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Review Article

Approach to Allergic Bronchopulmonary Aspergillosis (ABPA): Quick Review

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Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is a well known and often underreported allergic airway disease. Exposure to fungal spores mostly *Aspergillus fumigatus* leads to colonisation in airways in susceptible individuals and can have varied presentations. It is a chronic inflammatory disease characterised by exaggerated T helper 2 response to fungal antigens. *Aspergillus*-induced asthma, allergic bronchopulmonary aspergillosis and allergic *Aspergillus* sinusitis are common presentations. Combination of clinical, radiological and serological criteria are used to identify the entity and have been updated from time to time. High resolution tomography of chest has a compelling role in detecting early airway lesions. Central bronchiectasis with normal peripheral tapering is still considered di-agnostic of ABPA. Elevated serum IgE levels and *Aspergillus*-specific IgE and/or IgG are also vital for the diagnosis. Chronic cavitatory diseases may have saprophytic colonization of *Aspergillus* widely known as fungal balls. Tuberculosis is a common masquerader that can lead to misinterpretation and mistreatment. Early detection and aggressive management of ABPA can prevent end stage lung damage. Oral corticosteroids and antifungal therapy continue to be mainstay therapy.

Keywords: *Allergic Bronchopulmonary Aspergillosis; IgE Mediated Type I Hypersensitivity; Aspergilloma; Aspergillus fumigatus; Asthma*

Introduction

Aspergillus is ubiquitously present worldwide in moist soil, decaying matter and air duct systems. Allergic bronchopulmonary aspergillosis (ABPA) is an allergic inflammatory response to colonization of airways by *Aspergillus fumigatus* or other fungi. The entity was first described by Hinson., *et al*. in 1962 [1]. Subsequently, Scadding found association of aspergillosis with central bronchiectasis in patients with chronic lung conditions especially affecting up-per lobes. ABPA is suspected in poorly controlled/ difficult to control asthma patients when they present with atypical features and respond poorly to therapy. Cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and post tubercular lung disease are other predisposing conditions for development of ABPA [2-4].

Prevalence

ABPA is a relatively common entity but precise prevalence is still unknown. Variability in diagnostic criteria, non-specific symptoms and delays in diagnosis are the main reasons. In addition, there is lack of clear distinction be-tween ABPA and mold sensitive asthma.

Estimates suggest that ABPA complicates approximately 7% to 14% cases of chronic steroid–dependent asthma and approximately 7% to 15% of cases of CF. Prevalence of ABPA is showing rising trend with growing awareness and availability of laboratory tests for diagnosing the condition. It is mostly found in fourth and fifth decade of life but cases have been reported in children as young as 2 years also. The inflammatory process may start well in childhood but is not diagnosed till adulthood. Also, it can be easily misinterpreted as tuberculosis. This suggests that a large number of cases may go undiagnosed and are not reported [4-6]. Mean-while it has clinical implications; where ABPA responds to corticosteroids but tuberculosis can worsen. So, clinician should be vigilant while labelling a patient as ABPA. It is most commonly seen in asthmatics but why only few develop disease is not clear even after being familiar with the conditions for more than five decades.

Box 1: Reminder

- Exact prevalence of ABPA not known
- ABPA is under-reported
- Variability in diagnostic criteria
- Suspect in poorly controlled asthma cases
- Tuberculosis is common masquerader

