease.

Radiological findings

Radiological findings were documented in 13 observational studies [14, 27, 28, 30, 31, 36, 38, 41, 42, 48, 55, 57, 60] and two RCTs [53, 56]. The outcomes measured were changes in pulmonary infiltrates and consolidations on chest X-ray or CT scans. The RCTs yielded similar results for patients in the intervention and placebo groups, with no improvements noted. In the observational studies assessed, Tang et al. [57] reported no changes in pulmonary findings, Godet et al. [36] noted the appearance of new consolidations with itraconazole, followed by resolution with nebulized amphotericin B, and Henderson and Pearson et al. [38], in a nebulized natamycin intervention, described the appearance of new pulmonary infiltrates. The other studies all reported intervention-related improvements.

Steroid-sparing effects

Steroid-sparing effects were assessed as a reduction in oral steroid dose or the weaning of steroids during follow-up. This outcome was mentioned in 23 studies [26, 28, 30–33, 35–37, 40, 41, 43, 44, 46, 47, 49–52, 55, 56, 58, 61], two of which were RCTs [32, 56]. Corticosteroid weaning started after 2–12 months in all the studies. In the RCT by Stevens et al. [56], a reduction was seen with oral itraconazole in comparison with placebo. In the other RCT, however, no between-group differences were observed. All studies, except for two case series [35, 51], showed a reduction in steroid use.

Safety

Adverse effects were described in 14 observational studies [26, 33–35, 39, 44, 45, 47, 48, 54, 55, 60–62] and two RCTs [32, 56]. Adverse effects were reported in 71 of the 148 patients who received an antifungal agent and in 24 of the 37 patients who received placebo. Of note, the RCTs reported an adverse effect rate of 68% in the intervention group (vs. 65% in the placebo), whereas the observational studies reported a rate of 41%. Events were seen in studies in which antifungals were used alone or in association with corticosteroids [33, 52, 56, 59]. The most frequent adverse effects varied from increased dyspnoea, haemoptysis, transient liver function changes and photosensitivity to renal insufficiency, Cushing syndrome and rhabdomyolysis.

Discussion

This systematic review showed that antifungal interventions in ABPA, irrespective of whether they were used in patients with asthma or cystic fibrosis, resulted in a consistent improvement in disease symptoms, frequency of exacerbations and lung function, and also showed a steroid-sparing effect. Furthermore, they had a positive impact on biomarkers and radiological pulmonary infiltrates. These effects were more consistent with oral azoles. Adverse effects were frequently reported and should therefore not be underrated. However, recommendations for the use of antifungals in ABPA are hampered by the low and very low quality of evidence supporting these findings. The body of evidence is limited by the small number of controlled studies, heterogeneity between studies and the potential bias associated with the observational studies included. Therefore, efficacy of antifungal agents in ABPA cannot be accurately estimated and the recommendation to use antifungal agents in ABPA is weak.

The perpetuation of ABPA is caused by the immune response to *A. fumigatus* antigens. The rationale for using antifungal agents in ABPA is based on the antifungal and anti-inflammatory activities of these drugs [56]. It is assumed that the reduction of the fungal burden might decrease antigenic stimulation, reduce inflammation, ameliorate symptoms and, eventually, reduce the risk of disease progression. Antifungals are recommended as adjuvant therapy in the treatment of ABPA, the main therapy being oral steroids. Systemic corticosteroids are currently the most effective treatment for the acute phase of ABPA; however, long-term systemic corticosteroid therapy use is not recommended due to the risk of severe adverse effects [11, 64, 65]. Moreover, no standardized data exist to guide treatment options and therapeutic schemes, particularly in relation to doses and duration of corticosteroid therapy. Steroid-dependent patients are advised to use the lowest effective dose. The use of antifungal treatment, especially in association with corticosteroid therapy, has been questioned in several opinion articles, reviews, and previously published guidelines [11, 64, 65]. The emergence of life-threatening infections due to *Aspergillus* species, especially in immunocompromised individuals, was recently recognized in the clinical practice guidelines for the treatment of aspergillosis published by the Infectious Disease Society of North America [17]. According to these guidelines, antifungal treatment has a central role for invasive aspergillosis, chronic forms of aspergillosis and allergic forms of aspergillosis. We did not include immunocompromised patients in our review, neither patients with aspergilloma at their clinical presentation as they tend to have very specific forms of aspergillosis, namely invasive, chronic and

relapsing forms of the disease. However, previous experience of antifungal efficacy in this population, though limited by the small number of RCTs performed, further supports our hypothesis and the need for this review.

