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Updates in Allergic Bronchopulmonary Aspergillosis

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Introduction

Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex lung disorder that results from a hypersensitivity reaction to the fungus Aspergillus fumigatus following airway colonization in patients with chronic lung diseases. ABPA predominantly affects patients with asthma and cystic fibrosis, though it can occur in other bronchiectatic conditions. Worldwide, APBA is estimated to impact over four million people.[1,2]

The pathogenesis of APBA involves both type I and type III hypersensitivity reactions, creating a distinctive inflammatory cascade dominated by T-helper 2 (Th2) lymphocytes and eosinophils. This immune dysregulation leads to recurrent mucoid impaction, progressive bronchiectasis, and, if left untreated, irreversible lung damage.[2] As our understanding of ABPA pathophysiology has evolved, therapeutic approaches have advanced significantly, with biologic therapies offering promising steroid-sparing alternatives for refractory or steroid-dependent diseases.

The clinical presentation of ABPA often overlaps with poorly controlled asthma, making diagnosis challenging and frequently delayed. Patients typically present with worsening asthma symptoms, a productive cough containing brownish mucus plugs, and occasionally hemoptysis. Acute exacerbations may also be accompanied by constitutional symptoms, such as low-grade fever and malaise. The hallmark of ABPA is its tendency toward recurrent exacerbations interspersed with periods of relative stability.[3]

The 2024 guidelines from the International Society for Human and Animal Mycology (ISHAM) define distinct clinical states to guide management. Acute ABPA encompasses both newly diagnosed cases meeting diagnostic criteria and exacerbations in known patients, characterized by sustained clinical or radiological worsening with a 50% or more increase in serum total IgE from baseline stability values. Response to treatment is defined by at least 50% symptomatic improvement combined with either major radiological improvement or a 20% decline in IgE after 8 weeks. Remission requires sustained clinico-radiological improvement for at least 6 months without glucocorticoids and without a 50% rise or more in IgE levels; patients receiving biologics or long-term antifungal therapy may also achieve remission meeting these criteria. Treatment-dependent ABPA occurs when patients experience two or more consecutive exacerbations within 3 months of discontinuing glucocorticoids or develop worsening symptoms with imaging changes or IgE elevation within 4 weeks of steroid tapering on two separate occasions. Advanced ABPA is characterized by extensive bronchiectasis involving ten or more segments, accompanied by the development of cor pulmonale or chronic type 2 respiratory failure.[3] Recognizing these clinical states guides treatment intensity and monitoring frequency.

Diagnosis

The ISHAM working group published revised clinical practice guidelines in 2024, providing updated diagnostic criteria.[3]

Diagnostic Criteria

A diagnosis of ABPA requires three essential components:

1. A predisposing condition such as asthma, cystic fibrosis, chronic obstructive lung disease, or bronchiectasis, or compatible clinical features including expectoration of mucus plugs, fleeting pulmonary opacities, or finger-in-glove opacities on imaging.
2. Sensitization to *Aspergillus fumigatus* demonstrated by a positive skin test or elevated specific IgE.
3. Evidence of immunologic activity with elevated total serum IgE (typically ≥500 IU/mL in

asthmatic patients, though lower thresholds apply in cystic fibrosis).[3]

Additional supportive features that strengthen (but are not essential to) the diagnosis include: positive IgG against *Aspergillus fumigatus*, peripheral blood eosinophilia ≥500 cells/μL, and characteristic radiographic abnormalities.[3]

Radiological Features

Chest radiographs may demonstrate fleeting opacities or the pathognomonic finger-in-glove sign. High-resolution computed tomography (CT) offers greater sensitivity, typically revealing central bronchiectasis (affecting proximal airways), mucus plugging, and tree-in-bud opacities. The presence of high-attenuation mucus on CT is considered pathognomonic for ABPA and can independently confirm the diagnosis, even when other criteria are not fully met.[3,4]