Pathogenesis

The exact pathogenesis is not known. It is believed to occur as a result of exaggerated T helper 2 inflammation to fungal antigens. *Aspergillus* is a thermotolerant fungus found in soil. Fungal spores are immunologically inert and cause little or no symptoms when inhaled in immunocompetent individuals. However, in genetically predisposed individuals, spores colonise airways, germinate into hyphae and stimulate immediate type I IgE mediated hypersentivity reaction without clear tissue invasion. On repeated exposure to *Aspergillus* antigen, sensitised mast cells release cytokines like IL 4, 5, 13 and predominantly recruit eosinophils and mononuclear cells. Other cells involved are basophils and monocytes. Search of literature suggests involvement of Type III (immune complex formation) and type IV (delayed cell mediated) hypersensitivity as well. ABPA is most commonly seen in asthmatics but why only few develop disease is not clear. The susceptibility to develop disease depends on host factors like immune competence and severity of environmental exposure to *Aspergillus* spores. Moreover, genetics play an important role. Even though more than two hundred species of *Aspergillus* exist, the main species implicated are *A. fumigatus, A. flavus, A. niger, A. terreus*, and *A. nidulans*. Allergic bronchopulmonary mycosis (ABPM) is a similar syndrome caused by exposure to fungi other than *Aspergillus fumigatus*, most commonly Candida albicans. Others include *Heminthosporium, Alternaria, Stemphylium languinosum, Curvularia lunata, Saccharomyces cerevisiae, Pseudallescheria boydii* etc [4,6-8].

Genetics

The understanding of disease is evolving. Several candidate genes have been implicated in the pathogenesis of ABPA. Most notable is mutations in cystic fibrosis transmembrane conductance regulator (CFTR) gene. In addition, presence of major histocompatibility complex (MHC) Class II DR2 or DR5 alleles predispose patients to the disease, whereas the MHC DQ2 allele may be protective. Further studies suggested polymorphisms in the promoter region of Toll like receptor (TLR), collagen region of pulmonary surfactant protein A2 (SP-A2), mannan binding lectin, integrin beta3, IL 4,10 and protocadherin 1 polymorphisms may have a role in ABPA. Recently Chitotriosidase 1 (CHIT1) exon 10 mutation has been seen in children with ABPA [8-17].

Box 2: Reminder

- T Helper Type 2 predominant response
- Immediate type 1 IgE mediated hypersentivity reaction
- Not all asthmatics develop ABPA
- Genetics play role
- Host and environmental factors play role

Clinical features

The spectrum of disease is broad. It may range from asymptomatic condition or mild asthma to end stage lung disease (Table 1). Patient often presents with non-specific respiratory complaints like cough, wheezing, breathlessness and hemoptysis. Clinician should have a high degree of suspicion when asthmatic reports expectoration of mucus plugs, poor response to standard treatment and frequent exacerbations. Besides, history of atopy like rhinitis, drug allergy and/or allergic conjunctivitis is also common. Chronic fibrocavitary lung conditions like tuberculosis and cystic fibrosis can have saprophytic colonisation of *Aspergillus* called fungal balls. Invasive and necrotising presentations are seen generally in immunosuppressive conditions like post-transplant and hematological malignancies [18-21]. However, surprisingly similar presentation has been recently reported in immunocompetent sewer worker post massive exposure to *Aspergillus* spores at work [22].

Respiratory tract	Upper	Lower
Allergic	Allergic Aspergillus Sinusitis (AAS)	• Aspergillus induced asthma (AIA) • Allergic bronchopulmonary Aspergillosis (ABPA) • Hypersensitivity pneumonitis (HP)
Saprophytic	Sinus fungal balls	Aspergilloma • Simple • Complex
Invasive	• Acute fulminant • Chronic • Granulomatous	Invasive pulmonary aspergillosis • Acute • Subacute

Table 1: *Aspergillus associated respiratory disorders.*

Box 3: Reminder

- Spectrum of disease is broad
- Non-specific respiratory symptoms
- History of atopy common
- Various presentations discussed in table 1
- Radiological findings in table 2

