ISSN 2618-1584 Vol. 7, Issue 5: 18-22, DOI: 10.25236/FMSR.2025.070503

Research Progress of Allergic Bronchopulmonosis

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Abstract: *Allergic bronchopulmonary aspergillosis (ABPA) is a fungus caused by Aspergillus Th2 immune-mediated complex lung disease, most commonly associated with asthma and cystic fibrosis (CF), caused by Aspergillus fumigatus. In recent years, serological markers such as specific IgE and eosinophil counts, together with characteristic radiologic findings, have become established cornerstones of ABPA diagnosis. The combination of corticosteroids and antifungal agents remains a first-line treatment option, however, new biological targeted therapies have been gradually introduced into clinical practice for hormone-dependent and refractory cases and have demonstrated significant clinical efficacy. This article reviews the epidemiological characteristics, pathophysiological mechanisms, clinical manifestations, diagnostic criteria and treatment strategies of ABPA, aiming to provide evidence-based evidence for clinical diagnosis and treatment.*

Keywords: *Allergic Bronchopulmonary Aspergillosis; Asthma; Cystic Fibrosis*

1. Introduction

Allergic bronchopulmonary aspergillosis was first described by Hinson et al. 70 years ago [1], and in eight of the cases they described, persistent sputum and lung shadows were characteristic manifestations of the disease. ABPA was almost exclusively found in patients with asthma and cystic fibrosis (CF), and this characteristic suggests that ABPA should be included in routine screening in the clinical management of patients with asthma and CF[2, 3]. The prevalence of ABPA is estimated to be as high as 2.5% in patients with asthma[3]and 2%-15% in patients with cystic fibrosis[4]. ABPA has a high misdiagnosis rate, especially in developing countries, and is easily misdiagnosed as tuberculosis[5]. However, with the in-depth understanding of immune mechanisms and molecular diagnosis, ABPA management strategies continue to be optimized.

2. Epidemiology

Denning et al. estimated that the global burden of ABPA may exceed 4.8 million cases; there are significantly more reported cases in Europe and America than in Southeast Asia, Africa and the Mediterranean region, and this difference is mainly related to higher diagnostic ability and medical access in Europe and America, rather than actual incidence differences[3]. In addition, environmental factors also have an impact on the incidence of ABPA. Aspergillus fumigatus tends to grow in humid and hot environments, which may explain why the incidence of ABPA is higher in some countries such as India (16.8%) than in other countries (7.9%)[6]. The incidence of ABPA varies by age group. A systematic review and meta-analysis of asthmatic children showed that aspergillosis sensitization rates were as high as 16%, ABPA incidence was 10%, and ABPA incidence was 21% in asthmatic children sensitized by aspergillosis[7], which suggests that we should pay attention to fungal sensitization in children, especially Aspergillus fumigatus sensitization. At present, the incidence of ABPA in elderly patients is not clear, but it has been observed that ABPA is more common in the elderly population in Japan and South Korea[8, 9]. Muthu et al. conducted a study on 810 ABPA patients[10], comparing the differences in imaging characteristics, serological markers and clinical manifestations between elderly patients (age ≥60 years) and non-elderly patients. It was found that the elderly patients had longer asthma duration, but the serum total IgE and Aspergillus fumigatus IgE showed a significant downward trend. Radiographic findings of relatively mild bronchiectasis in older patients may indicate a relatively good prognosis in older patients.

At the genetic level, a recent study showed that the mutation frequency of cystic fibrosis

ISSN 2618-1584 Vol. 7, Issue 5: 18-22, DOI: 10.25236/FMSR.2025.070503

transmembrane conductance regulator (CFTR) in ABPA and asthma patients was significantly higher than that in healthy controls, and it was further enriched in severe ABPA patients [11], suggesting that CFTR mutation may serve as a potential biomarker for ABPA disease severity, and its clinical value needs to be verified by large sample studies.

3. Physiopathologic Mechanism

At present, the pathogenesis of ABPA has not yet been fully clarified. Bhushan et al. revealed that Aspergillus activates the JAKSTAT1 signaling pathway, which in turn inhibits this pathway, resulting in the blocking of interferon INF-β signaling. This process is accompanied by a decrease in the level of chemokine CXCL10, which in turn promotes the transition of the immune response of epithelial cells from Th1 to Th2[12]. This Th2 response releases a variety of cytokines and chemokines, including interleukin (IL)-4, IL-5, IL-13, CCL-17 and IL-9. typically characterized by mast cell degranulation and eosinophil and neutrophil infiltration, resulting in tissue damage (e.g. bronchiectasis, eosinophil pneumonia) and pathological changes.

