# 조절되지 않는 천식 환자에서 ABPA 의 진단

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# Allergic bronchopulmonary aspergillosis (ABPA)

- hypersensitivity response to the *Aspergillus fumigatus* in the airways
- usually affecting subjects with asthma and cystic fibrosis
- progressive disease → end-stage fibrosis with associated respiratory failure

**TABLE 58.1 Clinical Staging of Allergic Bronchopulmonary Aspergillosis**

| | | Clinical | Immunologic | Radiologic |
|---|---|---|---|---|
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| Stage 1 | Acute | Symptomatic | IgE >1000 IU/ml | Normal or presence of pulmonary infiltrates |
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# Allergic bronchopulmonary aspergillosis (ABPA)

- Early and aggressive treatment of ABPA has the greatest likelihood of preventing progression to end-stage fibrotic lung disease.

- Early symptoms can often be confused with symptoms of asthma or pneumonia.

- Therefore, clinical suspicion is important to diagnose ABPA.

# Epidemiology

- The prevalence varies depending on the diagnostic criteria.
  - Agarwal R et al. : 12.9% in asthmatic populations
  - Denning DW et al. : 2.5% in adults with asthma
- usually between the third and fourth decades
- no gender predilection

# Etiology : *Aspergillus fumigatus*

- widely in nature, particularly in decaying vegetable matter
- grow through the production of hyphae, from which sprout conidiophores (fungal spores)
- secrete extracellular proteolytic enzymes

# Allergic bronchopulmonary mycoses (ABPM)

- A number of other fungi or yeasts have been implicated as causing a similar clinical syndrome.

**TABLE I.** Fungi associated with ABPM

| Organism | Study |
|---|---|
| *Aspergillus fumigatus* | Hinson et al, 1952[3] |
| *Aspergillus ochraceus* | Greenberger, 1988[4] |
| *Aspergillus oryzae* | Akiyama at al. 1987[5] |
| *Aspergillus terreus* | Elliott and Newman-Taylor, 1997[6] |
| *Alternaria alternata* | Chowdhary et al, 2012[7] |
| *Bipolaris (Dreschleria) hawaiiensis* | McAleer et al, 1981[8] |
| *Candida albicans* | Akiyama et al, 1984[9] |
| *Cryptococcus neoformans* | Arora and Huffnagle, 2005[10] |
| *Curvularia lunata* | Halwig et al, 1985[11] |
| *Fusarium vasinfectum* | Backman et al, 1995[12] |
| *Geotricum candidum* | Elliott and Newman-Taylor, 1997[6] |
| *Helminthosporium* species | Hendrich et al 1982[13] |
| *Penicillium* species | Elliott and Newman-Taylor, 1997[6] |
| *Peudoallescheria boydii* | Elliott and Newman-Taylor, 1997[6] |
| *Sacchromycetes cerevisiae* | Ogawa et al, 2004[14] |
| *Schizophyllum commune* | Kamei et al, 1994[15] |
| *Stemphyllium lanuginosum* | Benatar et al, 1980[16] |
| *Torulopsus glabrata* (now designated *Candida glabrata*) | Patterson et al, 1982[17] |

# Pathogenesis

- adherence of spores to the airway epithelium → inflammatory responses
- individual susceptibility

- breakdown of local nonspecific immunity
  - mucociliary clearance

- genetic susceptibility
  - toll-like receptors, T cell chemokine receptor expression
  - HLA-DR2 genotype, IL-4 receptor polymorphism and other cytokine polymorphisms

# Pathogenesis

predominance of Th2 over the Th1 response

→ release of Th2 cytokines (IL-4, IL-5, and IL-13)

- total IgE and *A fumigatus*-specific IgE production
- mast cell degranulation
- exacerbated eosinophilic response
- tissue damage

# Clinical features

- cough with thick, brown sputum
- dyspnea, wheeze
- systemic symptoms such as fever, weight loss, and fatigue

# Diagnosis

- Widely accepted international criteria for the diagnosis of ABPA are lacking.