Radiological features

High-resolution computerized tomography (HRCT) is preferred imaging modality in ABPA. Central bronchiectasis (CB) and fleeting shadows (Figure 1 and 2) are the most common radiological findings both in children and adults. CB with normal peripheral tapering is still considered characteristic feature of ABPA but it has been seen that about 30% early mild cases may present with non-central bronchiectasis. Other CT findings in ABPA include: tram-line shadow, bronchocoele, glove-finger shadow, bronchial wall thickening, parallel-line

shadows, ring shadow, toothpaste shad-ow, hilar lymphadenopathy, parenchymal abnormalities and mass-like lesion (Table 2). High-attenuation mucus (HAM) is considered almost pathognomonic for ABPA but seen in less than 30% patients (Figure 3 and 4). It is seen as an opaque shadow in dilated bronchi that is denser than associated paraspinal muscle shadow due to deposition of iron and calcium salts [23-25]. Recently Dournes., *et al*. reported that magnetic resonance imaging of airway mucus was a use-ful tool to diagnose ABPA in CF patients [26].

	Permanent	Transient
Chest X Ray	• Bronchiectasis • Parallel line shadows • Ring shadows • Cavities • Fibrosis • Contracted upper lobes • Aspergilloma	• Consolidation • Collapse • Perihilar/pseudohilar shadows • Finger in glove shadows • V/Y shaped or wine glass shadows • Tramline shadows • Toothpaste shadows
HRCT* Chest	• Bronchiectasis usually central • (Signet ring and string of pearls sign) • Fibrocavitory changes • Fungal ball • Pleural thickening	• Consolidation • Non homogenous opacity • Tree in bud opacities • High attenuation mucus plugs • Centrilobular opacities • Collapse (segmental/lobar)

Table 2: *Radiological chest findings.*

**: High resolution computed tomography.*

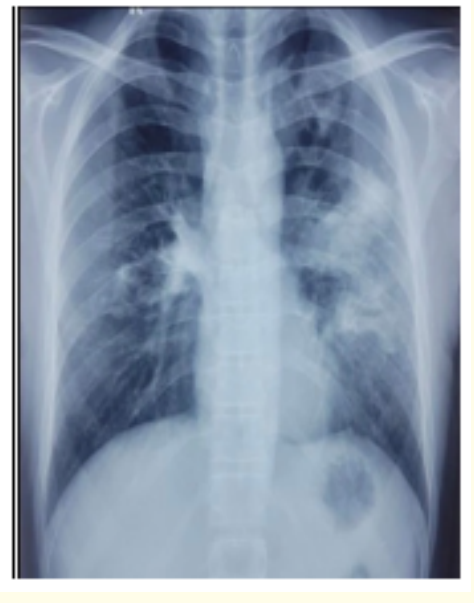

Figure 1: *Chest radiograph showing left-mid-zone opacity along with right hilar opacity.*

