

Chapter 21

Allergic Bronchopulmonary Aspergillosis

Satoshi Yoshida MD, PhD, FCCP, FAAAAI, FACAAI^{a*,b,1}

^a Department of Continuing Education, Harvard Medical School, Boston, MA, 02115, USA

^b Department of Allergy and Immunology, Oyamadai Family Clinic, 2-11-18 Todoroki, Setagaya, Tokyo, 158-0028, Japan

¹ Email: charmander3883@ymail.com

Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder caused by aberrant type 2 immune responses to *Aspergillus* species colonizing airways, occurring in 11% of asthmatics, 9-10% of cystic fibrosis patients, and increasingly recognized in COPD, bronchiectasis, and post-tubercular lung disorders. Remarkable research advances over the past several years have dramatically changed the clinical approach to ABPA, from understanding its pathogenesis to improving diagnostic rates and treatment with molecularly targeted drugs. The Th2-dominant response with massive IgE elevation and eosinophilic inflammation causes recurrent asthma exacerbations, mucus plugging, bronchiectasis, and progressive pulmonary fibrosis if untreated. The 2024 revised International Society for Human and Animal Mycology (ISHAM) guidelines introduced transformative advances of the clinical practice of ABPA. That guidelines established high-attenuation mucus (HAM) on CT as pathognomonic, improved sensitivity of diagnosis from 91% to 98%, and created separate criteria for ABPA (*Aspergillus* species) and ABPM (non-*Aspergillus* fungi). Traditionally, treatment has consisted of monotherapy with prednisolone or itraconazole for acute disease, and combination therapy for recurrent exacerbations. In recent years, the clinical introduction of new biologics, such as anti-IgE antibodies, anti-IL-5 antibodies, and anti-IL-4R α antibodies, has made it possible to treat refractory patients with corticosteroid resistance. However, early diagnosis is essential to prevent irreversible bronchiectasis that can lead to severe bronchitis. Approximately 50% of patients experience recurrent exacerbations, which require careful monitoring with serial measurements of IgE antibodies.

Keywords

Allergic bronchopulmonary aspergillosis (ABPA); Asthma; Cystic fibrosis (CF); *A. fumigatus*; Biologics; ISHAM guidelines.

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disorder caused by hypersensitivity response to *Aspergillus* antigens in the lung. It is an

uncommon but serious respiratory condition characterized by chronic airway inflammation and airway damage resulting from persistent colonization by and sensitization to the fungus *Aspergillus fumigatus* (*A. fumigatus*). The first cases of ABPA in the United States were identified more than 40 years ago, whereas the initial literature report in the United Kingdom was in 1952. Based on recent systematic reviews, the global prevalence of ABPA is estimated to be approximately 11% in adults with asthma and 10% in adults with cystic fibrosis. Children with asthma demonstrate a prevalence of 9.9%. It is estimated that globally there are about 4.8 million cases of ABPA. The occurrence of ABPA among asthmatic patients in specialized clinics may be as high as 13%. In corticosteroid-dependent asthma patients, ABPA might be complicated in as high as 7-14% of cases. In cystic fibrosis, the prevalence of ABPA ranges from 2 to 15%. ABPA is sometimes recognized in patients with allergic fungal sinusitis, though such an association is unusual. ABPA has been identified in patients with hyper-immunoglobulin E (IgE) syndrome and chronic granulomatous disease, which might create management dilemmas because of concerns about administration of prednisone. Recent studies have also identified ABPA in patients with chronic obstructive pulmonary disease (COPD) and bronchiectasis without underlying asthma or cystic fibrosis, expanding the spectrum of predisposing conditions. Post-tubercular structural lung disease (PTLD) has emerged as an important predisposing condition, particularly in tuberculosis-endemic regions, with 24.9% of ABPA patients having previous tuberculosis and 57.5% of ABPA cases initially misdiagnosed as tuberculosis. Approximately 7% of ABPA cases occur without underlying asthma or cystic fibrosis (ABPA sans asthma), often presenting with bronchiectasis of unclear etiology. In patients with asthma, ABPA is sometimes diagnosed in the absence of the typical proximal bronchiectasis; in such cases, it is designated ABPA serological (ABPA-S). Often, ABPA is suspected (1) because of an episode of "pulmonary eosinophilia" or tenacious mucus plugging, (2) when a chest roentgenogram shows an unexpected infiltrate, or (3) after skin testing and serologic testing. The prevalence of ABPA in patients admitted with acute severe asthma is even higher, with studies demonstrating *Aspergillus* hypersensitivity and ABPA in around 51% and 39%, respectively, significantly higher than in outpatient settings. The 2024 International Society for Human and Animal Mycology (ISHAM) guidelines have fundamentally revised diagnostic criteria, lowering the total IgE threshold from 1000 to ≥ 500 IU/mL (improving diagnostic sensitivity from 91% to 98%) and establishing high-attenuation mucus (HAM) on CT as pathognomonic for ABPA.

Pathogenesis

After inhalation of *Aspergillus fumigatus* conidia (spores), there is saprophytic growth in the hyphal form within the airways, resulting from complex interactions between fungal virulence factors, host immune responses, and defective mucociliary clearance

mechanisms. The fundamental pathogenic question remains: what specific survival factors enable *A. fumigatus* to persist and germinate in the airways of ABPA patients, and what abnormalities exist in bronchial mucus and epithelial barrier function that permit this growth—in stark contrast to the efficient fungal clearance observed in the vast majority of asthmatic patients who, despite equivalent environmental exposure, do not develop ABPA?

Genetic Susceptibility and Host Factors

Environmental factors alone are insufficient to explain ABPA pathogenesis, as not all asthmatics develop ABPA despite identical *Aspergillus* exposure. The disease requires a genetically predisposed host with specific immunogenetic vulnerabilities. Genome-wide association studies and candidate gene analyses have identified multiple susceptibility loci that contribute to ABPA development:

HLA Class II Associations: Specific HLA-DR and HLA-DQ alleles (particularly HLA-DR2, HLA-DR5, and certain DRB1 and DQB1 variants) confer increased risk by influencing antigen presentation of *Aspergillus* peptides to CD4⁺ T cells, thereby biasing the immune response toward pathogenic Th2 polarization rather than protective Th1 responses.

CFTR Gene Polymorphisms: Heterozygous mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene occur with significantly higher frequency in ABPA patients compared to asthmatics without ABPA or the general population. Even single CFTR mutations (carrier state) impair chloride transport and alter airway surface liquid composition, creating a microenvironment that favors *Aspergillus* persistence through altered mucus viscosity, reduced mucociliary clearance, and compromised antimicrobial peptide function.

Pattern Recognition Receptor Polymorphisms: Variants in toll-like receptors (particularly TLR2, TLR4, and TLR9), dectin-1 (a C-type lectin receptor critical for β -glucan recognition on fungal cell walls), and other pattern recognition receptors alter the initial innate immune recognition of *Aspergillus* antigens. These polymorphisms can result in inadequate or aberrant inflammatory responses that fail to clear the fungus while simultaneously promoting allergic inflammation.

Cytokine and Cytokine Receptor Polymorphisms: Genetic variants in IL-4R α , IL-10 promoter, IL-13, and surfactant proteins influence type 2 immune responses and have been associated with ABPA susceptibility. These polymorphisms may determine the threshold and magnitude of Th2 polarization following *Aspergillus* exposure.

Initial Fungal Colonization: Molecular Events at the Epithelial Interface

In genetically predisposed individuals with impaired mucociliary clearance (from asthma, cystic fibrosis, COPD, or bronchiectasis), inhaled *A. fumigatus* conidia evade initial clearance mechanisms and persist within the airway lumen. The molecular events governing this critical early phase involve sophisticated fungal survival strategies and epithelial barrier dysfunction:

Fungal Immune Evasion Mechanisms: *Aspergillus* conidia are covered by a hydrophobic rodlet protein layer and melanin pigmentation that render the resting conidia immunologically "silent"—essentially invisible to the innate immune system. Upon germination into metabolically active hyphae in response to favorable airway conditions (appropriate temperature, moisture, nutrients), the fungus sheds this protective outer layer and begins expressing immunologically active cell wall components including β -1,3-glucan, galactomannan, and various glycoproteins. This transition from dormant conidia to growing hyphae represents a critical determinant of immune recognition and subsequent pathogenic responses.

Fungal Protease Secretion: Germinating *Aspergillus* hyphae secrete a diverse arsenal of proteases, including alkaline proteases, serine proteases (particularly Asp f 13 and Asp f 18), and metalloproteinases. These enzymes serve multiple pathogenic functions: they directly compromise epithelial tight junction integrity by degrading E-cadherin, occludin, and claudin proteins, thereby breaching the epithelial barrier; they cleave host antimicrobial peptides and immunoglobulins, reducing local immune defenses; they liberate fungal allergens from the cell wall; and they activate protease-activated receptors (PARs) on epithelial cells, triggering inflammatory cascades.

Epithelial Barrier Dysfunction: The airway epithelium in ABPA patients exhibits fundamental defects beyond those attributable to the underlying predisposing condition. Fungal proteases, in concert with type 2 cytokines (particularly IL-13), induce profound alterations in epithelial barrier function. IL-13 downregulates tight junction proteins and stimulates epithelial-to-mesenchymal transition (EMT), contributing to airway remodeling. The compromised barrier permits enhanced penetration of *Aspergillus* antigens into the submucosa, facilitating antigen presentation to immune cells and perpetuating the inflammatory cascade.