**Key features**

- predisposing conditions : asthma, cystic fibrosis
- *A fumigatus*–specific IgE or immediate skin test reactivity
- *A fumigatus*–specific IgG or precipitating antibodies
- mucus plugs with *A fumigatus* hyphae
- serum total IgE level
- eosinophil count
- radiographic findings consistent with ABPA

## BOX 58.1 Diagnostic Classifications for Allergic Bronchopulmonary Aspergillosis

### Rosenberg-Patterson Criteria[a]

**Primary**

1. Asthma
2. Serum eosinophilia
3. Immediate skin reactivity to *Aspergillus*
4. Precipitins to *Aspergillus*
5. Elevated IgE
6. Pulmonary infiltrates (transient or fixed)
7. Central bronchiectasis

**Secondary**

1. *Aspergillus fumigatus* in sputum
2. Expectoration of brown plugs
3. Late skin reactivity to *Aspergillus*

### Schwartz and Greenberger Criteria[b,c]

**ABPA-CB: Minimal Essential Criteria**

1. Asthma
2. Immediate skin test reactivity to *Aspergillus*
3. Elevated *Aspergillus*-specific IgE and/or IgG
4. Elevated total IgE (>1000 ng/mL)
5. Proximal bronchiectasis

**ABPA-S: Minimal Essential Criteria**

1. Asthma
2. Immediate skin test reactivity to *Aspergillus*
3. Elevated total IgE (1000 ng/mL)
4. Elevated *Aspergillus*-specific IgE and/or IgG

**Additional Criteria**

1. Current or previous pulmonary infiltrates
2. Mucus plugs
3. Presence of *Aspergillus* in sputum
4. Precipitins to *Aspergillus*
5. Delayed skin test positive
6. Eosinophilia (>1000/μL)

### ISHAM Criteria[d]

**Predisposing Conditions**

Asthma, CF

**Obligatory Criteria (Both Should Be Present)**

1. Immediate skin test reactivity to *Aspergillus* or elevated *Aspergillus*-specific IgE
2. Elevated total IgE (>1000 IU/ml)

**Other Criteria (at Least 2 of 3)**

1. Presence of precipitating or IgG antibodies against *Aspergillus* in serum
2. Radiographic pulmonary opacities consistent with ABPA
3. Total eosinophil count >500 cells/μL in steroid naive patients

### CF Criteria[e]

**Classic Case**

1. Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, increased sputum) not attributable to another etiology.
2. Serum total IgE concentration of greater than 1000 IU/mL (2400 ng/mL), unless patient is receiving systemic corticosteroids (if so, retest when steroid treatment is discontinued).
3. Immediate cutaneous reactivity to *Aspergillus* extract or detectable

**Modified ISHAM criteria for diagnosis of ABPA in asthma (2020)[6]**

Presence of the following:

1. Asthma
2. *A fumigatus*-specific IgE level > 0.35 KUA/L
3. Serum total IgE levels > 500 IU/mL and ≥2 of the following:
   (a) *A fumigatus*–specific IgG level > 27 mg A/L
   (b) Bronchiectasis on chest CT scan
   (c) Eosinophil count >500 cells/μL
   (d) Mucus impaction on chest CT scan