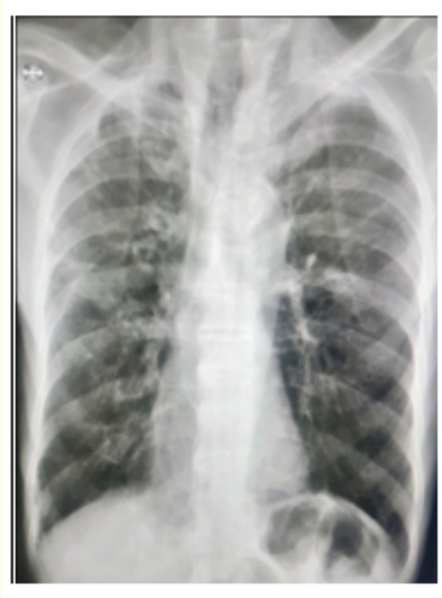

Figure 2: *Chest radiograph of patient showing resolution after treatment.*

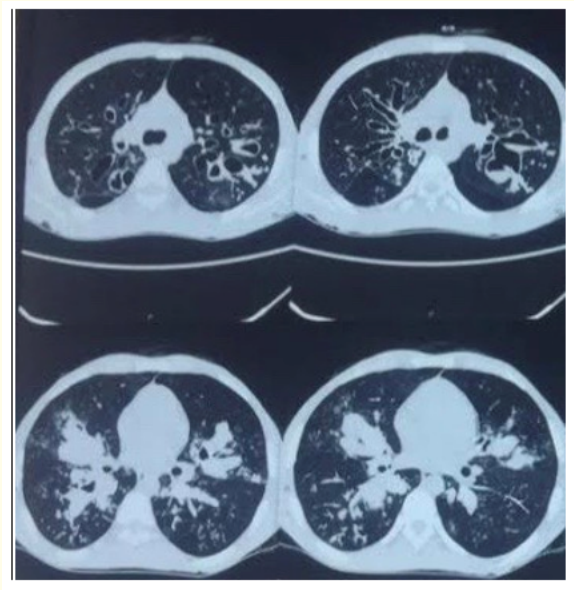

Figure 3: *High resolution computed tomography of thorax (lung window) showing central bronchiectasis and high attenuation mucus*

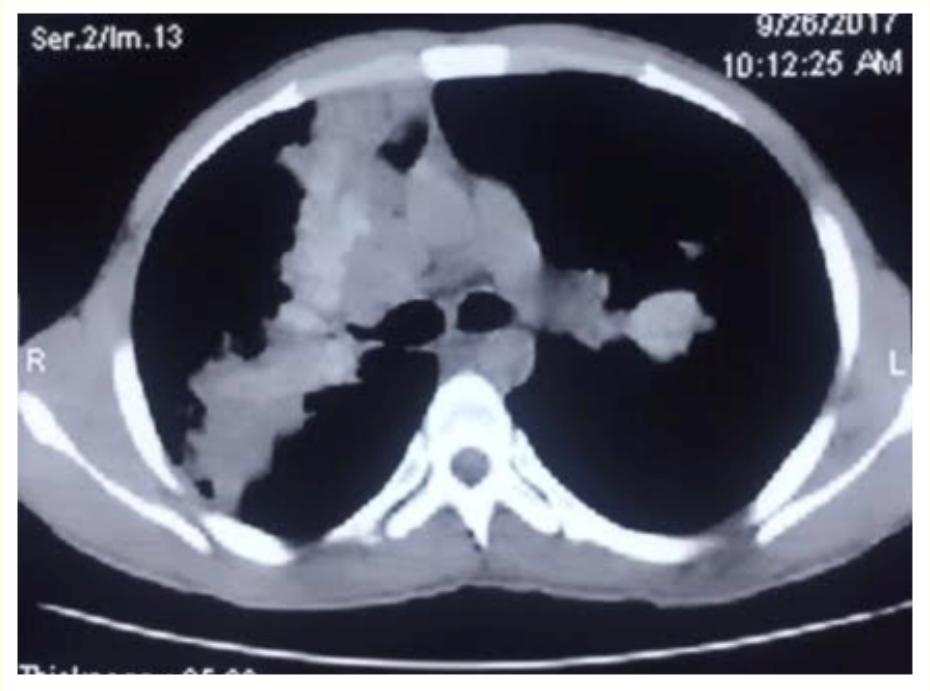

Figure 4: *High resolution computed tomography of thorax (mediastinal window) showing high attenuation mucus*

Laboratory findings

ABPA is characterised by both type I (immediate) and type IV (delayed) hypersentivity response. An immediate cutaneous hypersensitivity to *Aspergillus* antigens is the rule-in test with sensitivity of 88 - 94% for diagnosis of ABPA in bronchial asthma patients although it may be positive in about 40% asthmatics without ABPA. The pin-prick method is preferred over intradermal because there is higher possibility of false positives with the latter. Crude antigen prepared from three species of *Aspergillus* (A.) viz. *A. fumigatus, A. niger* and *A. flavus* is commonly used for skin testing. The lack of standardization of antigen extract and expertise lead to variable results. Recently, twenty two recombinant *Aspergillus* fumigatus (rAsp f) antigens are identified which can play promising role. Evidence suggests that rAsp f 4 and 6 can be utilized to differentiate ABPA from ASA whereas 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 asthma and CF patients. In addition, thymus and activation-regulated chemokine and basophil activation test (CD63 and CD203c) were found useful in differentiating ABPA from *Aspergillus* sensitive asthma (ASA) in CF patients.