The limitations of this review are primarily linked to the limitations of the studies retrieved. We were unable to analyse response to specific antifungal agents, due to the variety of drugs, doses and associations evaluated, as well as to the small number of studies analysing certain drugs. It is noteworthy that itraconazole was the most common antifungal mentioned, and was the treatment of choice in 21 studies, corresponding to 174 patients. Even in studies analysing the same antifungal agent, different doses and treatment durations were used. It is also difficult to isolate the effect of the antifungal agent from that of the corticosteroid, as the majority of patients were concomitantly treated with oral steroids and, in several cases, both drugs were initiated simultaneously. Furthermore, oral steroids were used in different doses and tapering schemes, which made the assessment of steroid-sparing effects challenging, particularly in studies without control groups (observational studies). The evaluation of adverse effects in the studies reviewed was also limited by the observational nature of many of the studies ($n = 11$) and the absence of a comparator, which is crucial for establishing a link between an observed effect and the study drug (antifungal in this case) or, in the absence of such a link, for attributing effects to interactions between drugs. In one RCT, adverse effects were considered to be related to the study drug in just five of the 25 patients who reported adverse effects in the intervention group [56]. Furthermore, 23 of the patients in the placebo group of the same trial also reported adverse effects. These findings highlight the need for controls.

We were also unable to analyse the evidence profile of the symptoms outcome, as improvement was evaluated subjectively in most cases. For the other outcomes, the GRADE profile showed a low and very low quality of evidence supporting the findings (Table 2), mainly due to the small number of properly controlled studies. It is also not possible to exclude potential publication bias, especially in case series and case reports, due to the tendency to publish positive rather than negative outcome effects; this could explain the global improvement observed with antifungal use in the observational studies analysed. The heterogeneity and potential bias associated with some of the quantitative outcomes in observational studies also precluded meta-analyses.

To our knowledge, this is the first systematic review to evaluate the efficacy of antifungal treatments in ABPA, and furthermore we collected data from studies of patients with asthma and cystic fibrosis. The pathogenesis of ABPA in these diseases shares common

pathways, including an immunological hypersensitivity response to Af [65] superimposed on a pre-existing airway disease, that is, cystic fibrosis (involving mainly genetic susceptibility) or allergic asthma (driven mainly by allergen exposure). Nevertheless, both asthma and cystic fibrosis are characterized by bronchial epithelium barrier dysfunction and a local environment prone to *Aspergillus* colonization and growth [64–67].

To answer the clinical investigation question (Are antifungal agents effective and safe in patients with ABPA and asthma or cystic fibrosis?), we adopted a wide review perspective, including patients with asthma and cystic fibrosis and all types of antifungal interventions, due to the low prevalence of ABPA. Furthermore, we analysed all types of observational studies, including mostly case reports and case series. The GRADE methodology is designed to permit both quality-of-evidence rating, adapted to each study design and accordingly to a specific outcome and the proposal of recommendations based on a balance between desirable and undesirable outcomes. Using the above-described review strategy, we were able to analyse a large number of patients ($n = 334$) with ABPA who had been treated with antifungals. The majority of patients ($n = 221$) were asthmatic. Although a direct comparison between asthma and cystic fibrosis patients was not possible, no differences were detected in the efficacy and safety of treatment. Oral azole interventions were predominant, and only when nebulized antifungal agents were used was a tendency to a lesser effect detected.