Mucus Hypersecretion and Altered Composition: *Aspergillus* colonization, combined with type 2 cytokine exposure (IL-4, IL-13), induces goblet cell hyperplasia and mucin gene upregulation (particularly MUC5AC and MUC5B). The resulting mucus is not only overproduced but qualitatively abnormal—exhibiting increased viscosity, altered glycosylation patterns, and impaired mucociliary transport. This creates a self-perpetuating cycle: abnormal mucus favors fungal persistence, which further stimulates mucus production and inflammation.

Innate Immune Activation and Pattern Recognition

The germinating *Aspergillus* hyphae activate innate immunity through multiple pattern recognition receptor (PRR) pathways:

C-Type Lectin Receptors: Dectin-1 recognizes β -1,3-glucan exposed on hyphal surfaces and signals through the CARD9 pathway, triggering NF- κ B activation and production of pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β) and chemokines (CXCL8/IL-8). Dectin-2 and DC-SIGN recognize fungal mannans and contribute to dendritic cell activation.

Toll-Like Receptors: TLR2 and TLR4 recognize various *Aspergillus* cell wall components and lipids, initiating MyD88-dependent signaling cascades. TLR9 recognizes fungal DNA containing unmethylated CpG motifs. These pathways collectively promote dendritic cell maturation and migration to lymph nodes.

NOD-Like Receptors and Inflammasome Activation: Recognition of *Aspergillus* by NLRP3 (NOD-like receptor family, pyrin domain containing 3) triggers inflammasome assembly, leading to caspase-1 activation and processing of pro-IL-1 β and pro-IL-18 into their mature, bioactive forms. IL-1 β amplifies inflammatory responses and contributes to neutrophil recruitment, while IL-18 can influence T-cell polarization.

Early Inflammatory Cell Influx: Activated epithelial cells and resident macrophages secrete chemokines (CCL2/MCP-1, CCL5/RANTES, CXCL8/IL-8, CXCL10/IP-10) that recruit neutrophils, eosinophils, dendritic cells, and additional monocytes/macrophages to the airways. This creates a complex inflammatory milieu that undergoes subsequent adaptive immune modulation.

Adaptive Immune Response: The Critical Th2 Polarization

The defining immunologic feature of ABPA is the aberrant, maladaptive Th2-dominant CD4+ T-cell response that fails to eradicate the fungus while generating destructive allergic inflammation. Understanding the molecular mechanisms governing this Th2 polarization is central to comprehending ABPA pathogenesis.

Normal Protective Response (Th1/Th17): In healthy individuals and most asthmatics who clear *Aspergillus* efficiently, dendritic cells process fungal antigens and present them via MHC class II molecules to naive CD4+ T cells in the context of IL-12 and IFN- γ production. This drives differentiation toward Th1 cells (producing IFN- γ , TNF- α) and Th17 cells (producing IL-17A, IL-17F, IL-22), which activate macrophages and neutrophils for effective fungal killing through oxidative burst, phagocytosis, and antimicrobial peptide production. This protective response efficiently eliminates *Aspergillus* without tissue-damaging inflammation.

Aberrant ABPA Response (Th2/Type 2 Inflammation): In ABPA patients, a fundamentally different adaptive immune program is activated. Multiple mechanisms contribute to this pathogenic Th2 polarization:

Epithelial-Derived Alarmins: Damaged airway epithelium releases thymic stromal lymphopoietin (TSLP), IL-33, and IL-25—three critical "alarmins" that initiate and amplify type 2 immune responses. TSLP activates dendritic cells to produce minimal IL-12 (required for Th1 differentiation) while promoting OX40L expression, which drives Th2 polarization. IL-33, released from necrotic epithelial cells, binds ST2 receptors on innate lymphoid cells type 2 (ILC2), mast cells, eosinophils, and Th2 cells, triggering production of IL-5 and IL-13 even before adaptive immunity is fully engaged. IL-25 similarly activates ILC2 cells and promotes Th2 development.

Dendritic Cell Polarization: *Aspergillus* proteases and specific allergens (particularly Asp f 1) can "educate" dendritic cells toward a Th2-polarizing phenotype by inducing expression of Jagged-1 (a Notch ligand that promotes Th2 differentiation) while suppressing IL-12p70 production. The balance of dendritic cell subsets (conventional DC1 favoring Th1 vs. DC2 favoring Th2) may be skewed in ABPA patients.

Regulatory T-Cell Dysfunction: Regulatory T cells (Tregs), which normally suppress excessive immune responses and maintain tolerance to environmental antigens, may be functionally deficient or numerically reduced in ABPA. Impaired Treg function fails to restrain pathogenic Th2 responses. Some studies suggest that *Aspergillus* antigens may actively inhibit Treg development or convert them toward Th2-promoting phenotypes.

Th2 Cytokine Cascade and Molecular Effector Mechanisms

Once established, the Th2 response generates a self-amplifying cytokine cascade with profound immunologic and pathologic consequences:

IL-4 Signaling Pathway: IL-4, the master regulator of Th2 differentiation, binds to the IL-4 receptor α (IL-4R α) complex (consisting of IL-4R α paired with either the common γ -chain for type I receptor or IL-13R α 1 for type II receptor). This activates JAK1/JAK3 and downstream STAT6 phosphorylation and nuclear translocation. STAT6 induces expression of GATA3, the master transcription factor that commits naive T cells to the Th2 lineage while simultaneously suppressing Th1 programs through epigenetic modifications. IL-4 also drives B-cell class switching to IgE production, upregulates MHC class II on antigen-presenting cells, and promotes alternative macrophage activation (M2 phenotype) that further reinforces type 2 inflammation.

IL-5 and Eosinophil Biology: IL-5 is the principal eosinophil growth factor, survival factor, and activator. Produced by Th2 cells, ILC2 cells, mast cells, and eosinophils themselves (autocrine loop), IL-5 binds to the IL-5 receptor (IL-5R α /CD125 paired with

common β -chain) on eosinophil progenitors in bone marrow, mature eosinophils in blood, and tissue eosinophils. Through JAK2/STAT5 signaling, IL-5 promotes eosinophil differentiation from CD34+ progenitors, prolongs eosinophil survival by upregulating anti-apoptotic proteins (Bcl-2, Bcl-xL), enhances eosinophil migration through chemokine receptor upregulation (particularly CCR3), and primes eosinophils for enhanced effector functions. The resulting massive eosinophil influx into airways is a pathologic hallmark of ABPA.

Eosinophil Effector Functions and Tissue Damage: Activated eosinophils degranulate, releasing a toxic arsenal of cationic proteins stored in cytoplasmic granules:

- **Major Basic Protein (MBP):** Highly cationic protein that is directly cytotoxic to respiratory epithelium through membrane disruption, activates mast cells and basophils, and stimulates mucus hypersecretion. MBP levels correlate with disease severity and contribute to epithelial denudation.
- **Eosinophil Cationic Protein (ECP):** RNase superfamily member with neurotoxic, helminthotoxic, and bactericidal properties; also toxic to mammalian cells. ECP induces mast cell degranulation and impairs surfactant function.
- **Eosinophil Peroxidase (EPO):** Generates reactive oxygen species (particularly hypobromous acid and hypothiocyanate) that oxidize biomolecules, causing lipid peroxidation, protein modification, and nucleic acid damage.
- **Eosinophil-Derived Neurotoxin (EDN):** Another RNase family member that activates dendritic cells and promotes antiviral immunity but also damages neurons and epithelial cells in ABPA.

Beyond degranulation, eosinophils release extracellular traps (EETosis)—web-like structures composed of mitochondrial DNA decorated with granule proteins that can trap and potentially kill pathogens but also cause extensive bystander tissue injury. Eosinophils also produce lipid mediators (leukotrienes C4, D4, E4; platelet-activating factor), cytokines (IL-4, IL-5, IL-13, TGF- β), and chemokines that amplify and perpetuate type 2 inflammation.

IL-13 and Airway Remodeling: IL-13, which shares signaling pathways with IL-4 through the IL-4R α /IL-13R α 1 type II receptor complex and STAT6 activation, exerts critical pathologic effects in ABPA:

- **Mucus Metaplasia:** IL-13 is the most potent inducer of goblet cell hyperplasia and mucin gene expression (MUC5AC, MUC5B), driving the excessive mucus production characteristic of ABPA.

- **Fibrosis and Collagen Deposition:** IL-13 directly stimulates fibroblast proliferation, myofibroblast differentiation (through TGF- β 1 upregulation), and extracellular matrix protein production (collagen types I, III, and V; fibronectin; tenascin). This contributes to subepithelial fibrosis and progressive airway remodeling.
- **Smooth Muscle Hyperplasia:** IL-13 promotes smooth muscle cell proliferation and contractility, contributing to bronchial hyperreactivity.
- **Epithelial Barrier Disruption:** IL-13 downregulates tight junction proteins and claudins, facilitating antigen penetration and perpetuating inflammation.

IL-9 and Mast Cell Activation: IL-9, produced by a subset of Th2 cells (sometimes called Th9 cells) and ILC2 cells, promotes mast cell proliferation, survival, and activation. Mast cells contribute to ABPA pathogenesis through:

- **IgE-Mediated Degranulation:** Crosslinking of *Aspergillus*-specific IgE bound to high-affinity Fc ϵ RI receptors on mast cell surfaces triggers explosive degranulation, releasing preformed mediators (histamine, tryptase, heparin) and newly synthesized mediators (prostaglandin D2, leukotriene C4, platelet-activating factor).
- **Bronchospasm and Vascular Permeability:** Histamine and leukotrienes cause immediate bronchial smooth muscle contraction (early asthmatic response), increased vascular permeability (edema), and mucus secretion.
- **Amplification of Type 2 Responses:** Activated mast cells produce IL-4, IL-5, IL-13, and other cytokines that reinforce Th2 polarization and recruit additional inflammatory cells.