Evaluation of total eosinophil count (TEC), serum IgE levels and *Aspergillus* fumigatus specific (Af) IgE/IgG levels are useful tests in both diagnosis and follow up of ABPA [14]. TEC > 500 cells per microlitre (µL) is recommended cut off for diagnosing ABPA because about 60% patients of ABPA can have values less than 1000 cells/µL. There is inconsistency in serum IgE levels in normal individuals, asthmatics and ABPA patients. Moreover, earlier serum IgE values were report-ed in different units which added to confusion (1 IU/mL =2.4 ng/ML; 1000 ng/mL = 417 IU/mL). Recently expert group suggested 1000 IU/mL (sensitivity 92% and specificity 40%) for diagnosis of ABPA as opposed to 417 IU/mL (sensitivity 96%; specificity 24%). A paediatric study proposed a cut-off of 1200 IU/mL for ABPA in children. Af-IgE is the rule-out test with cut-off value of 0.35 kUA/L (100% sensitivity and specificity 69 - 78%). Recently Agarwal et al recommended

levels more than 27 mgA/L diagnostic for ABPA. Serum galactomannan assay can be utilized to detect invasive pulmonary aspergillosis in patients with relevant cliniradiological findings [4,27,31].

Box 4: Reminder

- Skin test is rule in test
- *Aspergillus* specific IgE is rule out test
- Cut off for
- TEC: > 500 cells/μL
- Total IgE: > 1000 IU/mL
- Af-IgE: > 0.35 kUA/L
- Af-IgG: > 27 mg_A/L
- No clear cut off for pediatric ABPA

Diagnosis and staging

Diagnosis requires a combination of clinical, radiological and serological features in predisposed patients. Set of criteria in various combinations have been proposed with time as understanding of disease is evolving (Table 3). The most widely recognized are proposed by Rosenberg Patterson in 1977. It required a set of 8 major and one or more than 1 out of 3 minor criteria to be fulfilled to label a patient as ABPA. However, it had limitations. It was found that not every ABPA patient fulfills all criteria at all times. Also, serological parameters decrease after corticosteroid therapy [32,33]. In 2002, Greenberger advocated a set of minimally essential criteria and further proposed "truly minimal" diagnostic criteria in 2013 [34,35]. CB with normal peripheral tapering as pathognomic of disease is debatable as a subset of patients with milder disease may not have CB and about 40% of involved lobes have bronchiectasis ex-tending to periphery. Patterson., *et al*. proposed five stages of ABPA progression: (1) acute; (2) remission; (3) exacerbation; (4) corticosteroid-dependent asthma; and (5) fibrosis (end stage). Patient in acute stage has most of the features of disease and responds well to steroids. In remission stage there is no clinical or laboratory evidence of ABPA. The exacerbation stage simulate acute stage of ABPA. There is clinical and or radiological worsening with rise in serological parameters. The corticosteroid-dependent asthma stage is characterised by recurrent exacerbations of ABPA. Fibrosis stage is represented by end stage lung damage. Kumar [34] suggested three groups of patients based on immunological severity; mild ABPA-S (satisfying serological criteria), moderate ABPA-CB (ABPA with central bronchiectasis) and severe (ABPA with central bronchiectasis and other radiologic features; ABPA-CB-ORF). The International Society for Human and Animal Mycology working group (ISHAM) advocated one more radiological classification based on high attenuation mucus (HAM) that include ABPA-S, ABPA- CB, ABPA-CB-HAM and ABPA with chronic pleuropulmonary fibrosis (ABPA-CPF) [4,27,35]. Recently, Agarwal., *et al*. in 2016 suggested seven stages of ABPA; asymptomatic, acute, response, exacerbation, remission, treatment dependent and advanced [4] (Table 4).

