Review Article

Childhood allergic bronchopulmonary aspergillosis

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ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disease caused by *Aspergillus* induced hypersensitivity. It usually occurs in immunocompetent but susceptible patients with bronchial asthma and cystic fibrosis. If ABPA goes undiagnosed and untreated, it may progress to bronchiectasis and/or pulmonary fibrosis with significant morbidity and mortality. ABPA is a well-recognized entity in adults; however, there is lack of literature in children. The aim of the present review is to summarize pathophysiology, diagnostic criteria, clinical features, and treatment of ABPA with emphasis on the pediatric population. A literature search was undertaken through PubMed till April 30, 2018, with keywords "ABPA or allergic bronchopulmonary aspergillosis" with limitation to "title." The relevant published articles related to ABPA in pediatric population were included for the review. The ABPA is very well studied in adults. Recently, it is increasingly being recognized in children. There is lack of separate diagnostic criteria of ABPA for children. Although there are no trials regarding treatment of ABPA in children, steroids and itraconazole are the mainstay of therapy based on studies in adults and observational studies in children. Omalizumab is upcoming therapy, especially in refractory ABPA cases. There is a need to develop the pediatric-specific cutoffs for diagnostic criteria in ABPA. Well-designed trials are required to determine appropriate treatment regimen in children.

KEY WORDS: Allergic bronchopulmonary aspergillosis, children, itraconazole, omalizumab, steroids

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INTRODUCTION

A number of *Aspergillus* species, particularly *Aspergillus fumigatus,* cause diseases in humans.[1] Depending on quantity and virulence of inhaled *Aspergillus*, and host's genetic susceptibility and immunity, *Aspergillus* can cause saprophytic (e.g., aspergilloma), invasive (especially in immunocompromised patients), or allergic (*Aspergillus*-mediated asthma, hypersensitivity pneumonia and allergic bronchopulmonary aspergillosis [ABPA]) pulmonary diseases.[2] ABPA is a pulmonary disease caused by *Aspergillus*-induced hypersensitivity. It usually occurs in immunocompetent but susceptible patients with bronchial asthma and cystic fibrosis (CF).[3-5] If ABPA goes undiagnosed and untreated, it may progress to bronchiectasis and/or pulmonary fibrosis with significant morbidity and mortality. ABPA was first described by Hinson *et al*. in 1952 in asthmatic subjects.[6] Since then, there have been many advances in the understanding of pathophysiology and various treatment options for ABPA. ABPA is well-recognized entity in adults. It is increasingly being recognized in children in recent years. ABPA is one of reasons for poorly controlled asthma with significant morbidity in children. The use of oral steroids, the mainstay treatment of ABPA, may cause adverse effects in growing children. The aim of the present review is to summarize pathophysiology, diagnostic criteria, clinical features,

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and treatment of ABPA with emphasis on the pediatric population.

METHODS

A literature search was undertaken through PubMed till August 31, 2016, with key words "ABPA or allergic bronchopulmonary aspergillosis" with limitation to "title," The search was repeated on April 30, 2018, for relevant new articles. The relevant published articles, especially related to ABPA in pediatric population, were studied for writing this review.

EPIDEMIOLOGY

Although *A. fumigatus* is mostly responsible for ABPA,[7] other species of *Aspergillus* (*Aspergillus niger*, *Aspergillus flavus,* etc.) and other fungi (*Stemphylium lanuginosum*, *Helminthosporium* species, *Candida* species, etc.) have been occasionally reported in association with ABPA.[8] The disease caused by fungi other than *Aspergillus* is known as allergic bronchopulmonary mycosis (ABPM) and Candida albicans is most common cause for ABPM.[9] Out of many fungi, only few (*Aspergillus, Candida* etc.) causes human diseases including ABPA and ABPM because these are thermotolerant fungi which can grow both in environment and at body temperature whereas mesophilic fungi (that are unable to grow at body temperature) and thermophilic fungi (that are unable to grow in environment) do not cause ABPM.[10]

