Allergic Bronchopulmonary Aspergillosis - A review

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Abstract

ABPA is a hypersensitivity disorder induced by Aspergillus species colonizing the lung cavity predominantly in patients with asthma. It has varied presentations i.e. from mild form (ABPA-S) to fatal destructive severe lung disease (ABPA-CB, ABPA-CB-ORF). Serological markers such as specific IgE-Af and IgG-Af contributes to the diagnosis. Total serum IgE is elevated sharply but is non specific. Fleeting pulmonary shadows and central bronchiectasis remains the hallmark of disease on radiology. Early treatment with prednisolone could alter the course and may prevent the mild form of ABPA-S, from leading to ABPA-CB or ABPA-CB-ORF.

Key words: Aspergillus fumigatus, ABPA, Antigens, Aspergillosis, Fungal sinusitis, Aspergilloma

INTRODUCTION

Aspergillus is a predominant fungi worldover and responsible for ABPA and other hypersensitivity diseases in man12. The main pathogenic species is Aspergillus fumigatus (Af) followed by A.flavus, A.niger, A.terreus and A nidulans. The respiratory tract is the most frequent site of infection, however other tissues may be invaded including the external auditory canal, skin, nails, eyes, sinuses, meninges and bones. Pulmonary Aspergillosis is a general term for the lung disease caused by genus Aspergillus and includes the spectrum of disorder from saprophytic colonization of respiratory tract to rapidly invasive disseminated disease. The three commonly described categories are Allergic Aspergillosis, Colonizing Aspergillosis and Invasive disease. Overlap among these categories can occur or it can progress from one category to another e.g. Aspergilloma may change to invasive Aspergilloma34.

The genus Aspergillus derived its name due to resemblance of the fungi's spore offshoot to 'Aspergillaire' a device used by the priest to sprinkle holy water. Aspergillus species are ubiquitous soil dwelling organism found in organic debris, compost, foods and rotten plants. Approximately 200 species of Aspergillus are found but only a few are known to be pathogenic for humans. They reproduce by formation of conidia (2-3.5 µm) that are readily airborne and reach the airways following inhalation. Aspergillus species are thermo tolerant and are capable of growing at temperatures 15° to 49° C. Septate hyphae of 7-10 urn branched at 45° angle are the forms associated with disease. Hyphae from sputum or mucous plug may be demonstrated with the Gomori methanamine silver stain and PAS. Fungus ball specimens from cavities connected to open bronchi have hyphae that are often lifeless and stain poorly, but rare in occurrence.
Pulmonary diseases due to *A. fumigatus* have been recognized since the 19th century when Sluyton first discovered an *Aspergillus* fungal mass in lung cavity of a woman. Depending on the host's immunologic and genetic status, a variety of *Aspergillus* associated respiratory diseases have been recognized (Figure 1, Table 1). The examples are: (a) IgE-mediated Asthma, (b) Invasive aspergillosis, (c) Aspergilloma (mycetoma), (d) Hypersensitivity pneumonitis, (e) Chronic necrotizing pneumonia, (f) Allergic *Aspergillus* sinusitis and (g) Allergic broncho-pulmonary aspergillosis (ABPA).

**ASPERGILLUS SENSITIZATION IN PATIENTS WITH ASTHMA**

The data on sensitization to *Aspergillus* antigen in patients of bronchial asthma have been presented in Table 2. Henderson et al in a survey of pulmonary *Aspergillus* in chronic lung diseases observed immediate skin reaction to *A. fumigatus* in 23% cases. Hoehne and coworkers reported that 36% of asthmatics show positive immediate skin reaction and serum precipitins to *Aspergillus* antigen. Hendrich et al analyzed the result of skin prick test in 656 asthmatic patients. Positive immediate skin reactions to at least one of the 22 common allergens were observed in 84% cases whereas, 16% showed positively to *A. fumigatus*. In 1978 Schwartz et al compared the prevalence of sensitization to *Aspergillus* antigens among the asthmatics of Cleveland and London. Twenty eight percent of the asthmatics from Cleveland and 23% from London showed immediate skin reactivity to *Aspergillus*. Patients from Cleveland (7.5%) and in London (10.5%) also showed precipitins in the serum against *Aspergillus* antigens. They concluded that sensitivity to *Aspergillus* antigens occur in similar frequency in both United States and United Kingdom.