The beneficial role of azoles was shown in a meta-analysis by Wark et al. [15] that evaluated the efficacy of azoles in ABPA associated with asthma. Itraconazole was found to be associated with the best improvements in clinical outcomes, and it also modified immune activation. The findings of the meta-analysis are consistent with reports from *in vitro* studies, where azoles had the lowest minimal inhibitory concentrations in comparison with other antifungals [68]. New evidence suggests that resistance to *Aspergillus* species is emerging. The case of azoles, where this phenomenon is particularly evident, is a concern as resistance could jeopardize the potential effectiveness of these agents, which are needed for long treatment periods. Another recent meta-analysis addressed antifungal therapy in ABPA associated with cystic fibrosis [16]. The authors did not locate any new RCTs and concluded that much research remains to be done in this field. Due to the inclusion of observational studies in our systematic review, we were able to assess patients with cystic fibrosis receiving experimental antifungal treatments, mostly in association with corticosteroid treatment. The majority of studies showed potential benefits in terms of clinical outcomes. Recently, new definition and staging criteria were proposed for ABPA that may help to guide and standardize antifungal treatment

use [69]. However, adverse events reported, especially in patients receiving concomitant corticosteroid therapy, were consistent with the findings of the two previously published systematic reviews [15, 16] and should be taken in account.

Acute adverse events, such as dyspnoea and liver enzyme changes, were reported, but there was no clear association with antifungal treatment as these events were also common in the placebo group. Cushing syndrome was the most common long-term event reported, but few such events were described due to the short follow-up periods. In their review, Wark *et al.* [15] suggested that itraconazole might act on adrenal suppression and adverse effects of corticosteroids, thereby inducing osteoporosis, cataract formation and Cushing syndrome. This effect could be explained by the interaction of azoles with drugs that are metabolized by cytochrome P450 enzymes, as azoles are competitive inhibitors of CYP 3A4, 2C9 and 2C19. This interaction could also explain some expected adverse events described in this study and the literature, including nausea, vomiting, hypokalemia and hepatotoxicity with itraconazole and visual changes, photosensitivity and hepatotoxicity with voriconazole [70]. Other drugs with known interactions with azoles that are used in both asthma and cystic fibrosis patients are omeprazole, ibuprofen, benzodiazepines, calcium channel antagonists, statins and warfarin. Statins, for example, can potentiate rhabdomyolysis when used in association with azoles. The possibility of drug interactions is therefore an important consideration. A comprehensive individual approach should therefore be adopted when deciding on the introduction of antifungal treatment in ABPA patients with comorbidities, with a careful analysis of the trade-off between potential benefits and risks.

Conclusions

This systematic review showed that antifungal treatment in ABPA improves patient- and disease-oriented outcomes, such as symptoms, frequency of exacerbations, lung function, inflammatory biomarkers and pulmonary infiltrates, and also has a steroid-sparing effect. However, due to the small number of controlled studies analysed, the heterogeneity between studies and the potential bias associated with observational studies, the recommendation to use antifungal agents in ABPA is weak. Therefore, clinicians should closely weigh up desirable and undesirable effects and consider patient's individual conditions before introducing an antifungal.

Finally, more multicentre RCTs need to be conducted, particularly in cystic fibrosis, where controlled studies are lacking. Further research in antifungal efficacy in patients with ABPA is very likely to have an important impact on the confidence in the estimated effect of antifungal treatment on disease outcomes and on future treatment recommendations.