Agarwal *et al*.,[11] in a systematic review and meta-analysis, reported the prevalence of *Aspergillus* sensitization (AS) and ABPA in asthmatic adults of 28% (95% confidence interval [CI] 24–34) and 12.9% (95% CI 7.9–18.9), respectively. With time, there is increasing trend of ABPA prevalence in adults which may be due to increased awareness about ABPA among physicians and ready availability of laboratory investigations.[11]

ABPA in asthmatic children is not as common as in adults and it may be due to lack of well-conducted epidemiological studies in children. Slavin *et al*.[12] probably reported the first pediatric case of ABPA in 1970. Since then, there are case reports and small case series in asthmatic children.[13-22] Imbeau *et al*.[21] described the three youngest (<2 years of age) asthmatic children with ABPA. The one of the first prevalence study of ABPA in children was from India where ABPA was reported in 15% of children with perennial asthma and in 6.5% of total asthmatic children screened.[21] Recently, a study from North India in children with poorly controlled asthma reported prevalence of AS and ABPA as 29% and 26%, respectively.[23] Shah *et al*.[24] reported familial occurrence of ABPA in 4.9% of 164 patients. However, ABPA in asthmatic children seems to be underdiagnosed as latent period up to 10 years before diagnosis had been reported.[14]

ABPA in CF patients is not uncommon, even in pediatric age group. A systematic review including 64 studies reported the prevalence of ABPA in CF of 8.9% (95% CI: 7.4%–0.7%), and it was more in adults as compared to children (10.1% vs. 8.9%; $P < 0.0001$).[25] The studies including mainly CF children had reported the prevalence of ABPA from 4.7% to 10.0%.[26-30] The probable youngest CF child with ABPA had symptoms from the age of 11 months, though she was diagnosed with ABPA at age of 3.5 years.[31] A study from India, reported ABPA in 18.2% (95% CI: 6.9%–35.4%) children with CF.[32]

Although sensitization to *Aspergillus* is common in asthmatic and CF patients (20%–25% of asthmatic patients and 31%–59% of CF patients), only a small percentage of these patients develop ABPA.[3-5] A few authors tried to identify the risk factors for ABPA in CF children. Jubin *et al*.[33] reported an association between long-term azithromycin therapy and *Aspergillus* colonization (odds ratio = 6.4, 95% CI: 2.1–19.5). Ritz *et al*.[34] showed that bronchial colonization with Stenotrophomonas maltophilia was a risk factor for ABPA and higher cumulative doses of inhaled corticosteroids, and longer duration of *Pseudomonas aeruginosa* colonization were risk factors for *A. fumigatus* sensitization in CF children. In study from India, age more than 12 years, low-cystic fibrosis score, and presence of atopy and eosinophilia were risk factors for ABPA in CF children.[32]

ABPA had been described very rarely in nonasthmatic, non-CF children. Amin *et al*.[35] reported a case of ABPA in nonasthmatic 18 years male. Boz *et al*.[36] reported ABPA in a 11-year-old girl following active pulmonary tuberculosis. Recently, two cases of ABPA in children were reported with non-CF bronchiectasis.[37]

PATHOPHYSIOLOGY

Although underlying pathophysiology of ABPA is not yet clearly understood, *Aspergillus* spores adhere to preactivated epithelium in genetically susceptible patients with asthma or CF and grow into hyphae. After bronchial penetration, *Aspergillus* antigens activate immune response resulting in bronchial/bronchiolar inflammation and destruction.[3] The CD4+ Th2 cells along with their cytokines (especially interleukin [IL]-4) play an important role in pathogenesis of ABPA.[38]

Genetic factors

The balance between human leukocyte antigen (HLA)-antigen D-related molecules associated with susceptibility to ABPA (DR2, DR5, and possibly, DR4 or DR7) and resistance to ABPA (HLA-DQ2) determine the course of ABPA in patients with asthma and CF.[39] A number of genetic factors have also been identified in association with ABPA including CF transmembrane conductor regulator gene mutations,[40] SP-A2 (genes encoding surfactant protein-A),[41] IL-4 alpha-chain receptor polymorphisms,[42]

IL-10 polymorphisms,[43] toll-like receptor polymorphisms,[44] integrin β3 polymorphisms,[45] chitinase polymorphisms,[46] A disintegrin and metalloprotease 33 gene,[47] protocadherin 1 polymorphisms,[48] and mannan-binding lectin[49] polymorphism.

