

Allergic Bronchopulmonary Aspergillosis

Anubhab Moulik¹, Sayan Bhattacharyya²

Abstract

Extra intestinal Pathogenic *Escherichia coli* (ExPEC) is a leading cause of invasive infections. These include entities like bacteremia, respiratory tract infections, meningitis and sepsis among others. Invasive ExPEC infection complicates the clinical treatment of other conditions. It is also associated with increased mortality, duration of hospital stay, and worse clinical outcomes. Older adults having comorbidities are at highest risk of acquiring these infections. ExPEC is of particular interest in the Asia-Pacific region, due to aging populations and increasing antimicrobial resistance.

Keywords: ExPEC; Bacteremia; UTI.

Introduction

Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex hypersensitivity reaction to the fungus *Aspergillus fumigatus*. The entity primarily affects individuals having asthma or cystic fibrosis. This review highlights the pathogenesis, diagnosis, and management of ABPA, with a focus on recent advancements and challenges. Allergic bronchopulmonary aspergillosis is a form of lung disease that occurs in some people who are allergic to *Aspergillus* spp. With ABPA, this allergic reaction causes the immune system to overreact to *Aspergillus* spp which culminates in lung inflammation. ABPA causes bronchospasm (or tightening of airway muscles) and mucus build-up, leading to symptoms like coughing, breathing difficulty and airway obstruction.

Aspergillus species are molds which are ubiquitous in the environment, especially in

the organic matter. There are over 100 known *Aspergillus* species worldwide, but most of the illnesses are caused by *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, and *Aspergillus clavatus*. An infection by *Aspergillus* species usually causes a broad spectrum of illnesses in humans. However, this depends also on the immune status of the host. Symptoms range from hypersensitivity reactions to direct angioinvasion.¹

Aspergillus fumigatus is the most common ubiquitous airborne fungus that serves as the principal causative microorganism for ABPA.

Epidemiology

Allergic bronchopulmonary aspergillosis is a restrictive chest disease that commonly presents in man in their third to fifth decades of life. It is also commonly encountered in children. This entity is

AUTHOR'S AFFILIATION:

¹Consultant Microbiologist and Infection Control Officer, Department of Microbiology, Institute of Neurosciences, Kolkata 700017, West Bengal.

²Associate Professor, Department Microbiology, All India Institute of Hygiene and Public Health, Kolkata 700098, West Bengal, India.

CORRESPONDENCE AND REPRINT REQUESTS:

Sayan Bhattacharyya, Associate Professor, Department Microbiology, All India Institute of Hygiene and Public Health, Kolkata 700098, West Bengal, India.

E-mail: sayantheboss@yahoo.co.in

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also found in severe asthmatics and patients with cystic fibrosis. ABPA is seen mostly in adolescent and adult patients having asthma or cystic fibrosis. It has been estimated that about 2.5% (0.7–3.5%) of adult patients with asthma suffer from ABPA, too. In a recent meta-analysis, the pooled prevalence of *A. fumigatus* sensitisation in asthmatic adults was estimated to be about 25% in tertiary care. Of the *Aspergillus*-sensitised individuals, nearly 37% finally developed ABPA.⁹ ABPA may not always require a predisposing condition; the culprit environment or such predisposing conditions has been expanded to include bronchiectasis and COPD.¹⁰

Aspergillus fumigatus is the commonest causative fungus incriminated in ABPA. However, other *Aspergillus* species like *A. flavus*, *A. niger*, and *A. oryzae*, can also cause ABPA, albeit less frequently. *Schizophyllum commune*, a filamentous basidiomycetous mold commonly found on the rotten wood of trees, can lead to similar pathology and a condition coined as allergic bronchopulmonary mycosis (also called ABPM).²

Clinical features

Symptoms of ABPA mimic those of exacerbating asthma or pulmonary cystic fibrosis, with cough producing dirty-green or brown plugs. Haemoptysis is rare. Pyrexia, headache, and loss of appetite are also commonly observed systemic findings in severe cases. Signs of airway obstruction, manifesting as wheezing and prolonged expiration, are not differentiable from exacerbation of bronchial asthma, which is a close differential diagnosis.³ Actually, ABPA may be considered as an asthma endotype and is a treatable trait in bronchiectasis not withstanding the aetiology.^{11,12}