Malo and Paquin, in 1979 studied the incidence of immediate sensitivity to *A. fumigatus* in North American asthmatic population. The positive skin reactions were observed in 21.5% of asthmatics to *A. fumigatus* by prick tests and 39% by intradermal tests. In 1980, Benatar et al examined 500 consecutive asthmatic patients and from these, 312 showed positive reactions to *Aspergillus* antigens. Thus the incidence of cutaneous sensitization to *Aspergillus* sp. on patients of asthma was between 12-34%.

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![Fig. 1. The clinical spectrum of conditions resulting from the inhalation of Aspergillus spores](image-url)
ALLERGIC ASPERGILLUS SINUSITIS (AAS)

It occurs predominantly in patients with chronic nasal polyp who have mucoid impaction of the sinuses that morphologically resembles mucoid impaction of ABPA. It can occur with ABPA. First case of allergic fungal sinusitis (AFS) was recognized in 1791 by Plaignaud. Later in 1983, Katzenstein et al described the cases of AAS by retrospectively reviewing all tissue specimens removed from paranasal sinuses over a five year period.

The immunopathogenesis of AAS is similar to ABPA. Rhinitis is predisposing factor for developing AAS. Passage of nasal plugs, recurrent nasal polyps is an important feature. The mucous plugs contain eosinophils, charcot leyden crystals and hypae of *A. fumigatus*. The treatment includes initial debridement followed by oral corticosteroids.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

ABPA is a hypersensitivity reaction to *Aspergillus* antigen mostly due to *Aspergillus* species, (*A. fumigatus*, *A. flavus* and *A. niger*) which is characterized by bronchial asthma, pulmonary infiltrates and eosinophilia. It is most frequently recognized manifestation of allergic aspergillosis occurring worldwide.
We have come a long way since the time when the first case of ABPA was reported in England (1952) by Hinson et al. Sixteen years later Patterson and Golbert reported first case of ABPA in US. In Indian subcontinent reports started coming in 1960s and 70s. Since then several case reports from India have been documented.

**EPIDEMIOLOGY**

Several attempts have been made to estimate the prevalence of ABPA but the lack of uniform diagnostic criteria and standardized tests make it a tough task. Recent review by Novey suggest that prevalence of ABPA under existing limitation of diagnosis may be present in 0.25% - 0.8% of all asthma patients in US. Extrapolation from published studies suggest a rate of not more than 11%. In a study by Kumar and Gaur from India, the prevalence of ABPA in bronchial asthma is 16% (ABPA-S 4%, ABPA-CB 12%).

**IMMUNOPATHOGENESIS OF ABPA**

The pathogenesis of ABPA is still not fully understood. Repeated inhalation of *Aspergillus* spores principally Af leads to airway colonization in sputum plugs in the bronchi of asthmatics with little or no tissue invasion. *Aspergillus* spores, in humans, are inhaled usually at low concentrations. Spores are thermo tolerant and produce some proteolytic enzymes that result in intense bronchial wall inflammation with increased absorption of antigens. It is unknown why Af spores are able to colonize in some and not in all asthmatics.

Antigen release evokes production of IgE, IgG and IgA antibody against the Af and intense production of nonspecific total IgE. IgE mediated mast cell degranulation in the bronchi release mediators that, would cause bronchospasm as well as permeability changes in the epithelium. Eosinophilic chemotactic factors cause pulmonary and peripheral blood eosinophilia. IgG-Af, IgA-Af also causes activation of complement in the bronchi. It has been demonstrated that there occurs hyperreleasability of histamme from basophils of ABPA patients. Af causes increase in vitro histamine release from cells of ABPA patients compared to patients of asthma and also m patients with stage IV and V ABPA compared to stages I, II, III. This hyper releasability initiates lung injury. Lymphocytic transformation to Af also occurs in some patients, which results in