The host factor may also play a role in colonization and penetration of *Aspergillus* into respiratory epithelium, for example, impaired mucus clearance in CF may contribute to greater bronchial adherence of *Aspergillus*.[28]

Why does ABPA develop only in a proportion of *Aspergillus* sensitive asthmatic and CF patients? Knutsen *et al*.[38] hypothesized that ABPA develops in genetically susceptible patients with asthma and CF who have increased frequency and/or activity of *A. fumigatus* specific CD4+ Th2 cells.

Pathology of allergic bronchopulmonary aspergillosis

In ABPA, there is cylindrical bronchiectasis of central airways especially those to upper lobes.[3,5,28] Pathological bronchial specimens in ABPA, although not necessary for diagnosis, shows bronchial tree dilatation and lumen filled with mucus plugs containing eosinophils, macrophages, Charcot–Leyden crystals, and occasionally hyphal fragments.[3,5]

DIAGNOSIS OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

The diagnostic criteria for ABPA are described in adults, and the same is used in pediatrics as there are no separate criteria for children. In 1977, Rosenberg–Patterson criteria[50] were proposed for diagnosis of ABPA [Table 1]. The criteria for diagnosis of ABPA in asthmatic patients were later modified by Greenberger.[5] Recently, Agarwal *et al*. proposed new diagnostic criteria in 2013[51] and later modified in 2016 [Table 1].[52] The simple cutaneous sensitivity test (skin prick test) may be a useful screening test, as ABPA is very unlikely in patients with a negative skin test.[40] The cutoffs of total IgE for ABPA in children

Table 1: Changing diagnostic criteria for allergic bronchopulmonary aspergillosis in asthma with time

Rosenberg-Patterson criteria 1977[50]	**Greenberger criteria 2002[5]**		**Agarwal *et al*., 2013[51]**	**Agarwal *et al*., 2016[52]**
ABPA very likely if first 6 of 7 primary fulfilled. ABPA certain if all primary 7 present	ABPA-central bronchiectasis	ABPA-seropositive	ABPA is diagnosed if all of following criteria are met	ABPA is diagnosed if all of following criteria are met
Primary	**Essential criteria**	**Essential criteria**		
1.Asthma	1. Asthma	1. Asthma	1. Predisposing condition-Asthma or cystic fibrosis	1. Predisposing condition-Asthma or cystic fibrosis, COPD, post-TB fibrocavitary disease
2. Peripheral blood eosinophilia (>1.0×10^9/L)				
3. Immediate cutaneous reactivity to *Aspergillus* antigen	2. Immediate skin sensitivity to *Aspergillus* species or AF#	2. Immediate skin sensitivity to *Aspergillus* species or AF	2. Obligatory criteria 1- Immediate skin sensitivity to Aspergillus or increased IgE against AF (>0.35 kUA/L)	2. Obligatory criteria 1- Increased IgE against AF (>0.35 kUA/L) If this not available, Immediate skin sensitivity to AF may be considered
4. Precipitating antibodies against *Aspergillus* antigen	3.Elevated serum IgE and/or IgG against AF	3. Elevated serum IgE and/or IgG against AF		
5. Elevated total serum IgE (>1000 ng/mL)	4. Total serum IgE conc. (>417 kU/L or >1000 ng/mL)	4. Total serum IgE concentration >417 kU/L (1000 ng/mL)	3. Obligatory criteria 2- Total serum IgE >1000 IU/ml (2400 ng/mL)	3. Obligatory criteria 2- Total serum IgE>1000 IU/ml (2400 ng/mL)
6. Chest X-ray infiltrates (transient or fixed)				
7. Central bronchiectasis	5. Central bronchiectasis			
Secondary	**Nonessential criteria**		**4. Other criteria: At least 2 of three**	**4. Other criteria: At least 2 of three**
1. *Aspergillus* fumigatus in sputum (by culture or microscopy)	1. Chest X-ray infiltrates	1. Chest X-ray infiltrates	1. Radiographic findings consistent with ABPA*	1. Radiographic findings consistent with ABPA*
2. History of brown plugs in sputum	2. Serum precipitating antibodies to AF		2. Serum precipitating or IgG antibodies to AF	2. Serum IgG >27 mg_A/L against AF
3. Late (Arthus) skin reaction to *Aspergillus* antigen			3. Increased total eosinophils (>500) may be historical	3. Increased total eosinophils (>500) may be historical