Pathogenesis

ABPA is characterized by an exaggerated immune response to *Aspergillus fumigatus*. The pathogenesis involves both type I (IgE-mediated) and type III (IgG-mediated) hypersensitivity reactions. Eosinophilic mucus plugs in the bronchi and elevated levels of total and specific IgE are key features. Recent findings suggest that extracellular trap cell death of eosinophils plays a significant role in disease mechanisms. The cells (Helper T cells) play an essential role in the hypersensitivity reaction caused by the *A. fumigatus* antigen. It presents as IgE production, eosinophilia, mast cell degranulation and bronchiectasis.⁴ The interleukins primarily involved in the disease process are IL-4,5

and 13. There are also certain genetic factors which predispose to ABPA, like HLA DR2,5, mutations in CFTR, polymorphism in SP-A2 and mannose binding lectin (MBL) which also increase the overall probability of developing ABPA.

Diagnosis

The diagnosis of ABPA is indeed challenging due to its overlapping symptoms with other respiratory conditions. The International Society for Human and Animal Mycology (ISHAM) has proposed some diagnostic criteria that include patients with the following predisposing conditions:

- a) Positive immediate skin reaction to *Aspergillus* antigen. In the skin test, a positive Type I Hypersensitivity reaction is typical of ABPA. It represents the presence of *A. fumigatus*-specific IgE antibodies.
- b) Elevated total serum IgE levels. Elevated total serum IgE (usually over 500 IU/mL) is indicative of ABPA. The cut-off value has been reduced from 1000 IU/ml as the latter is less sensitive.^{13,14}
- c) Presence of precipitating antibodies (precipitins) to *Aspergillus* antigen.
- d) Gel diffusion tests: They can be done to detect antibodies to *Aspergillus* spp.
- e) Culture: *Aspergillus* spp. can be cultured from the sputum in up to two-thirds of patients having ABPA, but hyphae may not be clearly evident by direct microscopy.⁵ Since *Aspergillus fumigatus* is a ubiquitous fungus and can also be present naturally in humans, its isolation does not necessarily guarantee causality.

Histopathology

Histopathologically, in ABPA one can document chronic bronchial inflammation, eosinophilia (that may lead to the development of an area of lung parenchymal scarring), airway remodelling, and bronchiectasis. Bronchi may show impacted mucus plug containing fungal hyphae, Charcot-Leyden crystals, fibrin and Curschmann spirals. The dichotomous branching of hyphae occurs at 45 degree angles, indicative of *Aspergillus* spp.

Recent guidelines recommend screening for *A. fumigatus* sensitization using fungus-specific IgE in newly diagnosed asthmatic adults and difficult-to-treat asthmatic children as the skin test fared poorly in comparison to the antibody assay.^{13,14} The IgE immunoassay cut-off is 0.35 kUA/

L(Kilounits of allergen-specific IgE per liter) using FEIA (fluorescent enzyme immunoassay).¹⁵

- a) Chest X-ray: Imaging studies, such as high-resolution CT scans, can reveal central bronchiectasis and mucus plugging, which are indicative of ABPA. Chest X-ray has 50% sensitivity for the diagnosis of ABPA. It can show parenchymal infiltrate and bronchiectatic changes, mostly in the upper lobes. However, all lobes may exhibit involvement.

HRCT (High resolution CT scan) Chest is the investigation of choice for detecting bronchiectatic changes and other abnormalities that are undetectable on a chest X-ray, like centrilobular nodules and tree-in-bud lesions.

Patients of ABPA with no obvious abnormalities evident on HRCT chest are termed as serologic ABPA (or ABPA-S).