Conflict of interest

The authors declare no conflict of interests or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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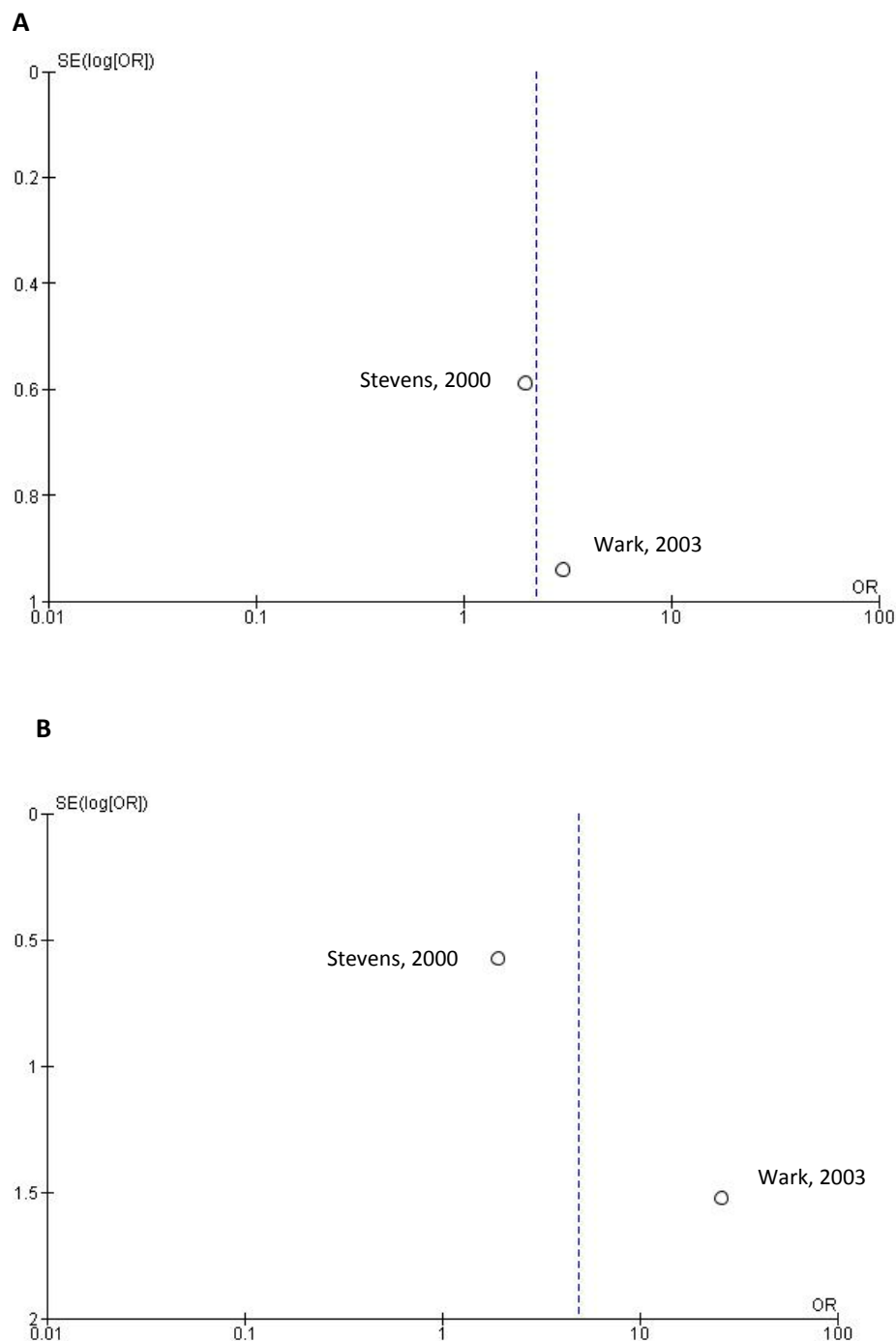
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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Supplementary Figure 1. Funnel plot of precision estimates calculated by using the inverse of the standard error (SE) of log (odds ratio); ie, the higher the estimate, the more precise the study. The vertical dashed line represents the summary estimate of the odds ratio for all studies. **A-** presents studies comparing improvement in FEV₁ with itraconazole intervention Vs conventional treatment; **B -** presents studies comparing decrease in serum total IgE with itraconazole intervention Vs conventional treatment