AF: *Aspergillus fumigatus*, Total IgE: 1 kU/L=2.4 ng/mL, 1 kU/L=1 IU/ml, *Transient (nodules, consolidation, tram-track sign, fleeting opacities, finger in glove/toothpaste opacities) or fixed (ring shadows, bronchiectasis, or fibrosis). AF: *Aspergillus fumigatus*, ABPA: Allergic bronchopulmonary aspergillosis, CF: Cystic fibrosis, CT: Computerized tomography

are not well defined. A pediatric study from India suggested a cutoff of total IgE of 1200 IU/ml for ABPA in children.[23] For ABPA in CF, Nelson *et al*.[53] proposed that at least five of the following seven criteria had to be present for diagnosing ABPA in CF patients, namely, wheezing, increased total serum IgE, positive specific IgE to *A. fumigatus*, serum *Aspergillus* IgG precipitins, positive skin test, radiological pulmonary infiltrates, and bronchiectasis. Recently, CF Foundation Consensus has laid down the diagnostic criteria of ABPA in CF as well as criteria for screening for ABPA in CF patients [Table 2].[28] Diagnosis of ABPA in CF patients may be difficult due to overlapping clinical features (frequent exacerbations with bronchial obstruction, pulmonary infiltrate, and bronchiectasis).[28] The central bronchiectasis, one of the diagnostic criteria for ABPA in asthma, cannot be used for CF patients as it is not uncommon in CF patients even without ABPA.

Patients with ABPA in asthma, in addition to diagnostic criteria, may have sputum containing *A. fumigatus*, mucus impactions, and peripheral blood eosinophilia.[5] Culture of *A. fumigatus* from the sputum is a nonspecific finding as many patients with asthma or CF without ABPA have *Aspergillus* on sputum cultures.[54]

Recombinant *Aspergillus fumigatus* allergens

About 22 recombinant *A. fumigatus* allergens (named from rAsp f 1 to rAsp f 22) had been identified.[3,5] *A. fumigatus* allergens, namely. rAsp f 1, rAsp f 2, rAsp f 3, rAsp f 4 and rAsp f 6 had mixed results in differentiating ABPA from sensitization both in asthmatic and CF patients.[55-57] A recent systematic review suggested that a combination of rAsp antigens may be more helpful than a single rAsp for diagnosis of ABPA, though grade of evidence was low to very low.[58] Therefore, to define the exact role of recombinant *A. fumigatus* allergens in diagnosing ABPA, especially in children, there is need for further research.

The thymus and activation-regulated chemokine[59] and basophil activation test (CD63 and CD203c)[60] were also found useful in differentiating ABPA from AS in CF patients.

RADIOLOGICAL FINDINGS

High-resolution computerized tomography (HRCT) is the investigation of choice to delineate lung lesions in ABPA. In ABPA, central bronchiectasis and fleeting shadows are the most common radiological findings both in children and adults.[19] Figure 1 shows a chest X-ray of child with advanced ABPA revealing bronchiectasis and fibrosis. Bronchiectasis in CT chest in a child with ABPA is shown in Figure 2. Other CT findings in ABPA include: tram-line shadow, dilated and totally occluded bronchi (bronchocele), glove-finger shadow, air-fluid levels within dilated bronchi, bronchial wall thickening, parallel-line shadows, ring shadow, toothpaste shadow, parenchymal abnormalities (homogeneous consolidation, collapse, and parenchymal scarring) with predilection for upper lobes, cavities, and mass-like lesion.[19,61,62] High-attenuation mucus (HAM), seen as opaque shadow in dilated bronchi that is denser than associated paraspinal muscle shadow, is considered almost pathognomonic for ABPA.[51] The hilar lymphadenopathy had also been reported in ABPA in children.[63] Recently, Dournes *et al*.[64] reported that inverted mucoid impaction signal (presence of mucus with high T1 and low T2 signal