Patients with central bronchiectasis on HRCT are, on the other hand, termed as ABPA Central Bronchiectasis (ABPA-CB). Typical radiological

abnormalities seen in ABPA are “Finger in glove” opacity which is suggestive of impaction of mucus in the dilated bronchi and “tramline shadows” suggestive of parallel linear shadows which extend from the hilum in bronchial distribution and represent longitudinal impression of the inflamed, edematous bronchi. Some other findings are “toothpaste shadows” highlighting mucoid impaction of the airways, and “ring shadows” which indicate dilated bronchi with inflamed bronchial walls. The higher sensitivity, identification of the type and distribution of bronchiectasis, and recognition of mucus plus are evident in CT scan in a better way than a digital X-ray. High attenuation mucus (HAM), or mucus which is visually denser than the paraspinal muscles on non-contrast CT thorax is said to be pathognomonic for ABPA.¹⁶ The sensitivity and specificity of HAM are 35% and 100% respectively.¹⁷

Appended below shows diagnostic algorithm in ABPA

Below shows Chest X-ray with typical findings of ABPA

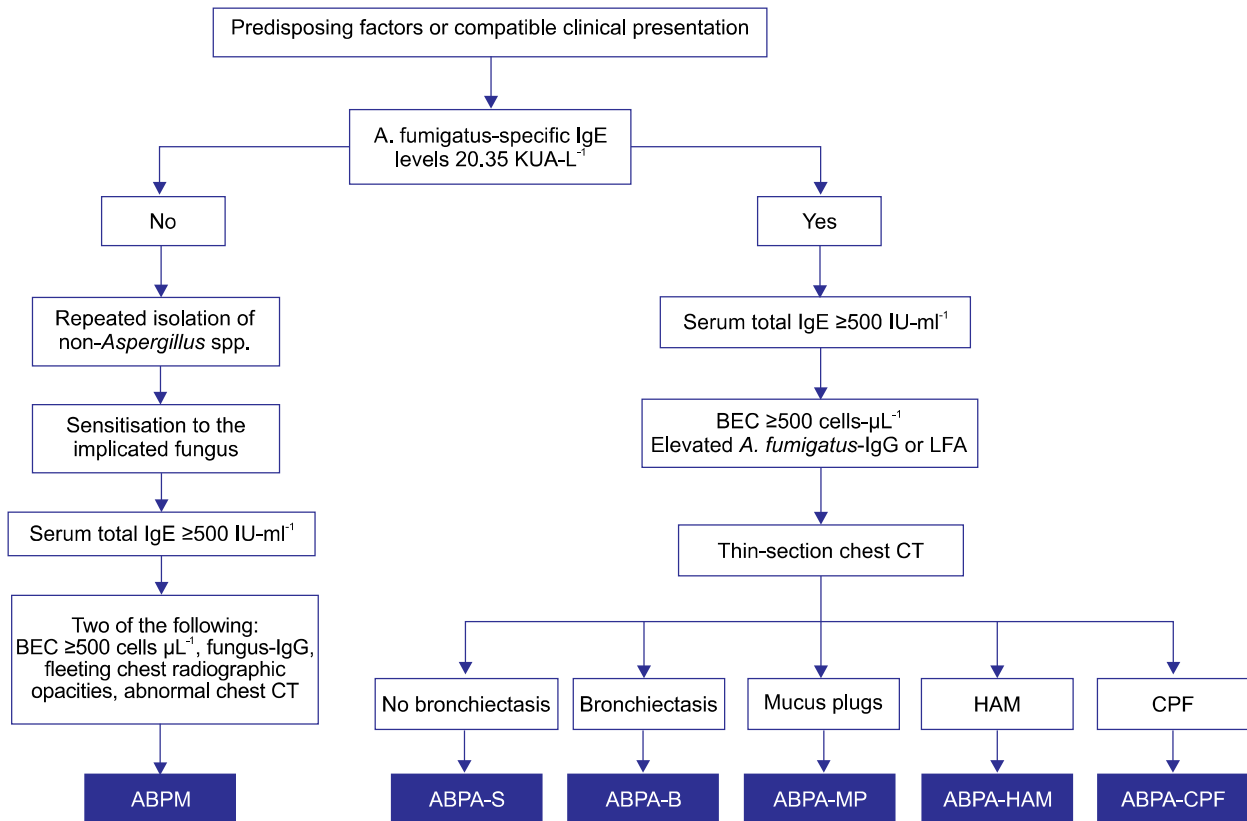


Figure 1: Diagnostic algorithm in ABPA

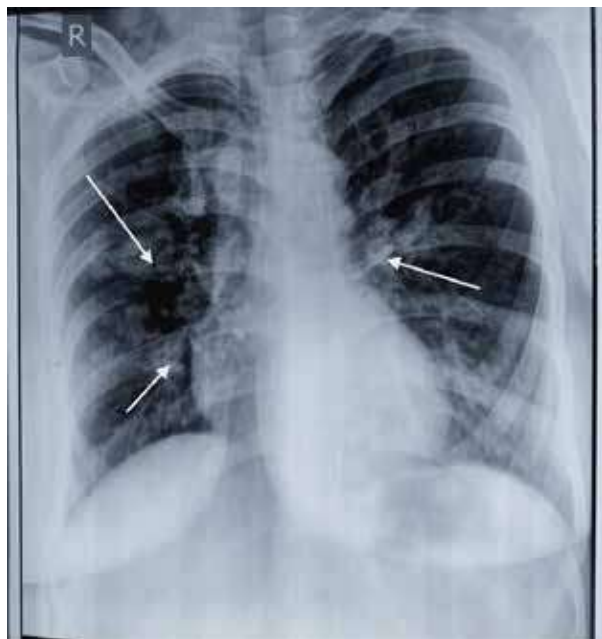


Figure 2: Chest X-ray of ABPA [source: ResearchGate]

Below shows CT scan findings of ABPA

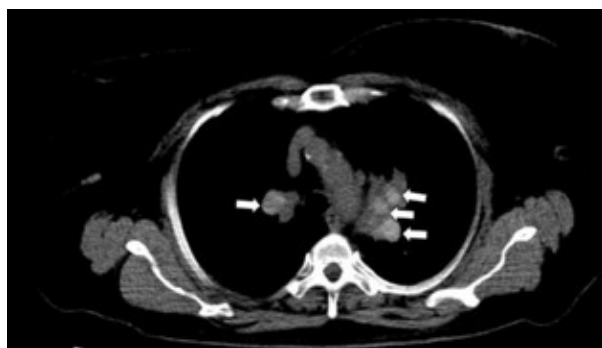


Figure 3: CT scan findings of ABPA [Source: www.eurorad.com]

Appended below summarizes comparative X-ray and CT findings and typical histopathology

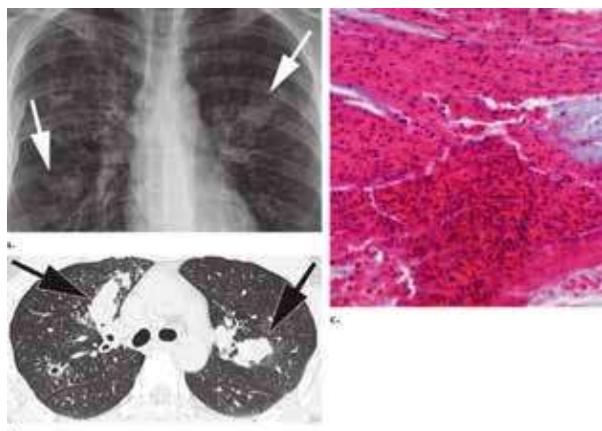


Figure 4: Comparative X-ray and CT findings and typical histopathology

Management and treatment

The management of ABPA involves a combination of pharmacological and non-pharmacological approaches. The primary goals are to control inflammation, reduce fungal load, and prevent disease progression. Treatment options include:

Corticosteroids: Oral prednisolone is the mainstay of treatment for acute ABPA and exacerbations. The ERS 2024 recommendation is to use a dose of prednisolone 0.5 mg/kg/day for 2-4 weeks with gradual tapering and completed over 4 months. In patients with co-existent asthma, the asthma treatment needs to be optimised as these disease entities operate on a vicious interplay between themselves.