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Results and Remarks</th>
<th>Year</th>
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<tbody>
<tr>
<td>Henderson et al</td>
<td>Survey of pulmonary aspergilosis in chronic lung diseases</td>
<td>Immediate skin test +ve in 23%</td>
<td>1968</td>
</tr>
<tr>
<td>Hoehne et al</td>
<td>6 (Asthma)</td>
<td>criteria Asthmatic — Prick test +ve; 36% of asthmatics showed +ve skin test to <em>Aspergillus</em> antigens</td>
<td>1971</td>
</tr>
<tr>
<td>Hendrik et al</td>
<td>656 (Asthma)</td>
<td>84% had +ve skin test to at least one of 22 common allergens.</td>
<td>1975</td>
</tr>
<tr>
<td>Schwartz et al</td>
<td>100 (Asthmatic)</td>
<td>Skin reactivity to mixed <em>Aspergillus</em> extract - 28% in Cleveland, 23% in London. <em>Aspergillus</em> Precipitin in - 7.5% in Cleveland, 10.5% in London</td>
<td>1978</td>
</tr>
<tr>
<td>Malo &amp; Paguin</td>
<td>200 (Asthmatic)</td>
<td>199/200 atopics. Skin test to A.F. by Prick test +ve in 21.5% &amp; Intradermal (ID) +ve in 30%</td>
<td>1979</td>
</tr>
<tr>
<td>Banatar et al</td>
<td>500 (Asthmatic)</td>
<td>312/500 skin test +ve reaction (240 multiple +ve), 22% +ve <em>Aspergillus</em> antigens. Out of 500 - 26% S.Prick (+) against <em>Aspergillus</em> strain.</td>
<td>1980</td>
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granulomatous lesion or mononuclear cell infiltration. However, delayed cutaneous reaction (type IV) to Af does not occur in ABPA because the release of mast cell mediators from the type I reaction increases permeability and blood flow.

So (a) chronic exposure to Af and (b) exaggerated host response including hypersensitivity reaction (type I - mediated by IgE; type III- mediated by IgG; type IV-by lymphocytic transformation), cytokine release, complement activators result in lung damage.

**PATHOLOGICAL FINDINGS**

Lung biopsy is not necessary as the diagnosis is made on clinical, serological and roentgenographic findings, but if taken will give different histological diagnosis even in same patient. Histological diagnosis such as mucoid impaction syndrome, bronchiolitis obliterans, granulomatous bronchiolitis, eosinophilic pneumonia and pulmonary fibrosis has been made. The bronchi contain thick tenacious mucous with fibrin, eosinophils and charcot leyden crystals. Both bronchi or lung parenchyma or both get involved but there is no invasion of bronchial wall, except in a single report. The bronchi may be dilated (consistent with bronchiecasis) or partially collapsed due to inspissated mucous. Bronchial wall inflammation with mononuclear cells and eosinophils, if uncontrolled causes central bronchiectasis (CB), collagen replaces the submucosal glands and smooth muscle fibers. In addition, there will be thickened basement membranes, smooth muscle hypertrophy, infiltrate with eosinophils, plasma cells and lymphocytes, mucosal gland hyperplasia and other expected morphological changes in asthma.

Defense against *Aspergillus* spores include both neutrophil and alveolar macrophages. Invasive aspergillosis is a frequent complication of leukopenia or associated pulmonary epithelium damage as in cancer treatment with chemotherapy.

**CLINICAL FEATURES**

Majority of patients of ABPA have asthma or cystic fibrosis (CF). However, there are several case reports of ABPA without coexisting bronchial asthma or CF. ABPA is usually seen in twenties or thirties but has also been reported in children and even in infants.

It is chronic persistent disease with repeated exacerbation interposed with periods of remission, and if untreated results in fatal destruction of lung. Patient usually presents with poorly controlled asthma. Symptoms include breathlessness, wheeze, cough with sputum, chest pain, golden brown plugs (in up to 56% of patients), malaise, fever and even hemoptysis. Some patients may altogether be asymptomatic. However symptoms bear little or no relationship to the severity or chronicity of the disease. Many times these patients are confused with tuberculosis and repeatedly treated with anti-tubercular drugs.

Examination findings of chest vary depending on severity of destruction. These include rhonchi, crepitation or bronchial breathing. Patients in end stage fibrotic lung disease have tachypnea, cyanosis and digital clubbing. Associated hypertrophic osteoarthopathy has been reported. Cor pulmonale can occur.