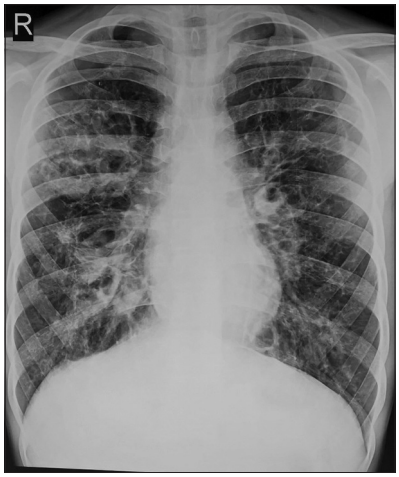

Figure 1: Chest X-ray of a child with advanced allergic bronchopulmonary aspergillosis showing bronchiectasis and fibrosis; note that bronchiectasis is more in central part

Table 2: Diagnostic criteria for allergic bronchopulmonary aspergillosis in cystic fibrosis[28]

Classic case	Minimal diagnostic criteria	Screening for ABPA in CF
1. Acute/subacute clinical deterioration* not due to another etiology	1. Acute/subacute clinical deterioration* not due to another etiology	1. High index of suspicion for ABPA in patients >6 years of age
2. Serum total IgE concentration of >1000 IU/mL (2400 ng/mL)	2. Serum total IgE conc. of >500 IU/mL (1200 ng/mL)	2. Test total serum IgE conc.$annually. If it is >500 IU/mL, test for immediate cutaneous reactivity or IgE antibody to AF
3. Immediate cutaneous reactivity to *Aspergillus* or presence of serum IgE antibody to AF	3. Immediate cutaneous reactivity to *Aspergillus* or presence of serum IgE antibody to AF	3. If the total serum IgE conc. is 200-500 IU/mL, repeat the test if there is increased suspicion for ABPA (disease exacerbation)
4. Precipitating antibodies to AF or serum IgG antibody to AF	4. One of the criteria 4 or 5, mentioned under classic case	
5. New or recent abnormalities on chest X-ray or CT, not cleared with antibiotics and physiotherapy		

*Cough, wheeze, exercise intolerance, decline in pulmonary function, increased sputum, AF: *Aspergillus fumigatus*, ABPA: Allergic bronchopulmonary aspergillosis, CF: Cystic fibrosis, CT: Computerized tomography

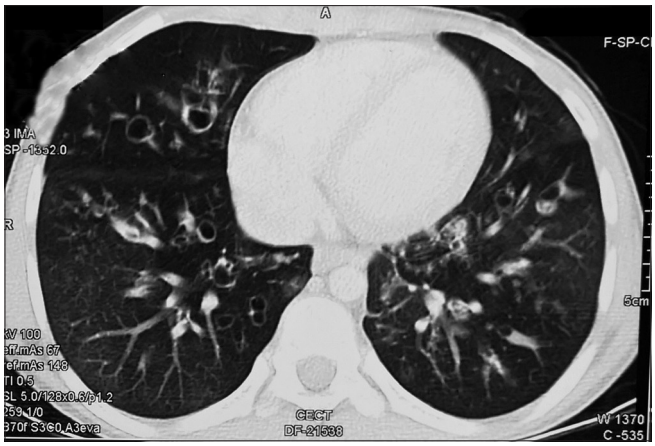

Figure 2: A computed tomography chest in child with allergic bronchopulmonary aspergillosis showing bronchiectasis

intensity) on noncontrast magnetic resonance imaging was 94% (95% CI: 73%–99%) sensitive and 100% specific (95% CI: 96%–100%) for diagnosing ABPA in CF patients.