Antifungal agents: Itraconazole is commonly used to reduce fungal burden. Oral itraconazole as alternative monotherapy may be used for 4 months; however, the evidence in its favour is less in comparison to steroid. Although Voriconazole has similar efficacy as steroids, it has poor patient tolerability, thus losing credit as first line therapy.¹⁹ The combination of steroids and azoles may even lead to exogenous Cushing's syndrome. The clinician must be aware of that. The combination of methylprednisolone and Itraconazole is particularly notorious in this regard. Since many of these patients are also poorly controlled asthmatics, the possibility of them being on high dose inhaled budesonide or fluticasone is also high which may also lead to exogenous Cushing's syndrome, an often missed entity⁽²⁰⁾.

Antifungal drugs can help reduce the exacerbations of allergic bronchopulmonary aspergillosis (ABPA). Other than Itraconazole and Voriconazole, Posaconazole may also be used.

Biologics: As per ERS (European Respiratory Society) 2024 recommendations, there is no role of biologics at present for treating ABPA.

Treatment of ABPA aims to control inflammation and prevent further injury to one's lung. ABPA is usually treated with a combination of oral corticosteroids and antifungal medications. Corticosteroids are used to treat inflammation and mitigate the allergic reactions. Examples of corticosteroids include prednisone, prednisolone or methylprednisolone. Inhaled corticosteroids alone, like those used for asthma treatment, are not effective in treating ABPA. Usually, treatment with an oral corticosteroid is needed for months. A patient should discuss with his or her health care provider about the possible adverse effects with oral corticosteroids and how well they can be tolerated.⁶ The treatment for ABPA exacerbations

(defined as sustained worsening for 2 weeks or more of clinical symptoms or the appearance of new infiltrates on chest imaging, along with an increase in total IgE by greater than or equal to 50% from the new baseline, achieved during clinical stability) follows the same guidelines as newly diagnosed ABPA. Pulsed doses of methylprednisolone have been used for treating exacerbations of ABPA which are refractory to oral glucocorticoids.²¹ The overall approach to monitoring response to treatment is using a visual analogue scale of more than or equal to 50%, along with at least a 20% reduction in serum total IgE levels. Response is usually assessed after 8-12 weeks of therapy.

Challenges and Future Directions

Despite advancements in diagnostics and therapeutics, several challenges and hurdles persist in the management of ABPA. These include the need for early and accurate diagnosis, the risk of possible adverse effects arising from long-term corticosteroid use, and the limited availability of biologics in some areas. Future research should thus focus on development of more precise diagnostic tools and also exploring novel therapeutic targets simultaneously.

Discussion

From the first case description in 1952, significant advances have been made in understanding the pathogenesis and the diagnosis and treatment of ABPA. In the last twenty years, most research on ABPA has been published from India.⁷ It is believed that across the world, there are about 5 million cases of ABPA. India alone accounts for nearly 1.4 million ABPA cases. The prevalence of ABPA among asthmatic patients in special clinics may be as much as 13%. Thus, a high degree of suspicion for ABPA should be present while treating a patient with bronchial asthma, particularly in specialized clinics. Early diagnosis and appropriate treatment can delay or even prevent the onset of bronchiectasis. This implies that all patients of bronchial asthma should be screened for ABPA, particularly in the chest clinics.⁸ In India, the prevalence of ABPA is greater than in other countries. Early identification is a prerequisite to prevent irreversible lung damage in ABPA. There is hence an urgent and pressing need for generating increased awareness of ABPA, its diagnosis, as well as management algorithms amongst all healthcare givers.

Conclusion

ABPA is a complex condition requiring a multidisciplinary approach for effective management. Advances in understanding its pathogenesis and the development of new diagnostic criteria and treatment options have improved patient outcomes. However, ongoing research and clinical vigilance are essential to address the remaining challenges and enhance the quality of care for individuals with ABPA.

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