**DIAGNOSTIC CRITERIA**

A set of criteria is required to establish a diagnosis of ABPA. The diagnostic features of ABPA are summarized in Table 3. The presence of central bronchiectasis (CB) labelled ABPA as ABPA-CB, and without CB as ABPA-S, which may occur in patients who have experienced one or few episodes of pulmonary infiltrates. Some patients currently considered ABPA-S require upto 5 yrs before a certain diagnosis can be established. One patient was treated as ABPA-S and developed ABPA-CB after five years. Presence of CB in the absence of distal bronchiectasis is *sine qua non* for ABPA. However, a minimal essential set of criteria has been proposed to diagnose ABPA which include - (a) Asthma (b) Immediate cutaneous reactivity to Af and (c) Central bronchiectasis. With the exception of CB and elevated serum IgE Af and IgG Af compared with asthmatic sera diagnostic criteria are not specific for ABPA. Twenty five percent of patients with asthma raised IgE Af and skin test positive and 10% have precipitating antibodies, yet ABPA occurs in about 6% of *Aspergillus* skin test positive asthmatic individuals while others have IgE mediated asthma.
STAGES OF ABPA

There are five stages of ABPA-CB. They are not phases, as some patients present with end stage pulmonary fibrosis at the time of recognition of ABPA. This is a clinical staging system. The important features of all the stages are summarized in Table 4.

**Stage I (Acute):** This is a stage when patients present for the first time to physician. All the classical radiological and serological findings are present.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total serum IgE</th>
<th>Precipitins</th>
<th>Peripheral blood eosinophilia</th>
<th>CXR abnormalities</th>
<th>IgE Af</th>
<th>IgG Af</th>
</tr>
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<tbody>
<tr>
<td>I (acute)</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>II (remission)</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>III (exacerbation)</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IV (corticosteroid dependent asthma)</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
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<tr>
<td>V (fibrotic)</td>
<td>+</td>
<td>±</td>
<td>-</td>
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<td>+</td>
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CB can be detected on chest X-ray and computed tomography. Treatment with steroids results in: (a) resolution of the roentgenographic infiltrate in almost all the cases by 4 weeks (b) decrease in associated symptoms of asthma (c) reduction of sputum plugs and/or conversion of AF positive to negative (d) decrease in peripheral blood eosinophilia and (e) decrease in total serum IgE by at least 35% in 6 weeks.

Stage II (Remission): It occurs, when there is no new infiltrate or rise in IgE levels for at least 6 months. During this period prednisolone has been tapered and discontinued without exacerbation. Total serum IgE levels declines and stabilizes but at increased level. Serological findings may or may not be positive.

Stage III (Relapse): Relapses can occur anytime, even after a prolonged remission. Marked increase in total IgE levels and new chest infiltrates labeled the patients in exacerbation. Doubling of total IgE levels is necessary but frequently 3-10 fold increase in levels occur. Patients may or may not present with constitutional symptoms but with new chest X-ray infiltrate, lung destruction can proceed silently, so there lies the importance of regular follow up. Prednisolone induces resolution of X-ray infiltrate and decline in total IgE levels. If patient is seen 1st time by any physician it can be confused with stage 1 as all the findings are similar to stage 1.

Stage IV (Corticosteroid Dependent Asthma): Stage IV ABPA may be present at the time of initial presentation. Exacerbations occur when repeated attempts are made to taper prednisolone in stages I and III. It is clinically indistinguishable from corticosteroid dependent asthma without ABPA.

Stage V (Fibrotic): End stage fibrosis occurs i.e. irreversible obstructive and restrictive pulmonary disorder. Stage V patients develop widespread honeycomb fibrosis, cyanosis, arterial hypoxemia, and respiratory failure. Total IgE levels are elevated. Prednisolone is essential for the management of asthma. Death occurs from cor pulmonale despite administration of corticosteroids.

Other proposed methods of staging: Kumar categorized ABPA into three stages as ABPA-S (serological positive), ABP-CB (with central bronchiectasis) and ABPA-CB-ORF (with central bronchiectasis and other radiological features) and labeled as mild, moderate and severe form of ABPA. This staging is as per serological, radiological and clinical severity of the patients. Patients with ABPA-CB or ABPA-CB-ORF have more sign/symptoms and high serological values compared to ABPA-S patients.

Seropositive ABPA (ABPA-S): In early stages of disease some patients may not have CB but fulfilling other criteria of ABPA. They are labeled as ABPA-S. Patients are classified as stage I. It has been shown that patients who fit into ABPA-S have less airway inflammation, sputum production and total IgE levels.

![Fig. 2. Initial and subsequent stages of ABPA](image-url)
PROGRESSION OF DISEASE

Figure 2 represents recognized patterns that may occur in ABPA. Stage I cases can go into remission or develop exacerbation even after prolonged remission. Sometimes, it is difficult to taper corticosteroids and they directly enter stage IV of corticosteroid dependent asthma. Stage III patients can revert back to stage II with corticosteroid therapy or enter stage IV.