In ambient air, spores of Aspergillus fumigatus are ubiquitous, making exposure to these fungal conidia virtually unavoidable. The spores, ranging from 3 to 5 μm in diameter, readily deposit in the lower bronchial regions of the human respiratory tract[13]. Studies have shown that a Th2 response is detectable only when peripheral blood mononuclear cells are stimulated with Aspergillus fumigatus, and that the production of Aspergillus-specific IL-5 and IL-13 is dependent on $CD4^+$ T cells, the pattern-recognition receptor CR3, and phagocytosis[14].

ABPA is common in patients with asthma and cystic fibrosis. These patients have impaired airway mucosal defense mechanisms, manifested by reduced cilial clearance and epithelial cell physiological dysfunction[12], resulting in Aspergillus fumigatus retention in the airway. A retrospective study by Ying Luo et al. analyzed 378 COPD patients who received aspergilla-specific IgE testing, of whom 29 were (7.7%) was identified as aspergillosis. The study found that compared with non-sensitized COPD group, aspergillosis sensitized COPD group had a significantly higher prevalence of lumen obstruction[15], suggesting that the mechanism behind this may be that Aspergillus fumigatus extract promotes the production of Muc5ac and Muc5b, which are the main mucin components in normal airway mucus.

4. Clinical manifestations and diagnostic criteria

ABPA often presents with nonspecific manifestations, including cough, expectoration of mucous sputum, and wheezing; some patients may also complain of chest pain, hemoptysis, or fever. In advanced stages, type 2 respiratory failure and cor pulmonale may develop, accompanied by diffuse bronchiectasis and pulmonary fibrosis[16]. Approximately one-third of affected individuals will discharge brown viscous sputum plugs[17]. ABPA can be divided into ABPA serotypes (ABPA-S) and ABPA central bronchiectasis (ABPA-CB) according to the presence or absence of central bronchiectasis. A retrospective study showed that ABPA-CB patients were more likely to be elderly than ABPA-S patients, with elevated blood eosinophil levels and decreased lung function [18], Notably, a recent retrospective analysis of 705 ABPA patients by Valliappan Muthu and colleagues revealed that the frequency of acute exacerbations rises markedly as the severity of bronchiectasis increases from mild to moderate to severe. Moreover, patients with more advanced bronchiectasis exhibited poorer pulmonary function and markedly higher serum total IgE levels[19], These findings underscore the importance of incorporating bronchiectasis severity into clinical stratification and prognostic assessment frameworks for ABPA.

A set of diagnostic criteria was first proposed by ROSENBERG et al.[20] in 1977, but this criteria has limitations, it takes an equal emphasis on all parameters, and in fact some components of the criteria are significantly more important than others. Therefore, in 2013, the International Society for Human and Animal Mycology (ISHAM) revised these criteria[21], as follows: Bronchial asthma and CF are still considered predisposing factors for ABPA. Both of the following criteria must be met: elevated total IgE levels exceeding 1000IU/mL and an immediate positive Aspergillus fumigatus skin test; and at least two of the following three criteria must be met: precipitated antibodies or IgG antibodies to Aspergillus fumigatus detected in serum; From the imaging features, the manifestations consistent with ABPA are mainly bronchiectasis, pleural fibrosis and HAM or transient chest radiograph infiltration consistent with ABPA, with specific manifestations of consolidation, nodules, "toothpaste sign" or "finger cuff sign", migratory shadow, etc.; previous tests showed that the total number of eosinophils

ISSN 2618-1584 Vol. 7, Issue 5: 18-22, DOI: 10.25236/FMSR.2025.070503

exceeded the normal range once, exceeding 500 cells/μL. However, until 2024, the ISHAM-AWG standard was further simplified by the expert group[22], and the new standard was as follows: A. Susceptibility conditions (asthma, CF, chronic obstructive pulmonary disease, bronchiectasis) or clinical-imaging findings; B. Essential elements: Aspergillus fumigatus specific IgE 0.35 kUA/L, serum total IgE500IU/mL; C. Other elements (any two): A. fumigatus specific IgG positive, blood eosinophil count 500/μL (may be a result of past examination), chest CT consistent with ABPA findings (bronchiectasis, mucus plug, HAM) or transient chest X-ray infiltration. They recommended a cut-off value of 500IU/mL total IgE to increase ABPA sensitivity from 91% to 98%.