Rosenberg Patterson 1977	
Major	**Minor**
1. Asthma 2. Presence of transient pulmonary infiltrates 3. Immediate cutaneous reactivity to Af 4. Elevated total Serum IgE 5. Precipitating antibodies against Af 6. Peripheral blood eosinophilia 7. Elevated serum Af- IgE and Af-IgG 8. Central bronchiectasis with normal tapering of peripheral bronchi	1. Expectoration of golden brownish sputum plugs 2. Positive sputum culture for *Aspergillus* species 3. Late (Arthus-type) skin reactivity to Af

Greenberger	
Minimal essential (2002)	**Truly minimal (2012)**
1. Asthma 2. Immediate cutaneous hypersensitivity to Af 3. Elevated total Serum IgE > 1000 ng/mL (417 kU/L) 4. Elevated serum IgE and IgG to Af 5. Central bronchiectasis in absence of distal bronchiectasis	1. Asthma 2. Immediate cutaneous hypersensitivity to Af 3. Total serum IgE> 1000ng/mL (417kU/L) 4. Central bronchiectasis in absence of distal bronchiectasis

ISHAM working group (Agarwal., et al. 2013)		
Predisposing conditions	**Obligatory criteria (all)**	**Other criteria (at least 2 of 3)**
1. Bronchial asthma or 2. Cystic fibrosis	1. Type 1 *Aspergillus* skin test positive (Immediate cutaneous hypersensitivity to aspergillus antigen) or elevated IgE levels against Af 2. Elevated total IgE (> 1000 IU/mL)	1. Presence of precipitating or IgG antibodies against Af in serum 2. Radiographic pulmonary opacities consistent with ABPA 3. Increased total eosinophils (> 500 cells/μL) may be historical

ISHAM working group (Agarwal., et al. 2016)		
Predisposing conditions	**Obligatory criteria (all)**	**Other criteria (at least 2 of 3)**
Modifications Addition of COPD and post tubercular fibrocavitory disease	Elevated IgE levels (> 0.35 kUA/L) against Af If this is not available, Immediate skin test to Af may be considered	Serum IgG > 27mg_A/L against Af

Table 3: *Diagnostic criteria of ABPA proposed with time [4,27,32-35].*

Af: Aspergillus fumigatus; IgE: Immunoglulin E; IgG: Immunoglobulin G; ISHAM: International Society for Human and Animal Mycology.

Stage 0	Asymptomatic	ABPA criteria are fulfilled in a patient of controlled asthma
Stage 1	Acute 1a with mucoid impaction 1b without mucoid impaction	ABPA criteria positive along with uncontrolled symptoms
Stage 2	Response	Clinical and or radiological improvement with total IgE decreased by > 25% of baseline at 8 weeks of therapy
Stage 3	Exacerbation	Clinically and or radiologically worsened with total IgE increased > 50% of baseline
Stage 4	Remission	Sustained clinicoradiological improvement with total IgE at baseline or increase is < 50% for more than 6 months without systemic corticosteroids.
Stage 5	5a: Treatment dependent ABPA	Either relapse occurs on two or more consecutive occasions within 6 months of stopping treatment or there is worsening of clinical, radiological or immunological parameters on tapering oral steroids/azoles
	5b: Glucocorticoid dependent asthma	When systemic steroids are required for control of asthma whilst activity of ABPA is under control
Stage 6	Advanced ABPA	Clinical signs of cor pulmonale and type-2 respiratory failure along with radiological features of fibrosis

Table 4: *Clinical staging in ABPA (ISHAM working group 2016) [4].*

ABPA: Allergic Bronchopulmonary Aspergillosis; ISHAM: International Society for Human and Animal Mycology.