Humoral Immunity: IgE and IgG Responses

The intense type 2 cytokine milieu, particularly IL-4 and IL-13, drives profound B-cell responses:

Polyclonal and *Aspergillus*-Specific IgE Production: B cells undergo class-switch recombination to IgE under the influence of IL-4 and CD40-CD40L interactions. This results in:

- **Massively Elevated Total Serum IgE:** Often exceeding 1000 IU/mL, sometimes reaching >10,000 IU/mL—far higher than typical allergic asthma. This reflects both polyclonal B-cell activation and specific anti-*Aspergillus* clones.

- **High-Affinity *Aspergillus*-Specific IgE:** Directed against multiple *Aspergillus* allergens (Asp f 1 through Asp f 34 identified to date). The most clinically relevant allergens include:
 - **Asp f 1** (ribotoxin): Major allergen; IgE against Asp f 1 distinguishes ABPA from simple *Aspergillus* sensitization
 - **Asp f 2** (fibrinogen-binding protein): Marker of genuine ABPA
 - **Asp f 3** (peroxisomal protein): Less specific for ABPA
 - **Asp f 4** (unknown function): High specificity for ABPA (particularly in CF)
 - **Asp f 6** (Mn-superoxide dismutase): High specificity for ABPA
 - **Asp f 13, Asp f 18** (serine proteases): Contribute to epithelial damage

IgG and Immune Complex Formation (Type III Hypersensitivity): Simultaneously, B cells produce high levels of *Aspergillus*-specific IgG (particularly IgG1 and IgG4 subclasses). These antibodies form immune complexes with fungal antigens, which:

- **Activate Complement:** Classical pathway activation generates C3a and C5a anaphylatoxins that recruit and activate neutrophils, contributing to tissue injury through release of proteases (elastase, cathepsins, matrix metalloproteinases) and reactive oxygen species.
- **Deposit in Airways:** Immune complexes precipitate in airways and lung parenchyma, triggering neutrophil-mediated inflammation (Arthus-type reaction) and contributing to the histopathologic picture.

This dual type I (IgE-mediated) and type III (immune complex-mediated) hypersensitivity creates a uniquely destructive immunologic environment.

Innate Lymphoid Cells Type 2 (ILC2) and Tissue-Resident Memory Cells

Recent research has illuminated the critical roles of tissue-resident immune populations in ABPA:

ILC2 Biology in ABPA: ILC2 cells are innate immune cells that lack antigen-specific receptors but respond rapidly to epithelial alarmins (IL-33, IL-25, TSLP). Upon activation, ILC2 cells produce copious amounts of IL-5 and IL-13, initiating type 2 inflammation even before T-cell responses develop. ILC2 cells may be particularly important in:

- **Early Phase Responses:** Providing immediate-early type 2 cytokines following *Aspergillus* exposure
- **Amplification of Adaptive Immunity:** Cross-talk with dendritic cells to promote Th2 polarization
- **Chronic Inflammation:** Sustaining persistent type 2 responses in established disease
- **Steroid Resistance:** ILC2 cells may be relatively resistant to corticosteroid-induced apoptosis compared to T cells, potentially contributing to persistent inflammation

Tissue-Resident Memory T Cells (TRM): Following initial ABPA episodes, *Aspergillus*-specific CD4+ TRM cells persist in airway tissues. These non-circulating, tissue-resident cells express CD69 and CD103 and provide rapid recall responses upon re-exposure to *Aspergillus* antigens. TRM cells may contribute to the high relapse rate (~50%) observed in ABPA by maintaining a "hair-trigger" state of type 2 immune activation.

Persistent Inflammation and Progressive Tissue Damage

The chronic, unresolved type 2 inflammatory response in ABPA leads to cumulative pathologic changes:

Mucus Plug Formation: Inspissated mucus plugs are pathognomonic of ABPA and result from multiple factors:

- **Mucin Hypersecretion:** IL-13-driven goblet cell hyperplasia and mucin gene upregulation produce excessive mucus
- **Altered Mucus Composition:** Eosinophil-derived proteins (MBP, ECP, EPO) and neutrophil elastase alter mucin cross-linking and viscosity
- **Cellular Debris:** Degranulated eosinophils, epithelial cells, Charcot-Leyden crystals (from eosinophil galectin-10), Curschmann spirals (from small airway mucus casts), fibrin, and fungal hyphae/debris accumulate in mucus
- **High-Attenuation Mucus (HAM):** In 20-28% of patients, mucus becomes impregnated with calcium salts, iron, and manganese (possibly from eosinophil peroxidase activity), creating the pathognomonic hyperattenuating mucus on CT (density >70 Hounsfield units). HAM indicates severe disease with extensive eosinophilic inflammation and correlates with poor prognosis.

Bronchiectasis Development: Persistent inflammation causes irreversible bronchial dilation through multiple mechanisms:

- **Proteolytic Damage:** Eosinophil and neutrophil proteases (MMP-9, elastase, cathepsins) degrade elastic fibers and collagen in bronchial walls
- **Chronic Infection and Obstruction:** Mucus plugs cause post-obstructive inflammation and infection
- **Vicious Cycle:** Bronchiectasis impairs clearance, favoring persistent *Aspergillus* colonization and continued inflammation
- **Preferential Upper/Middle Lobe Involvement:** Reasons incompletely understood, but may relate to regional differences in airway geometry, ventilation patterns, or immune cell distribution

Airway Remodeling: Chronic type 2 inflammation induces structural changes:

- **Subepithelial Fibrosis:** Myofibroblast activation and collagen deposition beneath the basement membrane
- **Smooth Muscle Hyperplasia:** Increased smooth muscle mass contributing to bronchial hyperreactivity
- **Epithelial-Mesenchymal Transition:** IL-13 and TGF- β promote epithelial dedifferentiation and acquisition of mesenchymal characteristics
- **Vascular Remodeling:** Angiogenesis and vascular wall thickening

Pulmonary Fibrosis (ABPA-CPF): In advanced, untreated disease, chronic inflammation transitions to irreversible fibrosis:

- **TGF- β Upregulation:** Eosinophils, macrophages, and epithelial cells produce TGF- β 1, the master profibrotic cytokine
- **Myofibroblast Differentiation:** TGF- β converts fibroblasts into collagen-secreting myofibroblasts
- **Extracellular Matrix Deposition:** Progressive accumulation of collagen types I and III, leading to restrictive lung disease
- **End-Stage Disease:** Upper lobe fibrosis, architectural distortion, and respiratory failure

Emerging Concepts: PANoptosis and Novel Inflammatory Pathways

Recent cutting-edge research has identified previously unrecognized cell death and inflammatory mechanisms in ABPA:

PANoptosis in ABPA: PANoptosis is a newly described form of inflammatory cell death characterized by coordinated activation of three programmed cell death pathways—pyroptosis, apoptosis, and necroptosis—through a unified molecular complex called the PANoptosome. *Aspergillus fumigatus* has been identified as one of the pathogens capable of triggering PANoptosis through Z-DNA binding protein 1 (ZBP1) pathway activation. This results in:

- **Massive Inflammatory Cell Death:** Epithelial cells and immune cells undergo PANoptosis, releasing intracellular contents and damage-associated molecular patterns (DAMPs)
- **Amplification of Inflammation:** DAMPs activate inflammasomes and pattern recognition receptors, creating a feed-forward inflammatory loop
- **Therapeutic Implications:** PANoptosome components (ZBP1, RIPK1, RIPK3, caspases) may represent novel therapeutic targets

Epithelial Barrier Dysfunction Beyond Physical Breach: Advanced molecular studies reveal that the epithelial barrier defect in ABPA extends beyond simple tight junction disruption:

- **Loss of Apical-Basal Polarity:** Chronic IL-13 exposure disrupts epithelial cell polarity programs
- **Altered Autophagy:** Defective autophagy pathways impair clearance of intracellular *Aspergillus* antigens and damaged organelles
- **Senescence-Associated Secretory Phenotype (SASP):** Chronic inflammation induces epithelial cell senescence, which perpetuates inflammation through secretion of pro-inflammatory mediators

Metabolic Reprogramming: Both immune cells and airway structural cells undergo metabolic shifts in ABPA:

- **Aerobic Glycolysis (Warburg Effect):** Activated immune cells upregulate glucose metabolism to support biosynthetic demands
- **Lipid Mediator Production:** Enhanced arachidonic acid metabolism generates prostaglandins and leukotrienes
- **Altered Redox Balance:** Eosinophil peroxidase and NADPH oxidase activity create oxidative stress that damages lipids, proteins, and DNA

ABPA: Clinical Picture And Management Epidemiology And Risk Factors Prevalence (Updated 2023-2024 Data)

In Asthma:

- Global prevalence: **11-13%** in adults with asthma at tertiary care centers
- Children with asthma: **9.9%** prevalence
- Acute severe asthma admissions: Up to **51%** show *Aspergillus* hypersensitivity; **39%** meet ABPA criteria
- Estimated **4.8 million cases worldwide** in asthmatic patients alone

In Cystic Fibrosis:

- Prevalence: **8.9-10%** in CF patients
- *Aspergillus* sensitization (without ABPA): **39-40%** in CF populations
- CF patients with ABPA have significantly worse lung function and poorer recovery from pulmonary exacerbations

Emerging Predisposing Conditions (New Recognition):