Supplementary Table 1. Search queries

EBSCO	PUBMED	SCOPUS
(bronchopulmonary aspergillosis OR aspergillosis OR aspergillos* OR "allergic bronchopulmonary mycosis" OR "allergic bronchopulmonary mycosis" OR "abpa" OR "allergic bronchopulmonary aspergilloses" OR "allergic bronchopulmonary aspergillosis") AND (antifungal agents OR azoles OR "antifungal agents" OR "antifungal drugs" OR "ketokonazole" OR "amphotericin" OR "itraconazole" OR "voriconazole" OR azole* OR triazole*) AND Cystic fibrosis AND (asthma OR bronchitis OR "asthma" OR "allergic asthma" OR asthm*) NOT animals	((((Aspergillosis[MeSH Terms])) OR (allergic bronchopulmonary aspergillosis[MeSH Terms])) OR (allergic bronchopulmonary mycosis[MeSH Terms])) AND (((antifungal agents[MeSH Terms])) OR (azoles[MeSH Terms])) OR (((((azole*) OR triazole*) OR itraconazole) OR ketoconazole) OR voriconazole) OR amphotericin B)) AND (((((Asthma[MeSH Terms])) OR (Bronchitis[MeSH Terms])))) OR (cystic fibrosis[MeSH Terms]))	ALL(cystic fibrosis) OR ("cystic fibrosis") AND (ALL(asthma) OR ALL(bronchitis) OR "asthma" OR "allergic asthma" OR asthm*) AND (ALL(antifungal agents) OR ALL(azoles) OR "antifungal agents" OR "antifungal drugs" OR "ketokonazole" OR "amphotericin" OR "itraconazole" OR "voriconazole" OR azole* OR triazole*) AND (ALL(aspergillosis) OR ALL(bronchopulmonary aspergillosis) OR (aspergillosis) OR aspergillos* OR "allergic bronchopulmonary mycosis" OR "allergic bronchopulmonary mycosis" OR "abpa" OR "allergic bronchopulmonary aspergilloses" OR "allergic bronchopulmonary aspergillosis") AND NOT animals

Information sources: EBSCO, Pubmed, SCOPUS. Last date of search: 10/10/2012

Supplementary Table 2. Excluded studies from systematic review

Reference	Study Design	Intervention	Outcome measure	Results	Reason for exclusion
Aaron SD et al, 2012[1]	Randomized controlled trial	Itraconazole	Exacerbation, lung function, adverse effects	Intervention had less exacerbations and more adverse effects than placebo Both groups had decrease in FEV1	Did not included ABPA patients only colonized with <i>Aspergillus</i>
Bains SN et al, 2012[2]	Classic Review	None	-	Descriptive analysis	No intervention
Calderón ALB et al, 2012[3]	2 Case reports	Corticosteroids	Clinical Improvement	Favourable clinical and functional evolution and decrease in IgE (patient 1)	No antifungal treatment assessed
Elphick HE et al, 2012[4]	Systematic review	None	-	Descriptive analysis	No intervention
Fanta CH et al, 2012[5]	Classic Review	None	-	Descriptive analysis	No intervention
Greenberger PA, 2012[6]	Classic Review	None	-	Descriptive analysis	No intervention
Gupta RK et al, 2012[7]	Classic Review	None	-	Descriptive analysis	No intervention
Rondeau S et al, 2012[8]	Letter to the editor	Voriconazole	Phototoxicity	58% photosensitivity in patients taking voriconazole	Voriconazole not assessed as treatment
Tillie-Leblond I et al, 2012[9]	Classic Review	None	-	Descriptive analysis	No intervention
Agarwal R et al, 2011[10]	Classic Review	None	-	Descriptive analysis	No intervention
Baxter CG et al, 2011[11]	Retrospective cohort	Triazole Therapy	Development of peripheral neuropathy	23 out of 222 patients developed peripheral neuropathy	Patients with chronic aspergillosis, not specified type ABPA
Eber E et al, 2011[12]	Classic Review	None	-	Descriptive analysis	No intervention
Fekih L et al, 2011[13]	Case report	Corticosteroids and Bronchodilators	Improve symptoms	2 stopped treatment, 1 improvement	No antifungal treatment evaluated
Hogan C et al, 2011[14]	Classic Review	None	-	Descriptive analysis	No intervention
Kousha M et al, 2011[15]	Classic Review	None	-	Descriptive analysis	No intervention
Le Bourgeois M et al, 2011[16]	Classic Review	None	-	Descriptive analysis	No intervention
Nariman-Shahhosseini et al, 2011[17]	Classic Review	None	-	Descriptive analysis	No intervention