5. Treatment Strategies

Currently, oral corticosteroids and antifungal agents remain the basis of ABPA therapy, oral corticosteroids control inflammation, and antifungal agents reduce fungal setting in the airway. Novel biologic agents such as omatuzumab have been initiated clinically for patients who are not responding well to treatment or who have recurrent attacks. ABPA treatment aims to reduce the number of acute attacks, improve asthma control, and prevent ABPA progression. For patients with bronchiectasis or cystic fibrosis, adjuvant therapy with enhanced mucus clearance can also help reduce lower respiratory tract microbial burden and reduce airway inflammation.

For patients with newly diagnosed or acute onset ABPA, prednisone is preferred orally, starting at 0.5 mg/kg/day for 2 weeks, followed by the same dose every other day for 8 weeks; thereafter, 5 mg is reduced every 2 weeks, and the drug is stopped within 3 - 5 months. Alternatively, itraconazole capsules 400 mg/day, taken in 2 divided doses for 4 months; the maximum dose does not exceed 600 mg/day[22]; Studies[23]have shown that the combination of antifungal triazoles can further reduce the occurrence of acute exacerbations compared with corticosteroids alone. ISHAM does not recommend nebulized amphoteric B as a treatment for acute exacerbations of ABPA. Although studies have shown no advantage in preventing acute exacerbations, nebulized liposomal amphoteric B may still have potential clinical benefits. Cendrine Godet et al.[24] demonstrated this in a clinical study of 174 ABPA patients, of whom 139 were stable after pulse therapy and randomized. The results showed that although there was no statistical difference in the incidence of the first serious clinical exacerbation within 24 months between the aerosolized liposomal amphoteric B group and the placebo group, the treatment group showed a longer duration of clinical remission and a significant decrease in serum total IgE and aspergillosis at the treatment endpoint.

Studies have shown that about 13.5% of ABPA patients do not respond well to conventional treatments and develop hormone-dependent ABPA[25]. For such refractory cases, new biological agents have begun to be used by clinicians, especially omalizumab. As a humanized anti-IgE monoclonal antibody, omalizumab acts by specifically binding to the CH3 domain of IgE molecules and blocking the binding of IgE to FcεRI receptors on the surfaces of mast cells and basophils. This effectively inhibits IgE-mediated allergic cascades[26]. Clinical study data confirm the significant efficacy of omatuzumab in ABPA treatment. A systematic review of 102 patients showed that this treatment significantly reduced serum IgE levels, reduced acute attack frequency and hormone dosage, and improved asthma symptoms and lung function indicators[27], The China multicenter study further confirmed that 26 patients treated with omatuzumab significantly reduced hormone dosage after 6 months, 73.68% of patients successfully discontinued hormones at 12 months of treatment, and antifungal drug dosage was also significantly reduced. Studies have also suggested that age and BMI may influence treatment outcomes[28]. Omalizumab dosage recommendations are based on weight and total IgE (0.016 mg/kg/IgE)[29]. because the serum IgE level of ABPA patients usually far exceeds 1000IU/ml and remains high after treatment, omatuzumab is often used in clinical practice at an off-label dose. Its common adverse reactions are mostly mild to moderate, including lower respiratory tract infection, nasopharyngitis, headache, arthralgia, and injection site pain or local reactions; Although serious events (such as death, asthma exacerbation, itching, appendicitis, butterfly sinusitis, intestinal obstruction and mild chest pain) have been reported individually, none have been judged to be drug-related[30].

In addition, in addition to omatuzumab, novel biologics show promising applications in the field of hormone-dependent ABPA therapy. Clinical study data show that dupreimumab (anti-IL-4R α monoclonal antibody), mepolizumab (anti-IL-5 monoclonal antibody), and tezerumab (anti-TSLP monoclonal antibody) have shown significant efficacy in case reports and small-scale retrospective studies[31-33], however, the clinical application of these drugs still needs to be further verified by large-scale, randomized, double-blind, multicenter clinical trials.

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6. Conclusion

Early recognition and standardized treatment of ABPA are not only the "first line of defense" against irreversible pulmonary damage—such as central bronchiectasis, pulmonary fibrosis, and cystic cavitation—but also the key to slowing lung-function decline, lowering long-term hospitalization rates, and reducing the complications linked to prolonged oral corticosteroid use (e.g., osteoporosis, diabetes, infections). Therefore, ABPA should be incorporated into the routine differential diagnosis for all patients with persistent or recurrent asthma exacerbations who require oral corticosteroids, as well as for children and adults with cystic fibrosis who repeatedly culture Aspergillus from sputum or whose imaging shows "finger-in-glove" or "tree-in-bud" signs. At the same time, it is necessary to establish a unified early screening tool, and verify the long-term efficacy and safety of biological targeted drugs through large-sample RCT, so as to realize accurate and de-hormonal whole-process management.

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