- **COPD:** Increasingly recognized as predisposing condition
- **Bronchiectasis** (non-CF): ABPA prevalence data emerging; risk factors include severe bronchiectasis (higher Bronchiectasis Severity Index), frequent antibiotic use (≥ 2 antibiotics for >14 days within 6 months), and hypoproteinemia
- **Post-tubercular structural lung disease (PTLD):** Major risk factor in TB-endemic regions; **24.9%** of ABPA patients have previous TB; critically, **57.5%** of ABPA cases were initially misdiagnosed as TB
- **ABPA sans asthma:** Approximately **7%** of ABPA cases occur without underlying asthma or CF—often underdiagnosed

Genetic Susceptibility

- **HLA class II associations:** HLA-DR2, HLA-DR5 alleles confer susceptibility
- **CFTR gene:** Heterozygous CFTR mutations occur more frequently in ABPA patients than in general asthmatic populations

- **Other susceptibility genes:** Polymorphisms in surfactant proteins, toll-like receptors, IL-4R α , IL-10 promoter

Environmental and Host Factors

- **Geographic variation:** Higher prevalence in regions with warm, humid climates favoring *Aspergillus* growth
- **Occupational exposure:** Increased risk with farming, composting, construction work
- **Pet contact:** Frequent pet exposure increases ABPA risk (likely through environmental fungal exposure)
- **Impaired mucociliary clearance:** Fundamental prerequisite for *Aspergillus* colonization

Pathology: Understanding The Immunologic Cascade

Stage 1: Fungal Colonization

Normal Response vs ABPA:

- In healthy individuals: *Aspergillus* conidia are rapidly cleared by mucociliary action and innate immunity
- In ABPA-susceptible patients: Impaired mucociliary clearance (from asthma, CF, bronchiectasis, COPD) \rightarrow conidia retention \rightarrow germination into hyphae \rightarrow persistent airway colonization

Key Point for Students: The *Aspergillus* remains in the airway lumen and does NOT invade tissue—this distinguishes ABPA from invasive aspergillosis, which occurs in immunocompromised patients.

Stage 2: Aberrant Immune Response

Type 2 Inflammation Dominance:

- **Th2 CD4+ T-cell activation:** Production of IL-4, IL-5, IL-13, IL-9
- **IgE production:** Polyclonal B-cell activation \rightarrow markedly elevated total IgE (often >1000 IU/mL, sometimes >10,000 IU/mL) AND *Aspergillus*-specific IgE
- **IgG response:** Type III hypersensitivity with immune complex formation \rightarrow *Aspergillus*-specific IgG (precipitating antibodies)
- **Eosinophil recruitment:** IL-5-driven eosinophilia in blood and airways

Why This Matters Clinically:

- Massive IgE elevation → mast cell/basophil degranulation → bronchospasm (asthma exacerbations)
- Eosinophil infiltration → release of toxic proteins (major basic protein, eosinophil cationic protein) → epithelial damage
- Immune complexes → complement activation → neutrophil influx → tissue injury

Stage 3: Tissue Damage and Remodeling

Progressive Pathologic Changes:

1. **Airway inflammation** → mucus hypersecretion with thick, tenacious plugs
2. **Bronchial wall injury** → airway remodeling and dilation (bronchiectasis)
3. **Mucus plug impaction** → post-obstructive changes, atelectasis
4. **Fibrosis** (in advanced cases) → irreversible lung damage

High-Attenuation Mucus (HAM)—Pathognomonic Finding:

- Occurs in **20-28%** of ABPA patients
- Represents mucus with calcium salts, iron, and manganese deposition
- CT density >70 Hounsfield Units (denser than paraspinal muscle)
- **PATHOGNOMONIC when present**—confirms ABPA diagnosis even without other criteria
- Correlates with immunologically severe disease: higher eosinophils, more extensive lung involvement, worse pulmonary function, higher relapse rates
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Classification

ABPA vs ABPM (Allergic Bronchopulmonary Mycosis)

The 2024 ISHAM guidelines now clearly distinguish:

- **ABPA:** Allergic mycosis caused by any *Aspergillus* species (not just *A. fumigatus*)

- **ABPM:** Allergic mycosis caused by fungi OTHER than *Aspergillus* (e.g., *Penicillium*, *Schizophyllum*, *Curvularia*)
- Both conditions share similar clinical presentations and immunologic features but require different diagnostic approaches

2024 Radiological Classification (ISHAM Revision)

- **ABPA-S** (Serological): Fulfills diagnostic criteria without radiological findings on HRCT
- **ABPA-B** (Bronchiectasis): Satisfies diagnostic criteria with presence of bronchiectasis
- **ABPA-MP** (Mucus Plugging) [NEW 2024]: Presence of non-hyperattenuating mucus plugs (associated with greater immunological severity)
- **ABPA-HAM** (High-Attenuation Mucus): Presence of high-attenuation mucus (pathognomonic finding)
- **ABPA-CPF** (Chronic Pleuropulmonary Fibrosis): Progressive fibrotic changes with chronic pleuropulmonary involvement

Clinical Significance: While classification doesn't currently dictate treatment, it may guide personalized therapies in future trials and helps predict prognosis (HAM correlates with severe disease and higher relapse rates).

Traditional Clinical Staging System (Still Used)

Stage I: Acute ABPA

- First presentation or exacerbation
- Elevated IgE, eosinophilia, pulmonary infiltrates, symptoms

Stage II: Remission

- Clinical and radiological improvement
- IgE decline (but still elevated above baseline)
- May occur spontaneously or with treatment

Stage III: Exacerbation (Recurrence)

- Return of symptoms, new infiltrates
- IgE rises $\geq 100\%$ from remission baseline (or $\geq 50\%$ if also with clinical/radiological worsening)
- Occurs in $\sim 50\%$ of patients

Stage IV: Corticosteroid-Dependent Asthma

- Requires continuous oral corticosteroids to control symptoms
- Frequent relapses when steroids tapered
- Candidate for biologic therapy

Stage V: Fibrotic Stage (End-Stage)

- Irreversible fibrosis, "destroyed lung"
- Severe bronchiectasis, pulmonary function decline
- Limited treatment options

Clinical Picture: Recognizing ABPA

Chief Complaints:

- **Worsening asthma control:** Most common presentation—patient with known asthma develops increasing symptoms despite escalating therapy
- **Recurrent asthma exacerbations:** Frequent need for oral corticosteroids (>2 -3 courses/year)
- **Productive cough:** Expectoration of thick, brownish or greenish mucus plugs (sometimes described as "casts" of airways)
- **Dyspnea:** Progressive or episodic breathlessness
- **Low-grade fever:** Occasionally present during exacerbations
- **Hemoptysis:** Uncommon but possible

Physical Examination:

- **Respiratory:** Diffuse expiratory polyphonic wheezing (asthma-like); coarse crackles if mucus plugging/consolidation present

- **General examination:** Usually unremarkable unless severe disease
- **Digital clubbing:** Rare, suggests advanced fibrocavitary disease

Clinical Presentations by Predisposing Condition

ABPA in Asthma (Most Common):

- Difficult-to-control asthma despite Step 4-5 GINA therapy
- Frequent exacerbations with fleeting pulmonary infiltrates
- May have seasonal variation correlating with *Aspergillus* spore counts

ABPA in Cystic Fibrosis:

- **Diagnostic Challenge:** Symptoms overlap with CF lung disease (cough, sputum, wheeze, declining FEV₁)
- **Red Flags:** Unexplained decline in lung function, new/worsening wheeze, increasing oxygen requirements, recurrent exacerbations not responding to antibiotics
- Total IgE may be elevated at baseline in CF, making diagnosis more difficult

ABPA in COPD/Bronchiectasis:

- **Presentation:** Increased exacerbation frequency, productive cough with thick plugs, declining lung function
- **Key Distinguishing Features:** Peripheral blood eosinophilia, extremely elevated total IgE (uncommon in COPD/bronchiectasis alone)
- Often misdiagnosed as infectious exacerbations and treated with repeated antibiotics

ABPA in Post-Tubercular Lung Disease:

- **High-Risk Scenario:** Patient with previous TB, now with cavitary disease/bronchiectasis, presents with worsening symptoms
- **Critical Diagnostic Pitfall:** ABPA misdiagnosed as TB reactivation (accounts for 57.5% of ABPA cases in TB-endemic regions!)

- **Key Differentiators:** Marked eosinophilia, extremely elevated IgE, positive *Aspergillus* serology (not seen in TB)

ABPA Sans Asthma (7% of Cases):

- No prior asthma diagnosis
- Presents with cough, sputum production, recurrent infiltrates
- Must maintain high clinical suspicion; diagnosis often delayed

Identifying New ABPA Infiltrates/Exacerbations

New ABPA infiltrates or exacerbations may be identified by:

1. **Clinical symptoms:** Cough, wheeze, or dyspnea with sputum production
2. **Pulmonary function decline:** Unexplained decreases in expiratory flow rates
3. **Immunologic markers:** Sharp ($\geq 100\%$) increases in total serum IgE concentration from baseline
4. **Radiological findings:** New infiltrates on chest imaging even in absence of symptoms

Diagnosis

When to Suspect ABPA—Clinical Triggers

High Suspicion Scenarios:

1. Asthmatic patient with frequent exacerbations (>2 -3/year requiring oral steroids)
2. Fleeting or migratory pulmonary infiltrates on chest X-ray
3. Central bronchiectasis on chest CT (especially in upper/middle lobes)
4. Peripheral blood eosinophilia in asthmatic/CF patient
5. Total IgE >500 IU/mL in appropriate clinical context
6. Expectoration of brownish mucus plugs
7. *Aspergillus* isolated from sputum in non-immunocompromised patient
8. Post-TB patient with worsening symptoms despite anti-tubercular therapy completion

Updated 2024 ISHAM-ABPA Working Group Diagnostic Criteria

The International Society for Human and Animal Mycology (ISHAM) working group published revised clinical practice guidelines in 2024 that represent significant advances in ABPA diagnosis and classification. The updated criteria lower the total IgE threshold from 1000 IU/mL to ≥ 500 IU/mL, improving diagnostic sensitivity from 91% to 98%.