# *Aspergillus* spp. sensitization

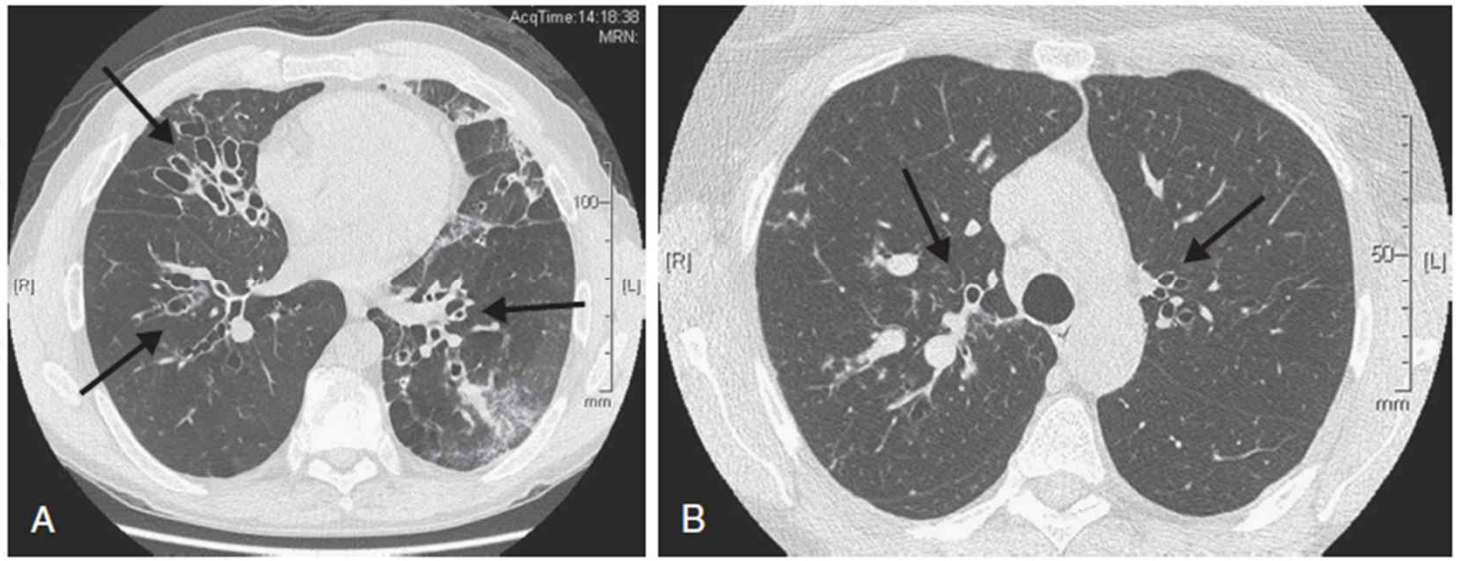
- Prevalence of fungal sensitization has been reported to be as high as 66% in severe asthma populations, with sensitivity to *Aspergillus* spp. of 45%.
- D/D with *Aspergillus* spp. sensitized asthma

- Concordance between blood and skin testing for specific IgE was only 54% for *Aspergillus* spp. antigens, so both blood and skin testing should be performed.

# Serum total IgE

- > 1,000 ng/mL (417 IU/mL), 1,000 IU/mL or 500 IU/mL ?
- concomitant allergic rhinitis and atopic dermatitis
- sensitive indicator of disease activity

# Radiologic Finc




- High-resolution compute
- transitory opacities
- central bronchiectasis with a predilection for the upper lobes ⟶ diagnostic
  - at lobar and segmental bronchus and involving the majority of airways (exceed two lobes)
- mucoid impaction leading to airway collapse (atelectasis)
  - high-attenuation mucus (HAM, airway luminal mucus at greater density than the surrounding paraspinal muscle)
- "tree-in-bud" opacities is also described
- more peripheral bronchiectasis and fibrosis associated with end-stage disease

# Treatment

**Treatment goals**

- control of symptoms
- prevent exacerbations
- reduce pulmonary inflammation
- prevent progression to end-stage fibrotic lung disease

# Corticosteroids (oral or intravenous)

- backbone of ABPA treatment
- 0.5 mg/kg and tapering for at least 3 months
- higher doses of corticosteroids for longer duration (6 to 12 months)

- inhaled corticosteroids alone : not effective

- monitor serum total IgE levels every 1 to 2 months

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- A decline in serum total IgE of 35% is considered diagnostic achieving remission.
  - Not all patients achieve such a reduction, especially those with lower total IgE levels of less than 2500 IU/mL.
- A doubling of serum total IgE is considered diagnostic of relapse.

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- Monitoring for corticosteroid side effects and prevention is important.

# Antifungal Agents in corticosteroid-dependent ABPA

- itraconazole 200 mg twice daily for 6 months for corticosteroid-dependent ABPA
- symptomatic improvement and decreased corticosteroid requirement in 46% of corticosteroid-dependent ABPA patients
- decreasing the burden of fungal colonization and attenuating inflammatory responses
- inhibitors of the cytochrome P450–dependent CYP3A4 enzyme : inhibit the metabolism of corticosteroids

# Biologics

- anti-IgE (omalizumab)
- anti-IL-5/5R (mepolizumab, reslizumab, benralizumab)
- anti-IL-4Ra (dupilumab)
- anti-TSLP (tezepelumab) ?

# When to Suspect ABPA

- severe asthma : uncontrolled despite maximal optimized treatment

- blood eosinophilia
- transitory opacities

- thick, brown sputum
- systemic symptoms such as fever, weight loss, and fatigue