LUNG FUNCTION TESTS

Kraemer *et al*.[65] reported severe progressive deterioration in all lung function parameters, volume of trapped gas, and effective airway resistance in CF children with ABPA.

CLINICAL FEATURES AND STAGES

ABPA patients, both children and adults, may present with poorly controlled asthma, wheezing, constitutional symptoms (fever, weight loss), mucopurulent expectoration, increased cough, dyspnea, chest pain, and hemoptysis.[3,5,14] ABPA in CF patients may be associated with exacerbation of symptoms, weight loss, and a marked increase in productive cough.[28] Even life-threatening presentation of ABPA in CF children has been reported.[66] Physical examination is usually not remarkable except for crackles and rhonchi. ABPA is frequently misdiagnosed initially for other diseases mainly tuberculosis, particularly in developing countries.[67] ABPA should be suspected in asthmatics who had difficult to control asthma despite good compliance to therapy. The diagnosis of ABPA should be suspected in children with CF who show wheezing, transient pulmonary infiltrates and had exacerbations responding poorly to antibiotics.

Patterson *et al*.[68] proposed five stages of ABPA progression: (1) acute; (2) remission; (3) exacerbation; (4) corticosteroid-dependent asthma; and (5) fibrosis (end stage). The acute stage has most of the features of disease and responds well to steroids. In remission stage, usually, there is no clinical or laboratory evidence of ABPA. The exacerbation stage has recurrence of acute stage of ABPA. The corticosteroid-dependent asthma stage is characterized by recurrent exacerbations of ABPA and severe asthma. Patients with fibrotic stage have severe dyspnea and cyanosis, and there is extensive bronchiectasis, cavitary lesions, and fibrosis in lungs, and they have poor prognosis. Kumar[69] divided patients with ABPA into three forms: mild (ABPA serologic positive; ABPA-S), moderate (ABPA with central bronchiectasis; ABPA-CB), and severe (ABPA with central bronchiectasis and other radiologic features; ABPA-CB-ORF). One more radiological classification based on HAM had been proposed by Agarwal *et al*.[70] that include ABPA-S, ABPA-CB, and ABPA-CB-HAM. Recently, Agarwal *et al*.[52] suggested the seven stages of ABPA: stage 0 (asymptomatic-ABPA criteria are fulfilled in a patient of controlled asthma), Stage 1 (Acute-ABPA criteria positive along with uncontrolled symptoms), Stage 2 (response-clinically better with total IgE decreased by >25% from baseline), Stage 3 (exacerbation-clinically worsened with total IgE increased >50% from baseline), Stage 4 (remission-clinically improved with total IgE at baseline or increase is <50%), Stage 5 (treatment dependent-≥2 exacerbations in 6 months or worsening on tapering steroids), and Stage 6 (advanced-extensive bronchiectasis and cor pulmonale). The ABPA in advanced stage may be complicated by cor pulmonale and pulmonary thromboembolism even in children.[71] There is no separate staging of ABPA for children. It has been suggested that early recognition and treatment may prevent the progression of ABPA from mild form to moderate and severe forms.[5]

TREATMENT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

The goals in the treatment of ABPA should be: (1) suppression of inflammatory response using corticosteroids; (2) to eradicate colonization and/or proliferation of *A. fumigatus* in lungs using antifungal agents; (3) to limit ABPA exacerbations by high index suspicion and prompt investigation; and (4) to prevent end-stage fibrotic disease.[3,28,38] Thus, corticosteroids and antifungal agents are the two mainstay modalities of treatment for ABPA.

CORTICOSTEROIDS

Systemic (oral) corticosteroids, usually prednisolone, are the most effective treatment for the acute phase of ABPA both in asthma and CF.[3,5,28] In asthmatic patients with ABPA, the recommended dosage of prednisolone is 0.5 mg/kg/day for the first 2 weeks, followed by a progressive tapering over the next 12–16 weeks.[3,38] Another regimen for steroids include high dose that is prednisolone 0.75 mg/kg for 6 weeks, 0.5 mg/kg for another 6 weeks, and then tapering for total duration of 6–12 months. A RCT in adults with asthma had shown that medium and high dose of steroids were equally effective for ABPA, though high-dose steroids had more side effects.[72] Long-term steroid therapy is not recommended for ABPA except for stage

IV (steroid-dependent asthma) where the minimal dose of steroids is required to stabilize the patient.