Treatment

Overview and Goals

The therapeutic approach incorporates anti-inflammatory medications, such as corticosteroids or biologics targeting type 2 immune pathways, to modulate immune activity, and antifungal therapy to reduce the fungal burden in the respiratory tract. Treatment goals include relieving clinical symptoms, achieving optimal asthma control, preventing exacerbations, halting the progression of bronchiectasis, and minimizing treatment-related adverse effects.[3,5]

Corticosteroids

Systemic corticosteroids remain the cornerstone of ABPA treatment. Oral prednisolone effectively suppresses the inflammatory cascade, reduces serum IgE levels, resolves pulmonary infiltrates, and improves clinical symptoms. The standard regimen involves initiating treatment with oral prednisolone at 0.5–0.75 mg/kg/day for 2–6 weeks, followed by gradual tapering over 3–6 months while monitoring clinical response, pulmonary function, and IgE levels.[3,5] High-dose inhaled corticosteroids alone are insufficient for acute ABPA but play an important and necessary role in maintenance asthma management.

Despite its effectiveness, corticosteroid therapy has significant limitations. Many patients require prolonged or repeated courses, which can lead to complications including weight gain, hyperglycemia, osteoporosis, increased infection risk, and adrenal suppression. In some cases, patients become steroid-dependent or develop steroid-refractory disease, necessitating alternative therapies.[6] These concerns have driven the search for effective steroid-sparing agents.

Antifungal Agents

For patients who cannot tolerate corticosteroids or fail to taper oral prednisolone, oral antifungal azoles serve as important alternatives. Oral itraconazole, the most studied antifungal in ABPA, reduces fungal burden and antigen load. It is typically dosed at 200 mg twice daily for 16 weeks or longer. Studies demonstrate that itraconazole can reduce corticosteroid requirements, decrease exacerbation frequency, and improve pulmonary function and quality of life.[5,6]

Essential monitoring includes measuring serum itraconazole levels to ensure adequate absorption, performing hepatic function tests, and assessing for drug interactions. Voriconazole and posaconazole represent alternatives for patients intolerant to itraconazole, though supporting evidence is more limited. Routine first-line management of acute ABPA should not combine itraconazole with glucocorticoids; however, a brief glucocorticoid course of under 2 weeks may be administered alongside oral itraconazole at initiation.[3]

Biologic Therapies

Recognizing ABPA as a Th2-mediated eosinophilic disease has opened the door for targeted biologic therapies that offer disease control while minimizing corticosteroid exposure. Although these biologic agents are approved for severe asthma, their use in ABPA remains off-label, though growing evidence supports their efficacy and safety in this population.

Anti-IgE Therapy: Omalizumab

Omalizumab, an anti-IgE monoclonal antibody, was the first biologic evaluated for ABPA. Studies have demonstrated its effectiveness in reducing exacerbations and enabling corticosteroid reduction.[7,8] However, omalizumab shows limited impact on radiological abnormalities such as bronchial mucus plugs. Additionally, the characteristically elevated serum IgE levels of ABPA (often >1000 IU/mL) frequently result in suboptimal dosing, as the maximum approved dose may provide insufficient IgE neutralization.[7]

Anti-IL-5 Pathway Therapies: Mepolizumab and Benralizumab

Therapies targeting interleukin (IL)-5 or its receptor are unaffected by IgE levels. IL-5 is the key cytokine responsible for eosinophil maturation, activation, and survival. Two antibody classes target this pathway: anti-IL-5 monoclonal antibodies (mepolizumab) and anti-IL-5 receptor-alpha chain antibodies (benralizumab).