Diagnostic Algorithm (2024 ISHAM Guidelines)

Step 1: Screen for *Aspergillus* Sensitization

- **Test:** Serum *A. fumigatus*-specific IgE (preferred over skin testing)
- **Interpretation:**
 - If ≥ 0.35 kUA/L \rightarrow proceed to Step 2
 - If < 0.35 kUA/L \rightarrow consider ABPM (test for other fungi)

Step 2: Measure Total Serum IgE

- **Threshold:** ≥ 500 IU/mL (NEW in 2024—previously 1000 IU/mL)
- **Sensitivity improvement:** 91% \rightarrow 98% with lowered threshold
- **Note:** Total IgE < 500 IU/mL may be acceptable if ALL other criteria fulfilled

Step 3: Confirm with Additional Criteria

Diagnostic Criteria for ABPA:

1. **Predisposing conditions or compatible presentation:**
 - Asthma
 - Cystic fibrosis
 - COPD
 - Bronchiectasis
 - Compatible clinico-radiological presentation (even without traditional predisposing condition)
2. **Mandatory criteria (BOTH required):**
 - *A. fumigatus*-specific IgE ≥ 0.35 kUA/L (or positive immediate skin test if IgE testing unavailable)

- Total serum IgE ≥ 500 IU/mL

3. Two of the following:

- *A. fumigatus*-specific IgG or precipitins (detected by lateral flow assay or ELISA)
- Radiological findings consistent with ABPA:
 - Bronchiectasis (central > peripheral)
 - Mucus plugging
 - Consolidation/atelectasis
 - High-attenuation mucus (HAM)
 - Centrilobular nodules ("tree-in-bud")
- Peripheral blood eosinophilia ≥ 500 cells/ μ L (in steroid-naive patients)

Important Update—Pathognomonic Finding:

High-attenuation mucus (HAM) on chest CT is pathognomonic for ABPA and confirms the diagnosis even if all other criteria are not fulfilled. The presence of HAM on imaging (visually denser than the paraspinal skeletal muscles or CT density ≥ 70 Hounsfield Units) indicates ABPA as the etiology of underlying bronchiectasis.

Component-Resolved Diagnostics (Advanced Testing)

Recombinant *Aspergillus* Allergens:

- **Asp f 1 and/or Asp f 2:** Markers of genuine *A. fumigatus* sensitization in ABPA
 - Combination achieves 96.7% sensitivity for ABPA diagnosis
 - Useful for differentiating ABPA from simple *Aspergillus* sensitization
- **Asp f 4 and/or Asp f 6:** Highest specificity (99.2%) for ABPA
 - Particularly useful in CF where diagnosis is challenging
- **Clinical utility:** When crude *Aspergillus* extract testing is equivocal, component-resolved diagnostics improve diagnostic accuracy

Imaging: The Critical Diagnostic Tool

Chest X-Ray Findings (Low Sensitivity—Often Normal):

- Fleeting/migratory infiltrates
- "Gloved-finger" sign (mucus-filled dilated bronchi)
- "Toothpaste shadows" (mucoïd impaction)
- Tramline shadows (thickened bronchial walls)
- **Clinical Pearl:** CXR normal in ~50% of ABPA cases—CT is essential

High-Resolution Chest CT (Diagnostic Modality of Choice):

Characteristic Findings:

1. **Central bronchiectasis** (78-87% of cases)
 - Varicose or cystic bronchiectasis
 - Upper and middle lobe predominance
 - Internal diameter of bronchus > adjacent pulmonary artery ("signet ring sign")
2. **Mucus plugging** (59-91% of cases)
 - Branching tubular opacities extending from hilum
 - "Finger-in-glove" appearance
3. **High-attenuation mucus (HAM)** (20-36% of cases)
 - **PATHOGNOMONIC when present**
 - Density >70 HU (visually denser than paraspinal muscle)
 - Correlates with severe disease, higher relapse risk
4. **Centrilobular nodules** (86% of cases)
 - "Tree-in-bud" pattern (bronchiolar inflammation)
 - More common in ABPA-related central bronchiectasis than asthma alone
5. **Consolidation/atelectasis** (58-70%)

- Post-obstructive changes from mucus plugging

6. Other findings:

- Mosaic attenuation (air trapping)
- Pleural thickening (advanced disease)

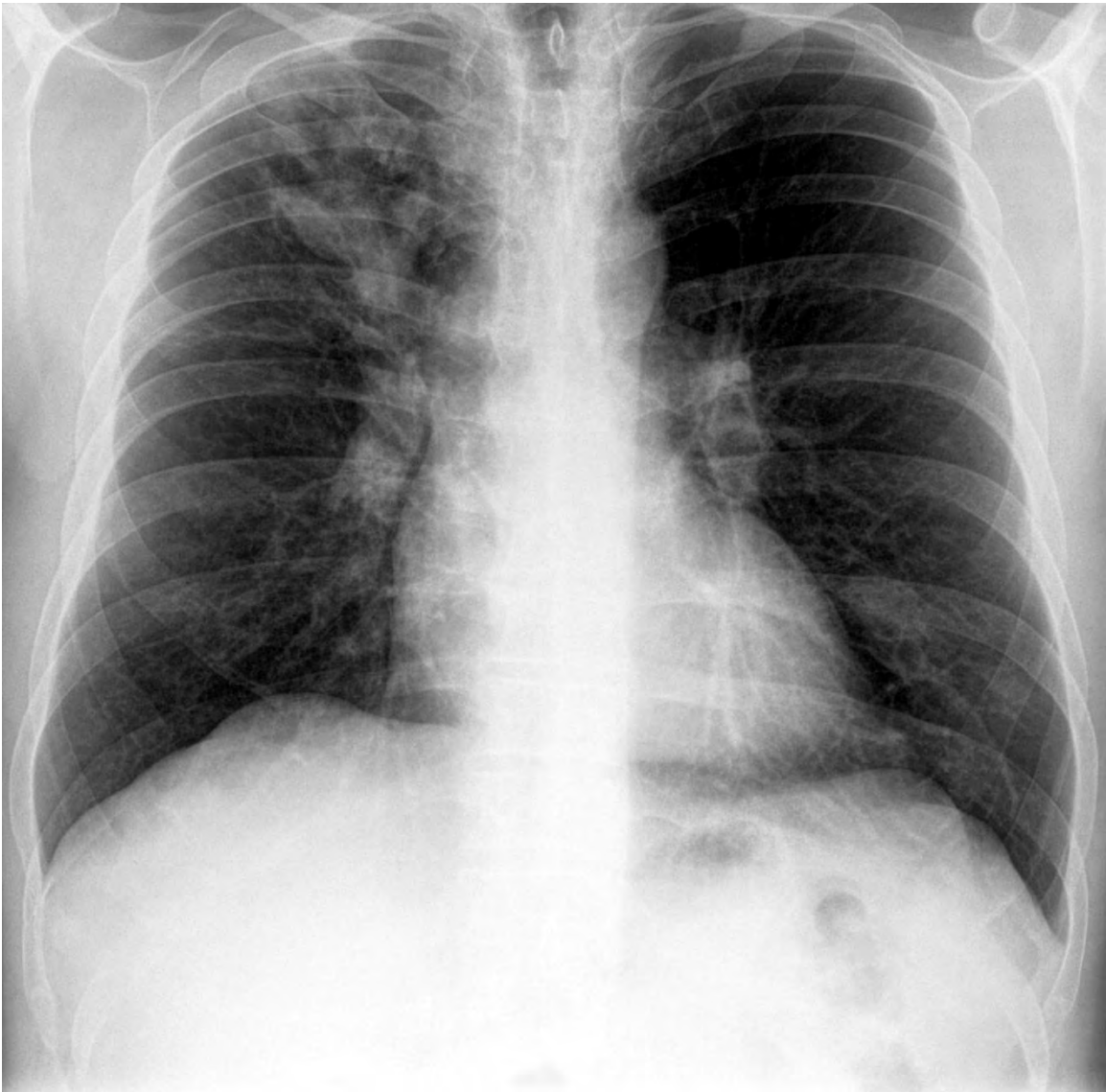


Fig. 21.1 Chest roentgenography showed pulmonary infiltrates, central bronchiectasis, glove-finger shadow, and nodular opacities