Higher dosage of corticosteroids had been recommended for ABPA in CF patients. For ABPA in CF patients, CF Foundation Consensus Conference report recommended an initial dose of prednisolone as 0.5–2.0 mg/kg/day (maximum 60 mg) for 1–2 weeks, then 0.5–2.0 mg/kg/day every other day for 1–2 weeks, and then taper in next 2–3 months.[28] Children on oral steroids should be monitored for side effects including cushingoid facies, hypertension, weight gain, height, and osteoporosis if used for long time or repeatedly.

Pulse methylprednisolone

Cohen-Cymberknoh *et al*.[73] used high-dose pulse methylprednisolone (10–15 mg/kg/d for 3 days per month) and itraconazole in nine patients with CF and ABPA (4 males, 5 females, age 7–36 years) with improvement in clinical and laboratory parameters and minor side effects. Thomson *et al*.[74] used pulse methylprednisolone to manage severe ABPA in four CF children out of which three children responded well although with troublesome side effects.

ANTIFUNGAL DRUG-ITRACONAZOLE

For allergic bronchopulmonary aspergillosis in asthma

A Cochrane meta-analysis, evaluating the role of azoles in ABPA in asthma, included three randomized controlled trials (RCT) and concluded that itraconazole improves clinical outcome in ABPA.[75] Adrenal suppression with inhaled corticosteroids and itraconazole is a potential concern. An RCT in adults compared monotherapy with steroids versus monotherapy with itraconazole in acute stage of ABPA and found that steroids were better.[76] There is hardly any study evaluating the efficacy of itraconazole for ABPA in asthmatic children, and it is difficult to recommend antifungal triazoles as first-line treatment with steroids in children with ABPA; though it used frequently based on data from adults. The itraconazole dose recommended for children include 5 mg/kg/day, maximum 400 mg/day (in two divided doses if total daily dose exceeds 200 mg).[28] The total duration of therapy should be 3–6 months.[28]

For allergic bronchopulmonary aspergillosis in cystic fibrosis patients

Skov *et al*.[77] reported 21 CF patients with ABPA (8–30 years of age, 17 were below 18 years) where the use of itraconazole (200–600 mg/day) with or without steroids decreased sputum culture for *Aspergillus*, precipitating antibodies and IgE levels, and increased FEV_1 without significant side effects. Lebeau *et al*.[78] used itraconazole (200 mg/day) in three CF children of ABPA (aged 8,10, and 11 years); two children responded but third child had liver abnormality requiring stoppage of treatment. There has been no RCT till date on the use of itraconazole in CF children with ABPA. The CF Foundation Consensus report recommended the use of itraconazole for ABPA in CF if there is a slow or poor response to steroids, for relapse of ABPA, in corticosteroid-dependent ABPA, and in cases of corticosteroid-induced toxicity.[28]

OMALIZUMAB (RECOMBINANT ANTI-IgE ANTIBODY)

For allergic bronchopulmonary aspergillosis in asthmatic patients

Aydin *et al*.[79] reported the benefits of omalizumab in 14 adult asthmatics with ABPA in the form of decreased exacerbations, lesser oral steroids use, and better pulmonary function. There is hardly any study of omalizumab use in asthmatic children with ABPA. A small RCT involving 13 adults patients with asthma and ABPA reported that the use of omalizumab resulted in significantly lower number of exacerbations as compared to placebo.[80]

Recently, an asthmatic women with refractory ABPA was successfully treated with a combination of omalizumab and mepolizumab (an anti-IL-5 monoclonal antibody).[81] There were two more adult cases who were treated successfully with mepolizumab.[82,83]