Patients may present with stage V ABPA at initial presentation. These are patients with long standing illness and receiving no or irregular treatment. It has been observed that no patient has progressed from stage IV to stage V, if disease is recognized and proper regular treatment is started. Kumar and Chopra evaluated ABPA-S and ABPA-CB where ABPA-CB was severe form of the disease clinically and serologically both.

ROENTGENOGRAPHIC FEATURES

ABPA is characterized by fleeting soft pulmonary infiltrates, central bronchiectasis, and wide spectrum of chest X-ray appearances. It forms a crucial part in diagnosis and also helps to monitor the progression of disease. On the basis of chest X-ray, either transient or permanent findings occur.

Transient changes: - Mucoid impaction or infiltrates.

Transient findings stay for short time, they appear and disappear involving segments, lobes or whole lung. They are not pathognomonic of ABPA, but reflect disease activity. Most of the findings occur in dilated bronchi and are often present in posterior segment of the upper lobe and so confused with tuberculosis.

The most common findings include soft non-homogenous shadows (75%), which are fleeting or migratory, line shadows (65%), which represents bronchial wall edema. It is not specific for ABPA but may be present in asthma, cystic fibrosis, and LVF with elevated pulmonary venous pressure.

Ring shadows (65%), massive homogenous consolidation (15%) occurred in patients as a result of markedly dilated bronchi and parenchymal infiltrates. Mucoid impactions in the bronchi of upper lobes may lead to V shaped shadows, known as "wine glass" shadow. Peripheral infiltrates simulate hilar adenopathy and are described as pseudohilar shadows. Mucoid impaction in dilated bronchi gives "tooth paste" shadow. "Glove finger" shadows occur when ends of distorted bronchi get occluded and filled with secretions. Air fluid levels are seen when dilated bronchi are filled with fluid and debris.

Lobar or segmental collapse is common in ABPA. Case of middle lobe syndrome due to mucoid impaction has been described. Pleural effusion has been reported with collapse, which disappeared on reexpansion of lobe after therapy with steroids. The reason given for pleural effusion is mechanical effect of collapse of the lung.

Permanent changes: - These changes are irreversible and associated with fibrosis in bronchial wall and/or parenchyma. "Parallel line shadows" and "ring shadows" represent CB. When the dilated bronchus is seen en face, it is known as ring shadow, which is 1-2 cm in diameter and when seen tangentially the dilated bronchus is called parallel line shadow. CB with normal distal tapering is sine qua non of ABPA. Other changes include pulmonary fibrosis, cavitations, contraction of upper lobes, blebs and bullae. Spontaneous pneumothorax can occur.

Bronchography: - It demonstrates CB and was earlier considered gold standard investigation for bronchiectasis but now it is replaced by CT (HRCT). It has been associated with wheezing despite 7 days of pre treatment with prednisolone.

CT: - CT is sensitive and specific in detecting CB in patients with ABPA. 'String of pearls', 'signet ring' appearance characteristic of bronchiectasis is seen. Other abnormalities seen are non-homogenous patchy consolidation, segmental or lobar collapse, cavities, emphysematous bullae and fibrosis. All this with parenchymal volume loss is confused with fibrocavitary pulmonary TB.

Attempts to classify or grade stages of ABPA has been made recently on the basis of rotenegraphographic and CT findings which are found to correlate with peak Af-index, eosinophil counts and total IgE levels.
LABORATORY FINDINGS

Nearly every patient has an immediate cutaneous reaction (type 1) but 25% of asthmatics without ABPA can have skin test positive.\textsuperscript{11} Type III i.e. Arthus type reaction can also be observed after 4-6 hours.

Sputum production is excessive in patients with CB, with sputum eosinophilia. Fungal hyphae may be demonstrated in sputum smear examination. Sputum may yield \textit{Aspergillus} species in about 58% of cases.\textsuperscript{38} However, sputum cultures may be negative at time of ABPA exacerbation.

Peripheral eosinophilia is present in stage I and III when new pulmonary infiltrate is present on CXR, in patients not receiving corticosteroids. Most patients\textsuperscript{64} have between 1000-3000 eosinophils per mm\textsuperscript{3}.