Nowicka U et al, 2011[18]	Case report	Itraconazole	Radiologic and Biomarkers	Improvement in radiologic and decrease of IgE	No measurement for outcome was given in the text
Schwerk N et al, 2011[19]	Case report	Corticosteroid (prednisolone)	Clinical Improvement	After 12 months, patient was asymptomatic, had stopped antibiotic therapy, had normalized lung function, serum IgE and eosinophil counts	No antifungal treatment assessed
Cheng MP et al, 2010[20]	Case series	Voriconazole	Adverse drug reaction	Of 6 patients, 5 developed photosensitivity and 6 reported visual disturbances	Did not included patients with ABPA, but with chronic necrotizing pulmonary aspergillosis.
Sharif MA et al, 2010[21]	Case report	Itraconazole	Clinical Improvement	Improvement after 2 weeks of treatment	Did comply with all ABPA criteria
Germaud P et al, 2010[22]	Letter to the editor	Omalizumab	Clinical Improvement	In remission for 22 months without corticoids or antifungals	No antifungal treatment assessed
Hodgson U, 2010[23]	Classic Review	None	-	Descriptive analysis	No intervention
Hsu LY et al, 2010[24]	Classic Review	None	-	Descriptive analysis	No intervention
Moss RB, 2010[25]	Classic Review	None	-	Descriptive analysis	No intervention
Mulliez P, 2010[26]	Opinion article / editorial	None	-	Descriptive analysis / opinion	No intervention
Patterson K et al, 2010[27]	Classic Review	None	-	Descriptive analysis	No intervention
Boz AB et al, 2009[28]	Case report	Itraconazole	Lung function, radiologic and steroid sparing effect	Respiratory status improved over time, dose of steroids decreased	No measurement for outcome was given in the text
Hatziagorou E et al, 2009[29]	Classic Review	None	-	Descriptive analysis	No intervention
Howard SJ et al, 2009[30]	Case report	Itraconazole	Response to azoles	Development of resistances	No patient oriented outcome
Kirsten A et al, 2009[31]	Classic Review	None	-	Descriptive analysis	No intervention
Moss RB et al, 2009[32]	Classic Review	None	-	Descriptive analysis	No intervention
Segal BH, 2009[33]	Classic Review	None	-	Descriptive analysis	No intervention, review focus on Invasive aspergillosis not ABPA
Çelik U et al, 2008[34]	Classic Review	None	-	Descriptive analysis	No intervention, review of antibiotic use on ABPA, not antifungal

Greenberger PA, 2008[35]	Classic Review	None	-	Descriptive analysis	No intervention
Jensen SG et al, 2008[36]	Case report	Voriconazole + caspofungine	Symptoms and Radiologic	Improvement of asthmatic symptoms, radiologic deterioration	Invasive ABPA (chronic necrotizing aspergillosis)
Laoudi Y et al, 2008[37]	Case report	Itraconazole	-	Descriptive analysis	No measurement for outcome was given in the text
Lazarus AA et al, 2008[38]	Classic Review	None	-	Descriptive analysis	No intervention
Menz G, 2008[39]	Classic Review	None	-	Descriptive analysis	No intervention
Tonnel AB, 2008[40]	Classic Review	None	-	Descriptive analysis	No intervention
Walsh TJ et al, 2008[41]	Classic Review	None	-	Descriptive analysis	No intervention
Braun JJ et al, 2007[42]	Case series	flucytosine; itraconazole; association flucytosine + itraconazole + ketoconazole	Clinical evolution	3 cases resolved, 1 case improved, 2 therapeutic failures	Invasive ABPA (allergic fungal sinusitis)
Camuset J et al, 2007[43]	Retrospective study	Voriconazole	Clinical Improvement and control of the disease	Improvement in 58%	No ABPA patients included
Erwin GE et al, 2007[44]	Case report	2 courses itraconazole followed by 2 courses voriconazole	Lung function, biomarkers, exacerbations and steroid sparing effect	No change in FEV1, high total IgE, no exacerbations, improvement in steroid requirements	Invasive ABPA (allergic fungal sinusitis)
Zmeili OS et al, 2007[45]	Classic Review	None	-	Descriptive analysis	No intervention
Agarwal R et al, 2006[46]	Cohort study	None	-	Descriptive analysis	No intervention
Almeida MB, 2006[47]	Classic Review	None	-	Descriptive analysis	No intervention
Barnes PD et al, 2006[48]	Classic Review	None	-	Descriptive analysis	No intervention
Gibson PG, 2006[49]	Classic Review	None	-	Descriptive analysis	No intervention
Hughes R et al, 2006[50]	Case report	Corticosteroid (prednisolone)	Clinical Improvement	Improved after 1 month of treatment	No antifungal treatment assessed
Huttegger I et al, 2006[51]	Classic Review	None	-	Descriptive analysis	No intervention