Treatment

The goals in the treatment of ABPA should be suppression of inflammatory response, eradicating colonization and/or proliferation of *A. fumigatus*, limitation of ABPA exacerbations by prompt treatment and prevention of end - stage fibrotic lung disease. Oral corticosteroids and antifungal agents are the two mainstay treatment options for ABPA [38].

Oral corticosteroids

Systemic (oral) corticosteroids, usually prednisolone, are the most effective treatment for the acute phase of ABPA both in asthma and CF. Regimen 1: Prednisolone 0.5 mg/kg/day for one to two weeks, then on alternate days for six to eight weeks followed by dose reduction @ 5 - 10 mg every 2 weeks. Regimen 2: Prednisolone, 0.75 mg/kg for 6 weeks, 0.5 mg/kg for 6 weeks, subsequently tapered by 5 mg every 6 weeks to continue for a total duration of at least 6 - 12 months [4,27]. A randomized controlled trial in adults with asthma showed that medium and high dose of steroids were equally effective for ABPA, however high-dose steroids had more side effects. Long term steroid therapy is not recommended for ABPA except for stage steroid-dependent asthma. For ABPA in CF patients, CF Foundation Consensus Conference report [39] 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 taper in next 2 - 3 months. Patients on long term/repeated courses of oral steroids should be monitored for side effects. Data regarding Pulse methylprednisolone is scarce. Cohen Cymberknoh [40] used high dose pulse methylprednisolone (10 - 15 mg/kg/d for 3 days per month) and itraconazole in nine patients (age 7 - 36 years) with CF and ABPA with improvement and minimal adverse effects. Thomas., *et al.* [41] reported similar findings in children with CF and ABPA.

Antifungal drugs

These agents decrease fungal load thereby decreasing antigenic response and inflammation [42]. Azoles especially itraconazole has been found to be effective in ABPA but remains an attractive alternative therapy. It is used with oral corticosteroids. The dose is 200 mg twice a day for at least 16 weeks. Response often takes longer than 16 weeks. It can be used as recurrent short courses or long-term therapy. Newer agents like voriconazole and posaconazole have a promising future. Long term treatment with voriconazole can cause skin cancer [45]. Data is limited whether itraconazole and other newer azoles would successfully replace oral steroids as first-line therapy for ABPA. A recent randomized trial of voriconazole and prednisolone monotherapy in acute-stage ABPA complicating asthma by Agarwal., *et al.* 2018 showed voriconazole appears to be as effective as glucocorticoids in acute-stage ABPA. Larger trials are required to verify the results [4,46].

Other therapies

Review of literature suggested successful management of ABPA with anti IgE antibody, Omalizumab [47,48]. Recently treatment of patient with severe bronchial asthma and ABPA with mepolizumab was reported. It could be promising treatment option with steroid sparing effects. Randomized trials with omalizumab and possibly other antibodies to IL-4Ra (dupilumab), IL 5 (mepolizumab), and IL 13 (lebrikizumab) may be conducted to assess their routine usage in ABPA [49,50].

Box 5: Reminder

- Oral corticosteroids are mainstay therapy
- Antifungals play adjunctive role
- Newer azoles: voriconazole, posaconazole
- Others include, Omalizumab, Mepolizumab
- Role of antifungals as primary treatment is being explored

Conclusion

ABPA is a well-known *Aspergillus* associated lung disease caused by exaggerated type 1 hypersentivity reaction to fungal antigen. The exact prevalence and pathogenesis is still unknown. Clinicians should have high degree of suspicion when patients with allergic asthma have atypical symptoms, poor response to therapy and repeated episodes of lower respiratory tract infections. Also in view of striking radiological similarities to tuberculosis, one should be extra vigilant before starting patients on treatment [4,27,51,52]. There is no clear consensus on diagnostic criteria. Early diagnosis and aggressive treatment is the key for successful management of ABPA.

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