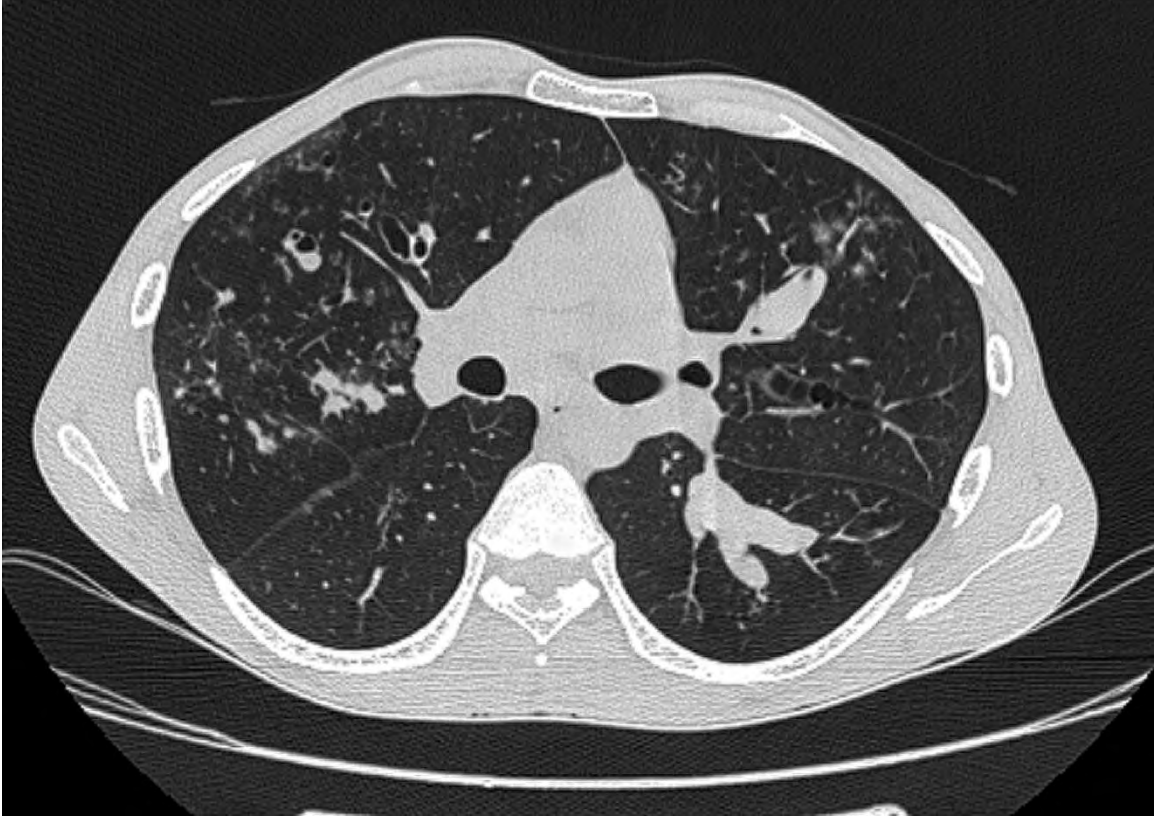


Fig. 21.2 High-resolution CT scan (*HRCT*). Proximal bronchiectasis is defined as being present when there are bronchi that are dilated in comparison with the caliber of an adjacent bronchial artery in the inner two thirds of the lung CT field

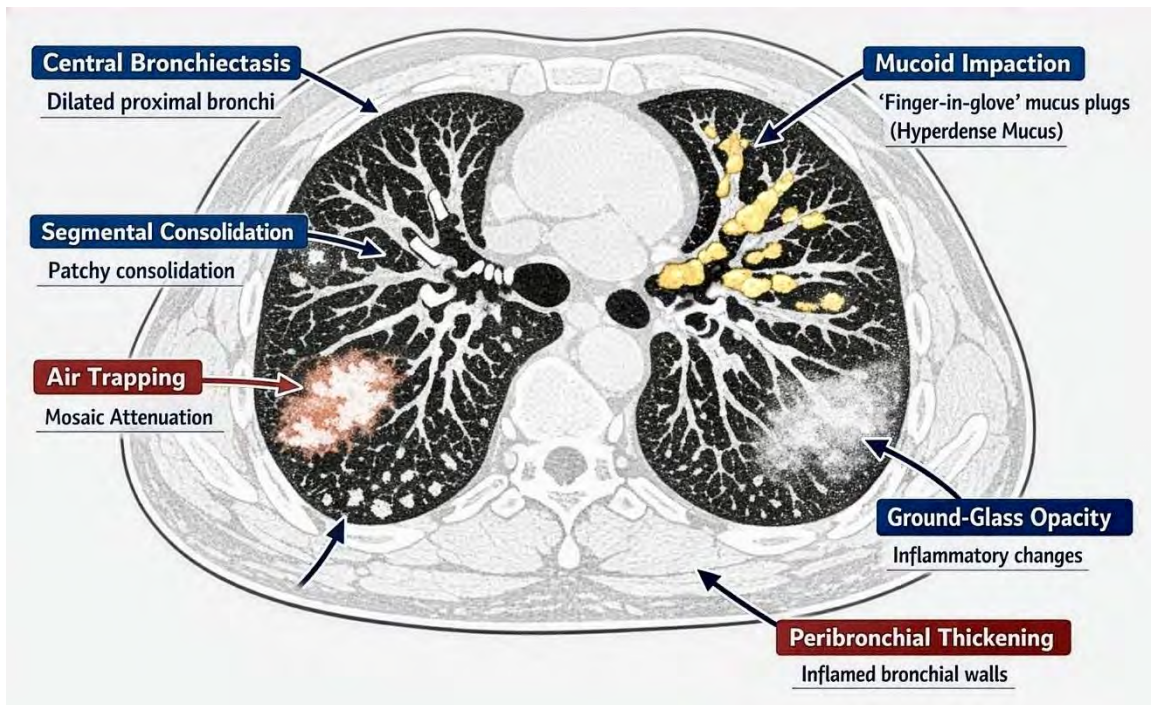


Fig. 21.3 HRCT Findings in ABPA. This is a diagram summarizing typical findings seen in ABPA. Not all findings are necessarily seen, and the actual picture can be more complicated if there are residual shadows due to complications or sequelae of previous lung disease.

Differential Diagnosis

Key Conditions to Differentiate

1. Severe Asthma with Fungal Sensitization (SAFS)

- **Clinical features:** *Aspergillus* sensitization present (positive skin test or specific IgE); poorly controlled asthma
- **Distinguishing features:** Does NOT meet full ABPA criteria—usually lacks radiological findings (no bronchiectasis or mucus plugging); total IgE may be <500 IU/mL; peripheral eosinophilia may be absent
- **Management implications:** May benefit from antifungal therapy even without ABPA diagnosis; consider itraconazole trial

2. Pulmonary Tuberculosis

- **Clinical features:** Cough, hemoptysis, weight loss, night sweats, cavitory upper lobe disease
- **CRITICAL in TB-Endemic Regions:** 57.5% of ABPA cases initially misdiagnosed as TB!
- **Differentiating features:**
 - **ABPA:** Marked eosinophilia (>500/ μ L), extremely elevated IgE (often >1000 IU/mL), positive *Aspergillus* serology, central bronchiectasis, negative acid-fast bacilli, no constitutional symptoms
 - **TB:** Normal or low eosinophils, normal IgE, positive AFB smear/culture, cavitory upper lobe disease, constitutional symptoms
- **Important:** ABPA can coexist with TB (2.6% of cases) or develop after TB (24.9%)—post-TB structural damage predisposes to ABPA
- **Management implications:** Do NOT start anti-tubercular therapy without microbiologic confirmation; ABPA requires corticosteroids which are contraindicated in active TB

3. Chronic Eosinophilic Pneumonia (CEP)

- **Clinical features:** Peripheral blood and tissue eosinophilia, subacute onset of dyspnea, cough, fever, night sweats

- **Distinguishing features:** "Photographic negative" of pulmonary edema on imaging (peripheral predominant infiltrates); normal or mildly elevated IgE; absence of *Aspergillus* sensitization; no bronchiectasis; dramatic response to corticosteroids (within 24-48 hours)
- **Management implications:** Requires prolonged corticosteroid therapy but no antifungals

4. Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- **Clinical features:** Asthma, eosinophilia, pulmonary infiltrates, systemic vasculitis
- **Distinguishing features:** Multi-organ involvement (peripheral neuropathy, sinusitis, skin lesions, cardiac involvement, renal disease); ANCA positivity (40-60% of cases, usually MPO-ANCA); normal or mildly elevated IgE; no *Aspergillus* sensitization; elevated inflammatory markers (ESR, CRP)
- **Management implications:** Requires immunosuppressive therapy (corticosteroids + cyclophosphamide or rituximab); not responsive to antifungals

5. Invasive Pulmonary Aspergillosis (IPA)

- **Clinical features:** Fever, cough, hemoptysis in severely immunocompromised patient (neutropenia, hematologic malignancy, solid organ transplant, high-dose corticosteroids)
- **Key Difference:** ABPA occurs in NON-immunocompromised; IPA in severely immunocompromised
- **Distinguishing features:** Tissue invasion on biopsy; angioinvasion; "halo sign" (early) or "air crescent sign" (late) on CT; positive serum galactomannan or β -D-glucan; normal IgE; no eosinophilia
- **Management implications:** Medical emergency requiring immediate systemic antifungal therapy (voriconazole, isavuconazole, or liposomal amphotericin B) \pm surgical resection

6. Aspergilloma (Fungal Ball)

- **Clinical features:** *Aspergillus* colonization in pre-existing cavity (from TB, sarcoidosis, bullous emphysema); hemoptysis is common presentation
- **Distinguishing features:** "Mobile mass" within cavity on CT; "air crescent sign" (air surrounding fungal ball); no systemic immunologic response (normal IgE, no

eosinophilia, no *Aspergillus*-specific antibodies); cavity pre-exists fungal colonization

- **Important:** May coexist with ABPA—patients can have both conditions simultaneously
- **Management implications:** Observation if asymptomatic; antifungals ineffective (poor penetration); surgical resection for massive hemoptysis

7. Bronchiectasis (Non-ABPA Etiology)

- **Clinical features:** Chronic productive cough, recurrent bacterial infections (*Pseudomonas*, *H. influenzae*, MRSA), dyspnea
- **Distinguishing features:** Normal IgE levels; no *Aspergillus* sensitization; no peripheral eosinophilia; sputum cultures positive for bacteria; bronchiectasis typically cylindrical rather than varicose/cystic
- **Challenge:** ABPA can be CAUSE of bronchiectasis, and bronchiectasis predisposes to ABPA—complex bidirectional relationship
- **Management implications:** Airway clearance techniques, antibiotics for exacerbations, consideration of long-term macrolide therapy