Moss RB, 2006[52]	Opinion article / editorial	None	-	Descriptive analysis / opinion	No intervention
Woods DR, 2006[53]	Case report	Itraconazole and corticosteroids	Clinical Improvement	Side-effects	Patient did not fulfil the criteria for ABPA
Braun JJ et al, 2005[54]	Case series	ORL surgery + corticotherapy + antifungal	Clinical evolution	3 cases had good evolution, 1 therapeutic failure	Invasive ABPA (allergic fungal sinusitis)
Freymond N et al, 2005[55]	Case report	Voriconazole	Clinical Improvement	Improved after 1 month of treatment	Patient did not fulfil the criteria for ABPA
Germaud P, 2005[56]	Classic Review	None	-	Descriptive analysis	No intervention
Jankowska-Konsur A et al, 2005[57]	Classic Review	None	-	Descriptive analysis	No intervention
Menz G et al, 2005[58]	Classic Review	None	-	Descriptive analysis	No intervention
Moss RB, 2005[59]	Classic Review	None	-	Descriptive analysis	No intervention
Tillie-Leblond I et al, 2005[60]	Classic Review	None	-	Descriptive analysis	No intervention
Couturaud F, 2004[61]	Classic Review	None	-	Descriptive analysis	No intervention
Garcia G et al, 2004[62]	Classic Review	None	-	Descriptive analysis	No intervention
Judson MA, 2004[63]	Classic Review	None	-	Descriptive analysis	No intervention
Malde B et al, 2004[64]	Classic Review	None	-	Descriptive analysis	No intervention
Marcq M et al, 2004[65]	Case reports	Itraconazole	Exacerbation, biomarkers, radiologic and steroid sparing effect	New exacerbations, eosinophils normalized and IgE decreased (1 patient), 2 patients had regression of radiologic infiltrates, no steroid sparing effect	Invasive ABPA and different forms of aspergillosis
Sánchez CD et al, 2004[66]	Classic Review	None	-	Descriptive analysis	No intervention
Wark P et al, 2004[67]	Systematic review	None	-	Descriptive analysis	No intervention
Chiu AM, 2003[68]	Classic Review	None	-	Descriptive analysis	No intervention
Greenberger PA, 2003[69]	Classic Review	None	-	Descriptive analysis	No intervention
Guillot M et al, 2003[70]	Classic Review	None	-	Descriptive analysis	No intervention
Khan NA et al, 2003[71]	Classic Review	None	-	Descriptive analysis	No intervention