Mepolizumab, typically administered subcutaneously at 100–300 mg every 4 weeks, blocks IL-5, preventing eosinophil recruitment and activation. Benralizumab, administered as 30 mg subcutaneously every 4 weeks for the first three doses, and then every 8 weeks, binds the IL-5 receptor-alpha expressed on eosinophils and basophils, inducing antibody-dependent cell-mediated cytotoxicity and causing rapid, near-complete eosinophil depletion.[9]

Studies demonstrate that both agents significantly reduce exacerbation frequency, improve forced expiratory volume in one second (FEV1), resolve radiological abnormalities (particularly mucus plugs), and provide substantial corticosteroid-sparing effects.[9,10,13] Notably, benralizumab may offer superior efficacy in clearing mucus plugs, with studies showing resolution rates of 82–100%, likely due to its more potent eosinophil-depleting mechanism.[9] Some patients with inadequate response to mepolizumab have achieved mucus plug clearance after switching to benralizumab.[9]

The choice between mepolizumab and benralizumab may be guided by several factors including dosing frequency preferences (every 4 weeks versus every 8 weeks after loading), cost and insurance coverage considerations, previous treatment responses, and clinician experience. Although both agents target the IL-5 pathway, benralizumab's mechanism of direct eosinophil depletion may be preferable in patients with markedly elevated eosinophil counts or those who respond inadequately to mepolizumab.

Anti-IL-4 Receptor Alpha Therapy: Dupilumab

Dupilumab, which blocks both IL-4 and IL-13 signalling, has shown promise in ABPA case reports. Interestingly, some mepolizumab-refractory patients have improved with dupilumab, suggesting that targeting different Th2 pathways may benefit distinct patient subgroups.[11] However, given that ABPA typically involves pronounced eosinophilia, dupilumab's safety profile warrants careful evaluation, as post-treatment eosinophilia could lead to complications.[9,11] Further studies are needed to establish its role in ABPA management.

Indications for Biologic Therapy

Not all ABPA patients require biologics. Ideal candidates include those with frequent exacerbations despite optimized conventional therapy, patients requiring maintenance oral corticosteroids or frequent bursts, those experiencing significant corticosteroid-related adverse effects, and patients with persistently elevated eosinophil counts and deteriorating lung function.[3,13]

Before initiating biologic therapy, clinicians should confirm an accurate diagnosis, optimize conventional management, including inhaled corticosteroids and bronchodilators, address comorbidities, and consider antifungal therapy. Baseline assessments should include pulmonary function tests, total IgE levels, peripheral eosinophil counts, and high-resolution CT imaging.[3]

Monitoring Treatment Response

Regular monitoring is essential. Clinical parameters include symptom control, exacerbation frequency, and corticosteroid requirements. Laboratory monitoring involves serial IgE levels (typically every 2–3 months initially, then every 6–12 months), though IgE may not decline proportionally to clinical improvement, emphasizing the importance of patient-centred outcomes.[9,11,13] Pulmonary function testing every 3–6 months provides objective assessment, while follow-up CT imaging at 6–12 months helps assess radiological response, particularly mucus plug resolution and bronchiectasis stability.[3,9,11,13]

The therapeutic benefit of biologics appears more pronounced in ABPA associated with asthma versus cystic fibrosis, particularly in reducing exacerbations and enabling steroid-sparing.[11,12] Current evidence derives primarily from case series and retrospective studies; rigorous randomized controlled trials are essential to definitively establish safety and efficacy.[11,13] Since omalizumab, mepolizumab, benralizumab, and dupilumab are approved for severe asthma, and most ABPA studies involve asthma patients, additional studies are needed to demonstrate efficacy specifically in ABPA with underlying cystic fibrosis.[12]

Conclusion

ABPA is a challenging clinical entity requiring prompt recognition and timely treatment to prevent significant morbidity. While corticosteroids and antifungal agents remain the foundation of treatment for ABPA, biologic therapies, although currently off-label, have transformed management for refractory or steroid-dependent disease. These targeted therapies offer effective disease control with acceptable safety profiles and steroid-sparing benefits, underscoring the importance of obtaining more rigorous evidence to support their role in ABPA management.

As biologics become more integrated into ABPA management, thoughtful patient selection, systematic monitoring, and vigilance for long-term effects are essential. The 2024 ISHAM guidelines provide an updated framework for diagnosis and management, though continued research will further refine therapeutic approaches.[3]

Familiarity with these emerging therapies and their appropriate application is essential for optimizing outcomes in this complex patient population.

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Financial Disclosures

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