8. Hypersensitivity Pneumonitis

- **Clinical features:** Exposure history (birds, hot tubs, mold in home/workplace); dyspnea, cough, systemic symptoms
- **Distinguishing features:** Ground-glass opacities, centrilobular nodules, mosaic attenuation on imaging; restrictive pattern on PFTs; specific IgG antibodies to inciting antigen; normal or mildly elevated IgE; no eosinophilia
- **Management implications:** Antigen avoidance is primary therapy; corticosteroids for severe cases

Complications

Acute Complications

1. **Severe asthma exacerbations:** Requiring hospitalization, ICU admission, mechanical ventilation

2. **Massive mucus plugging:** Lobar or complete lung collapse, acute respiratory failure
3. **Hemoptysis:** From bronchiectasis, usually mild but can be massive and life-threatening
4. **Pneumothorax:** Rare complication from ruptured bullae in advanced disease
5. **Acute hypoxemic respiratory failure:** From extensive consolidation or atelectasis

Chronic Complications (If Untreated/Inadequately Treated)

1. **Progressive bronchiectasis:**
 - Irreversible airway dilation and destruction
 - Leads to chronic bacterial colonization (*Pseudomonas*, MRSA, *Stenotrophomonas*)
 - Vicious cycle of infection, inflammation, and further structural damage
2. **Pulmonary fibrosis (ABPA-CPF):**
 - Upper lobe predominant fibrosis
 - Restrictive lung disease pattern
 - May develop secondary pulmonary hypertension
 - Associated with poor prognosis
3. **Chronic respiratory failure:** Progressive hypoxemia, eventually requiring supplemental oxygen; may progress to hypercapnia in advanced cases
4. **Aspergilloma formation:** Development of fungal ball in bronchiectatic cavities or destroyed lung segments
5. **Corticosteroid-related complications (in inadequately managed patients):**
 - Osteoporosis and pathologic fractures
 - Diabetes mellitus or worsening glycemic control
 - Hypertension
 - Weight gain and cushingoid features

- Increased infection risk
 - Avascular necrosis
 - Cataracts and glaucoma
 - Psychiatric disturbances
6. **Quality of life impairment:** Chronic symptoms, frequent hospitalizations, exercise limitation, anxiety and depression

Prognostic Factors

Good Prognosis Indicators:

- Early diagnosis (before bronchiectasis develops)
- ABPA-S stage (serological only, no radiological findings)
- Good initial response to treatment
- Absence of high-attenuation mucus (HAM)
- Ability to achieve and maintain remission
- Good asthma/CF control

Poor Prognosis Indicators:

- Delayed diagnosis with established bronchiectasis
- Presence of HAM (associated with severe disease, higher relapse rates, more extensive lung involvement)
- ABPA-CPF (fibrotic stage)—end-stage disease
- Frequent exacerbations (>3 per year)
- Corticosteroid dependence
- Declining pulmonary function despite treatment
- Development of chronic bacterial colonization

Overall Prognosis:

- ~50% experience recurrent exacerbations during or after steroid taper

- With appropriate early treatment: Most patients maintain good respiratory function and quality of life
- Without treatment: Progressive lung damage leading to respiratory failure and reduced life expectancy
- Modern biologic therapies substantially improve outcomes for refractory disease, offering effective steroid-sparing alternatives

Treatment

General Principles

The 2024 ISHAM guidelines recommend a stratified approach to ABPA treatment based on disease severity and clinical presentation:

- **ABPA-S (Serological):** Managed like asthma; ABPA-specific therapy reserved only for recurrent asthma or ABPA exacerbations despite optimal asthma management
- **Asymptomatic ABPA-B:** Close monitoring without immediate treatment; initiate therapy if clinical, radiological, or immunological status worsens
- **Symptomatic ABPA:** Active treatment required
- **Acute ABPA or exacerbation:** Oral prednisolone OR itraconazole monotherapy
- **Recurrent exacerbations:** Combination therapy with prednisolone and itraconazole
- **Corticosteroid-dependent or refractory disease:** Consider biologic therapies

Standard Therapy

Systemic corticosteroids remain the cornerstone of ABPA treatment. The 2024 ISHAM guidelines recommend oral prednisolone or itraconazole monotherapy for treating acute ABPA (newly diagnosed or exacerbation). Combination therapy with prednisolone and itraconazole is recommended only for treating recurrent ABPA exacerbations. Asymptomatic ABPA patients are not routinely treated.

For new ABPA infiltrates, typical regimen includes prednisone 0.5 mg/kg/day for 1-2 weeks, then on alternate days for 6-8 weeks, followed by gradual tapering. Total serum

IgE concentration should be repeated in 6-8 weeks and then every 8 weeks for 1 year to determine the range of IgE concentrations. Increases of $\geq 100\%$ over baseline can signify a silent ABPA exacerbation.

Itraconazole (200 mg twice daily for 16 weeks) has shown efficacy in reducing corticosteroid requirements and improving clinical outcomes. Voriconazole and posaconazole may be considered as alternatives in patients with itraconazole intolerance or resistance.

Systemic Corticosteroids

Typical Regimen for Acute ABPA:

- **Prednisone 0.5 mg/kg/day** (maximum 40-60 mg/day) for 1-2 weeks
- Then **alternate-day dosing** at same dose for 6-8 weeks
- **Gradual taper** over subsequent 2-3 months
- **Total duration:** Typically 4-6 months

Monitoring During Corticosteroid Therapy:

- Total serum IgE should be repeated in 6-8 weeks, then every 8 weeks for the first year to establish the patient's IgE range
- If IgE does not decline by $\geq 25\%$ at 6-8 weeks, consider adding itraconazole or alternative diagnosis
- Monitor for corticosteroid side effects (glucose, bone density, ophthalmologic examination)

Important Considerations:

- Rapid or premature discontinuation leads to high relapse rates
- Slow taper over 4-6 months is essential
- Do NOT abruptly stop corticosteroids

Antifungal Therapy

Itraconazole (First-line antifungal):

- **Dosing:** 200 mg twice daily for 16 weeks (minimum); may extend to 6 months
- **Mechanism:** Reduces fungal burden, thereby decreasing antigenic stimulation
- **Efficacy:** Demonstrated reduction in corticosteroid requirements, fewer exacerbations, improved clinical outcomes, decreased IgE levels
- **Monitoring:**
 - Serum itraconazole levels (target trough >1 µg/mL, ideally 1-2 µg/mL)
 - Liver function tests at baseline, 2 weeks, then monthly
 - Monitor for drug interactions (CYP3A4 inhibitor)
- **Side effects:** Hepatotoxicity, heart failure exacerbation, drug interactions, gastrointestinal disturbances

Alternative Antifungals:

- **Voriconazole:** 200-400 mg twice daily (monitor levels, more drug interactions, better CNS penetration)
- **Posaconazole:** 300 mg once daily or 200 mg three times daily (delayed-release tablets)
- Considered in patients with itraconazole intolerance, resistance, or inadequate response

Important Note on Combination Therapy:

The 2024 ISHAM guidelines specify that **combination therapy (prednisolone + itraconazole) is recommended ONLY for treating recurrent ABPA exacerbations**, not for initial treatment of acute ABPA.

Biologic Therapies - Major Update 2023-2025

Recent evidence demonstrates significant efficacy of biologic agents in treatment-refractory ABPA, offering important steroid-sparing alternatives. Biologics should be considered for:

- Corticosteroid-dependent ABPA

- Frequent exacerbations (≥ 3 per year despite standard therapy)
- Inability to taper corticosteroids without relapse
- Unacceptable corticosteroid side effects
- Inadequate response to standard therapy

Omalizumab (Anti-IgE)

Mechanism: Binds free IgE, preventing IgE-mediated mast cell and basophil activation

Evidence: Multiple studies demonstrate that omalizumab significantly reduces exacerbation rates (mean reduction 2.29 exacerbations/year), oral corticosteroid dosage (mean reduction 10.91 mg/day), and total IgE levels (mean reduction 273 IU/mL) while improving pulmonary function (FEV₁ improvement 10.09% predicted).

Dosing: The 2024 ISHAM guidelines recommend dosing based on body weight and serum total IgE values, **not exceeding 375 mg subcutaneous injection twice monthly**. Treatment is effective despite markedly elevated IgE levels characteristic of ABPA.

Duration: Typically continue for at least 4-6 months; assess response and consider long-term therapy if beneficial

Limitations: Does not effectively clear mucus plugs; ~50% radiographic improvement rate

Mepolizumab and Benralizumab (Anti-IL-5/Anti-IL-5R α)

Mechanism:

- Mepolizumab: Binds IL-5, preventing eosinophil maturation and survival
- Benralizumab: Binds IL-5 receptor α , inducing eosinophil apoptosis

Evidence: These agents targeting eosinophils have shown robust efficacy, with particular benefit in reducing mucus plugs. Studies demonstrate that **82% of patients treated with mepolizumab or benralizumab showed radiographic improvement** compared to 50% with omalizumab.