Levy MB, 2003[72]	Classic Review	None	-	Descriptive analysis	No intervention
Menz G et al, 2003[73]	Classic Review	None	-	Descriptive analysis	No intervention
Stevens DA et al, 2003[74]	Classic Review	None	-	Descriptive analysis	No intervention
Wachter E et al, 2003[75]	Case report	Itraconazole	Adverse effects	Develop Cushing Syndrome	Patient did not fulfil the criteria of ABPA
Casey P et al, 2002[76]	Case report	Itraconazole followed by amphotericin B	Lung function and steroid sparing effect	Increase in FEV1, steroid reduction when amphotericin B was added	Post-transplant - immunosuppressed patient
Greenberger PA, 2002[77]	Classic Review	None	-	Descriptive analysis	No intervention
Main KM et al, 2002[78]	Case report	Withdraw itraconazole and budesonide	Clinical improvement	Adrenal function improved, but not yet normalized	Patient did not fulfil the criteria of ABPA
Moss RB, 2002[79]	Classic Review	None	-	Descriptive analysis	No intervention
Parmar JS et al, 2002[80]	Case report	Itraconazole	Adverse effects	Hepatic cytolysis and Cushing's syndrome	Patient did not fulfil the criteria of ABPA
Shah A et al, 2002[81]	Classic Review	None	-	Descriptive analysis	No intervention
Soubani AO et al, 2002[82]	Classic Review	None	-	Descriptive analysis	No intervention
Daly P et al, 2001[83]	Classic Review	None	-	Descriptive analysis	No intervention
Denning DW, 2001[84]	Classic Review	None	-	Descriptive analysis	No intervention
Germaud P et al, 2001[85]	Classic Review	None	-	Descriptive analysis	No intervention
Judson MA et al, 2001[86]	Classic Review	None	-	Descriptive analysis	No intervention
Maitre B, 2001[87]	Classic Review	None	-	Descriptive analysis	No intervention
Mastella G et al, 2001[88]	Letter to the editor	None	-	Descriptive analysis / opinion	No intervention
Maurer C, 2001[89]	Case report	Itraconazole 2 weeks	Clinical Improvement	Improved after treatment	Patient did not fulfil the criteria for ABPA
Vlahakis NE et al, 2001[90]	Classic Review	None	-	Descriptive analysis	No intervention
Wark PAB et al,	Classic Review	None	-	Descriptive analysis	No intervention

2001[91]					
González IO et al, 2000[92]	Case report	Corticosteroid (prednisone)	Clinical Improvement	Normalization of the chest X-ray and a decrease of >50% in IgE	No antifungal treatment assessed
Hanley-Lopez J et al, 2000[93]	classic Review	None	-	Descriptive analysis	No intervention
Stevens DA et al, 2000[94]	Classic Review	None	-	Descriptive analysis	No intervention
Taylor NA, 2000[95]	Classic Review	None	-	Descriptive analysis	No intervention
Brémont F et al, 1999[96]	Classic Review	None	-	Descriptive analysis	No intervention
Cockrill BA et al, 1999[97]	Classic Review	None	-	Descriptive analysis	No intervention
Leon EE et al, 1999[98]	Classic Review	None	-	Descriptive analysis	No intervention
Clément A, 1998[99]	Classic Review	None	-	Descriptive analysis	No intervention
Elliott MW et al, 1997[100]	Classic Review	None	-	Descriptive analysis	No intervention
Klein NC et al, 1996[101]	Classic Review	None	-	Descriptive analysis	No intervention
Hiller EJ, 1992[102]	Classic Review	None	-	Descriptive analysis	No intervention
De Beule K et al, 1988[103]	Cohort study	Itraconazole	Clinical improvement	2 patients went into remission, 2 patients had marked improvement, 1 patient did not change	No specific outcome was measured
Fournier EC, 1987[104]	Letter to the editor	None	-	Descriptive analysis and Opinion	No intervention
Patterson R et al, 1982[105]	Cohort study	None	-	Descriptive analysis	No intervention
Pennington JE, 1980[106]	Classic Review	None	-	Descriptive analysis	No intervention
Berger IRA et al, 1972[107]	Case report	Amphotericin B	Clinical Improvement	Decrease of radiological lung infiltrates, renal function impairment	Patient did not fulfil the criteria of ABPA
Henderson AH, 1968[108]	Cohort study	None	-	Descriptive analysis	No intervention

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