Serological tests are most valuable in confirming or excluding ABPA. Total IgE levels are generally >1000 ng/ml in type I, III, IV although some patients have elevated IgE in stage II, V also. Total IgE level decline, at least 35% in 8 weeks with prednisolone treatment but never touches the level below 1000 and thus used as monitor of treatment.\textsuperscript{64}

Precipitating antibodies in gel are found in over 90% of patients in stage V and III but are less frequently present in all stages.\textsuperscript{41}

IgE-Af, IgG-Af antibodies are able to distinguish between ABPA patients and patients with bronchial asthma with immediate cutaneous reaction positive to \textit{Aspergillus}. The levels of IgE-Af, IgG-Af are doubled in former than later.

PULMONARY FUNCTION TEST (PFT)

One can not judge the extent of disease with PFT. Not all the patients have inexorable course of deterioration of pulmonary function with progression to stage V, despite multiple exacerbations.\textsuperscript{50} However some patients do present with irreversible PFT that do not improve with therapy.\textsuperscript{50}

During exacerbations PFT reveal restriction with reduction in lung volumes and diffusion capacity. Obstruction alone may occur in some patients. These parameters may return to baseline after treatment with prednisolone. Patients in stage V have irreversible obstruction and restrictive findings.\textsuperscript{48} Early intervention and treatment with prednisolone appears to prevent progressive PFT loss.\textsuperscript{53}

DIFFERENTIAL DIAGNOSIS

1. Inadequately controlled asthma
2. Pulmonary tuberculosis in high prevalent areas
3. Bacterial, viral, fungal pneumonia
4. Eosinophilic pneumonia, bronchocentric granulomatosis
5. Churg-Strauss syndrome
6. Hypersensitivity pneumonitis

TREATMENT

Goals of treatment are described below:

1. Early detection and prompt treatment of ABPA exacerbations, so as to prevent or minimize bronchiectasis.\textsuperscript{14}
2. Manage associated asthma or irreversible obstructive and restrictive lung disease.\textsuperscript{14}
3. Exclude others having ABPA in family,\textsuperscript{14} and
4. To identify potential environmental source of incremented fungus.\textsuperscript{65}

Patients may have exacerbations (i.e. new infiltrates on CXR, doubling of IgE levels) but without or minimal symptoms in about 33% of cases.\textsuperscript{66} There is lack of correlation of chest roentgenogram with clinical symptoms or physical findings. Corticosteroids remain the early treatment options and are cornerstone of treatment. Aggressive treatment of early stages, may halt progression to stage of fibrosis.

For stage I & III:

Oral prednisolone is given at dose of 0.5mg/kg/d. i.e. 35-40mg as a single morning dose for 2 weeks, then converted to an alternate day dose for 2-3 months. Serial measurements of total IgE and CXR should be obtained. There is resolution of X-ray infiltrate and reduction in serum IgE levels by 35% within 2 months of initiating treatment.\textsuperscript{66}
After 3 months of alternate day therapy with prednisolone, it is tapered off by 2.5mg every 2 weeks unless other exacerbation occurs. If prednisolone can be discontinued, patients should be evaluated for 4-6 weeks initially to help determine whether (stage II) occur (no chronic prednisolone and no new roentgenographic infiltrates for 6 months) or whether stage III, IV or V occur.

Stage IV is managed with prednisolone usually on alternate day of 10-40mg for several years, as repeated attempts to discontinue might result in unacceptable wheezing.

Stage V patients may require daily prednisolone and when marked lung destruction occurs, they require treatment for cor pulmonale and arterial hypoxemia until death. Stage V may require in addition LTOT.

Additional anti asthma agents like inhaled corticosteroids, β2 agonists may help to control the symptoms of asthma but do not have any influence either in preventing exacerbations of ABPA or on progression of lung damage.

ANTIFUNGAL AGENTS

Role of anti fungal agents in treatment of ABPA is still debatable. It was thought that by decreasing the fungal load, there would be a reduced antigenic stimulation and thus a decrease in the inflammatory response.

Trials of anti fungal agents for ABPA till now yielded unsatisfactory results and they have proved ineffective as the main form of treatment. Ketoconazole and or Itraconazole are thought to decrease the antigen load by reducing immune response to Aspergillus and thus showing symptomatic improvement as well as reduce risk of further lung damage produced by immune complexes. Itraconazole prevents exacerbations, reduces or even eliminates the dose of corticosteroids required in the management of ABPA.

ACKNOWLEDGEMENT

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