Key Advantages:

- Superior efficacy for mucus plug clearance
- Effective regardless of peripheral blood eosinophilia magnitude
- Work even without decreasing total IgE levels

- Particularly effective for patients with prominent mucus plugging on imaging

Dosing:

- **Mepolizumab:** 100 mg subcutaneous every 4 weeks (asthma dosing); may use 300 mg for severe disease
- **Benralizumab:** 30 mg subcutaneous every 4 weeks for first 3 doses, then every 8 weeks

Evidence of Superiority: Case reports demonstrate successful treatment with benralizumab of mucus plugs resistant to mepolizumab, suggesting potential sequential therapy approach.

Dupilumab (Anti-IL-4R α) - Emerging as Superior Option

Mechanism: Blocks IL-4 receptor α , inhibiting both IL-4 and IL-13 signaling pathways, providing broader immunomodulation of type 2 inflammation

Evidence: Recent evidence suggests dupilumab may be the most effective biologic for ABPA. Multiple case reports demonstrate successful treatment of ABPA refractory to omalizumab, mepolizumab, or benralizumab.

Key Advantages:

- Broadest immunomodulation (blocks IL-4 and IL-13 pathways)
- Particular efficacy in eliminating mucus plugs
- Achieves complete glucocorticoid withdrawal in some patients
- Effective for patients failing other biologics
- May be considered first-line biologic in severe, refractory ABPA

Dosing:

- **Loading dose:** 600 mg subcutaneous (two 300 mg injections)
- **Maintenance:** 300 mg subcutaneous every 2 weeks

Important Consideration: Transient peripheral blood eosinophilia may occur after dupilumab administration, occasionally exceeding 2000/mm³. Particular caution should be exercised when oral corticosteroids and anti-IL-5 therapy are not administered concomitantly. Monitor eosinophil counts during treatment.

Future Directions: The ongoing **LIBERTY ABPA AIRED clinical trial** will provide definitive prospective evidence on dupilumab efficacy in ABPA.

Tezepelumab (Anti-TSLP)

Mechanism: Blocks thymic stromal lymphopoietin (TSLP), an upstream regulator of type 2 inflammation

Current Evidence: Limited data; shows only weak evidence of efficacy in ABPA; should not be prioritized over other biologics at this time

Selecting the Appropriate Biologic

Clinical Decision-Making:

- **Prominent mucus plugging:** Consider mepolizumab, benralizumab, or dupilumab (superior to omalizumab for this indication)
- **Very high IgE levels:** Omalizumab or dupilumab
- **Failed omalizumab:** Consider switching to anti-IL-5 agent or dupilumab
- **Failed anti-IL-5 agent:** Consider switching to dupilumab
- **Multiple comorbidities (atopic dermatitis, nasal polyps):** Dupilumab may address multiple conditions
- **Severe, refractory disease:** Dupilumab emerging as potentially most effective option

Treatment of Underlying Predisposing Condition

Optimize Asthma Management:

- Ensure appropriate inhaled corticosteroid + long-acting β -agonist therapy
- Address triggers, allergen avoidance
- Consider additional controllers (LAMA, LTRA)

Optimize CF Management:

- Airway clearance techniques
- CFTR modulators if appropriate genotype

- Nutritional support
- Management of CF-related complications

Manage Concomitant Conditions:

- Allergic rhinitis
- Chronic rhinosinusitis
- Gastroesophageal reflux disease
- These conditions can worsen ABPA control

Monitoring And Follow-Up

Regular monitoring is essential for ABPA management to detect exacerbations early, assess treatment response, and prevent complications. Total serum IgE should be measured every 6-8 weeks during the first year, then every 2-3 months. A doubling ($\geq 100\%$ increase) in total IgE from baseline suggests exacerbation. Chest imaging should be repeated after 4-8 weeks of treatment to assess response. Pulmonary function tests should be monitored regularly to detect declining lung function.

New ABPA infiltrates may be identified by: (a) cough, wheeze, or dyspnea with sputum production; (b) unexplained declines in expiratory flow rates; (c) sharp ($>100\%$) increases in total serum IgE concentration; or (d) absent symptoms but new infiltrates on chest imaging. Concomitant conditions such as allergic rhinitis, sinusitis, and gastroesophageal reflux disease should also be diagnosed and managed.

Monitoring Schedule

Total Serum IgE:

- Measure every **6-8 weeks during the first year** after diagnosis
- Then every **2-3 months** thereafter during stable disease
- Establish patient's baseline IgE range during remission

Interpretation:

- **IgE decline of $\geq 25-50\%$ from baseline** at 6-8 weeks indicates treatment response
- **IgE increase $\geq 100\%$ (doubling) from baseline** suggests exacerbation (even without symptoms)
- **IgE increase $\geq 50\%$ with clinical/radiological worsening** also indicates exacerbation

Pulmonary Function Tests:

- **FEV₁ and FVC** at baseline, then every **3-6 months**
- More frequently if symptoms worsen or during exacerbations
- Assess for progressive airflow obstruction or restrictive defect

Chest Imaging:

- **Chest X-ray:** At each clinic visit to compare with baseline
- **HRCT chest:**
 - At **4-8 weeks** post-treatment initiation to assess response
 - Then **annually** for stable patients
 - More frequently if clinical deterioration, suspected exacerbation, or new symptoms
- **Assess for:** New infiltrates, mucus plug clearance, progression of bronchiectasis, development of fibrosis

Peripheral Blood Eosinophil Count:

- Monitor at each visit to track inflammatory burden
- Particularly important for patients on biologics (watch for paradoxical eosinophilia with dupilumab)

Clinical Assessment:

- Symptom control (asthma control, cough, sputum production)
- Exacerbation frequency
- Quality of life assessment
- Corticosteroid and antifungal side effects

Identifying Exacerbations

New ABPA infiltrates or exacerbations may be identified by:

1. **Clinical deterioration:** Cough, wheeze, or dyspnea with increased sputum production
2. **Pulmonary function decline:** Unexplained decreases in expiratory flow rates (FEV₁ decline $\geq 10\%$)
3. **Immunologic markers:** Sharp ($\geq 100\%$) increases in total serum IgE concentration from baseline
4. **Radiological findings:** New infiltrates on chest imaging, even in absence of symptoms ("silent exacerbation")

Management of Exacerbations

First Exacerbation:

- Restart or increase corticosteroids (prednisolone 0.5 mg/kg/day)
- Consider adding itraconazole if not already on therapy
- Re-evaluate and optimize inhaled asthma therapy

Recurrent Exacerbations (≥ 2 per year):

- **Combination therapy:** Prednisolone + itraconazole
- **Consider biologic therapy:** Particularly if corticosteroid-dependent
- Investigate for adherence issues, environmental triggers, concomitant infections

Frequent Exacerbations (≥ 3 per year) Despite Standard Therapy:

- **Strong indication for biologic therapy**
- Consider omalizumab, mepolizumab, benralizumab, or dupilumab based on patient characteristics
- May require long-term biologic therapy to maintain remission

Long-Term Management Goals

1. **Prevent exacerbations:** Goal < 1 exacerbation per year

2. **Minimize corticosteroid exposure:** Achieve lowest effective dose or complete withdrawal
3. **Preserve lung function:** Prevent decline in FEV₁
4. **Prevent bronchiectasis progression:** Early treatment before irreversible damage
5. **Maintain quality of life:** Control symptoms, prevent hospitalizations
6. **Address comorbidities:** Optimize management of underlying asthma, CF, or other conditions

Evidence-Based Medicine

Diagnosis

This landmark systematic review represents the most comprehensive epidemiological assessment of ABPA prevalence worldwide. The study pooled data from multiple international cohorts to establish that the global prevalence of ABPA is approximately 11% in adults with asthma, significantly higher than previously estimated. This meta-analysis provides critical baseline data for understanding disease burden and emphasizes the need for systematic screening in asthma clinics. The study demonstrates that ABPA prevalence varies substantially by geographic region and healthcare setting, with specialized tertiary care centers reporting rates up to 13%. By synthesizing evidence from diverse populations, this systematic review established new benchmarks for ABPA epidemiology and underscored the importance of universal screening protocols in high-risk populations. The findings directly influenced the 2024 ISHAM guidelines' recommendation for routine *Aspergillus fumigatus* sensitization screening in newly diagnosed adult asthmatics at tertiary care facilities.

Agarwal R, Muthu V, Sehgal IS, et al. Prevalence of *Aspergillus* Sensitization and Allergic Bronchopulmonary Aspergillosis in Adults With Bronchial Asthma: A Systematic Review of Global Data. *J Allergy Clin Immunol Pract.* 2023;11(6):1734-1751.e3. **Evidence grade: 1a (A).**

Management

This landmark consensus-based guideline represents the most authoritative and comprehensive diagnostic framework for ABPA/ABPM developed using a modified

Delphi method involving international experts from 13 countries. The 2024 guidelines introduced transformative changes including: (1) lowering the total IgE diagnostic threshold from 1000 to ≥ 500 IU/mL, improving sensitivity from 91% to 98%; (2) creating separate diagnostic criteria for ABPA and allergic bronchopulmonary mycosis (ABPM); (3) expanding predisposing conditions to include COPD, bronchiectasis, and compatible clinico-radiological presentations; and (4) establishing that high-attenuation mucus (HAM) on CT is pathognomonic and diagnostic even without meeting other criteria. The guidelines recommend universal screening for *A. fumigatus* sensitization using fungus-specific IgE in all newly diagnosed adult asthmatics at tertiary care. This evidence-based consensus document synthesizes decades of clinical experience and research evidence to provide practical diagnostic algorithms that balance sensitivity and specificity while being applicable across diverse clinical settings globally.

Agarwal R, Sehgal IS, Muthu V, et al. Revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying and treating allergic bronchopulmonary aspergillosis/mycoses. *Eur Respir J.* 2024;63(4):2400061. **Evidence grade: 1a (A).**

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