For allergic bronchopulmonary aspergillosis in cystic fibrosis patients

van der Ent *et al*.[84] first described the use of omalizumab in a 12-year-old CF girl with ABPA and there was a dramatic and rapid improvement of respiratory symptoms and lung function after a single dose. Nové-Josserand *et al*.[85] reported the steroid-sparing effect of omalizumab in 32 CF patients with ABPA (21 adults and 11 children) in a multicentric retrospective study. Li *et al*.[86] also reported the beneficial effect of omalizumab in patients with ABPA in a review of 102 cases from 40 published records that included both asthmatic and CF patients and both adults and children. A recent Cochrane review found only one RCT and that was also terminated prematurely and suggested further large trials of omalizumab in CF patients with ABPA.[87]

The role of other adjuvant therapies in ABPA is summarized in Table 3.

MONITORING FOR TREATMENT RESPONSE

The treatment of ABPA should be monitored by clinical features (including lung function tests), serum total IgE levels and chest imaging (X-ray or HRCT).[3,4] The total IgE level is a useful marker of disease activity in ABPA, and it can be used to monitor patients for "exacerbations." A study in adults with ABPA suggested that total IgE decreased at least 25% from baseline along clinical improvement after therapy and it increased by >50% with exacerbation.[98] The *Aspergillus*-specific IgE is not useful

Table 3: Miscellaneous therapy for allergic bronchopulmonary aspergillosis

Name of therapy	Evidence	Comments
Amphotericin B	Two studies[88,89] in seven and three pediatric CF patients showed good response of nebulized amphotericin B A small pilot study in adults with asthma and ABPA in remission showed no benefit of nebulized amphotericin in primary outcome, though number of ABPA exacerbation (one of the secondary outcome) were less in nebulized amphotericin B group[90]	Needs more studies to establish benefit
Voriconazole	Two observational studies in CF with ABPA including children showed benefit,[91,92] however, there is no RCT	Needs more studies, but may be alternative to itraconazole
Isavuconazole (a new triazole)	It was used successfully to treat asthmatic women with ABPA who did not tolerate itraconazole and voriconazole[93]	Needs more studies
Vitamin D	An *in vitro* study demonstrated that vitamin D3 attenuates the Th2 responses to Aspergillus fumigatus mounted by CD4+ T-cells from CF patients with ABPA.[94] However, in a study in adults from India, Vitamin D deficiency was not different among controls, asthmatics, and asthmatic with ABPA suggesting that Vitamin D may not play an important role in ABPA[95]	There is no study in children
Bronchoscopy	Bronchoscopy (rarely rigid bronchoscopy) may be required to remove massive mucus plugs in ABPA[96]	Limited role in selected patients
Environmental factor	Seasonal variation of ABPA suggest that avoidance of places with high Aspergillus spores, for example, damp areas, basements, decaying vegetables etc., may be beneficial for patients with ABPA[38] A case-control questionnaire-based study in adults found no difference in environmental factors in asthmatics and asthmatic with ABPA[97]	It needs more studies, especially in children

ABPA: Allergic bronchopulmonary aspergillosis, CF: Cystic fibrosis, RCT: Randomized controlled trials

to monitor response to treatment.[98] Although there are no such studies in children.

CONCLUSIONS

ABPA in children with asthma is increasingly being recognized. The ABPA is not uncommon in children with CF. Early and aggressive treatment of ABPA is crucial for preventing the serious sequelae of central bronchiectasis, pulmonary fibrosis, severe impairment in lung function and cor pulmonale. Corticosteroids and azoles are mainstay of treatment for ABPA in asthma and CF, though there is lack of RCTs regarding usefulness of azoles for ABPA in children. Omalizumab may be a potential therapy for refractory ABPA in asthma and CF patients. There is not much evidence available for other adjuvant therapies for ABPA. Monitoring of patients with ABPA is recommended using clinical, laboratory (mainly total IgE), and radiological parameters.

There is need for more vigilance for diagnosing ABPA in asthmatic children. The role of itraconazole and voriconazole in asthmatic and CF children with ABPA is yet to be established. Future research, particularly RCTs, is needed for other adjuvant therapies before they can be used for ABPA.

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Conflicts of interest
There are no conflicts of interest.

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