Allergic Bronchopulmonary Aspergillosis [ABPA]

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Pulmonary Aspergillosis

- **Classification of respiratory diseases caused by Aspergillus depending on the host immunity and the organism virulence**
  - **saprophytic**
    - **Aspergilloma**
  - **Allergic**
    - **allergic Aspergillus sinusitis**
    - **allergic bronchopulmonary aspergillosis [ABPA]**
    - **hypersensitivity pneumonias**
  - **Invasive**
    - **airway invasive aspergillosis**
    - **chronic necrotizing pulmonary aspergillosis**
    - **invasive aspergillosis)**

Soubani AO et al. Chest 2002; 121:1988–1999

Allergic Bronchopulmonary Aspergillosis Defintion and Manifestations

- **ABPA is an allergic pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus***
  - ***Allergic Bronchopulmonary Mycosis is a* rare syndrome similar to ABPA, but caused by fungi other than *A. fumigatus***
- **Clinical signs and symptoms**
  - **chronic asthma**
  - **Recurrent pulmonary infiltrates,**
  - **bronchiectasis**

Greenberger PA. J Allergy Clin Immunol 2002; 110:685– 692

Allergic Bronchopulmonary Mycosis

Fungi	Study/Year
A niger	Sharma et al[218]/1985
Helminthosporium spp	Dolan et al[226]/1970
Penicillium spp	Sahn and Lakshminarayan[227]/1973
Aspergillus ochraceus	Novey and Wells[228]/1978
Stemphylium spp	Benatar et al[229]/1980
Aspergillus terreus	Laham et al[230]/1981
Drechslera spp	McAleer et al[231]/1981
Torulopsis spp	Patterson et al[232]/1982
Mucor-like spp	Patterson et al[232]/1982
Candida spp	Akiyama et al[234]/1984
Pseudallescheria spp	Lake et al[235]/1990
Bipolaris spp	Lake et al[236]/1991
Curvularia spp	Lake et al[236]/1991
Schizophyllum spp	Kamei et al[237]/1994
Fusarium spp	Backman et al[238]/1995
Cladosporium spp	Moreno-Ancillo et al[239]/1996
Saccharomyces spp	Ogawa et al[240]/2004

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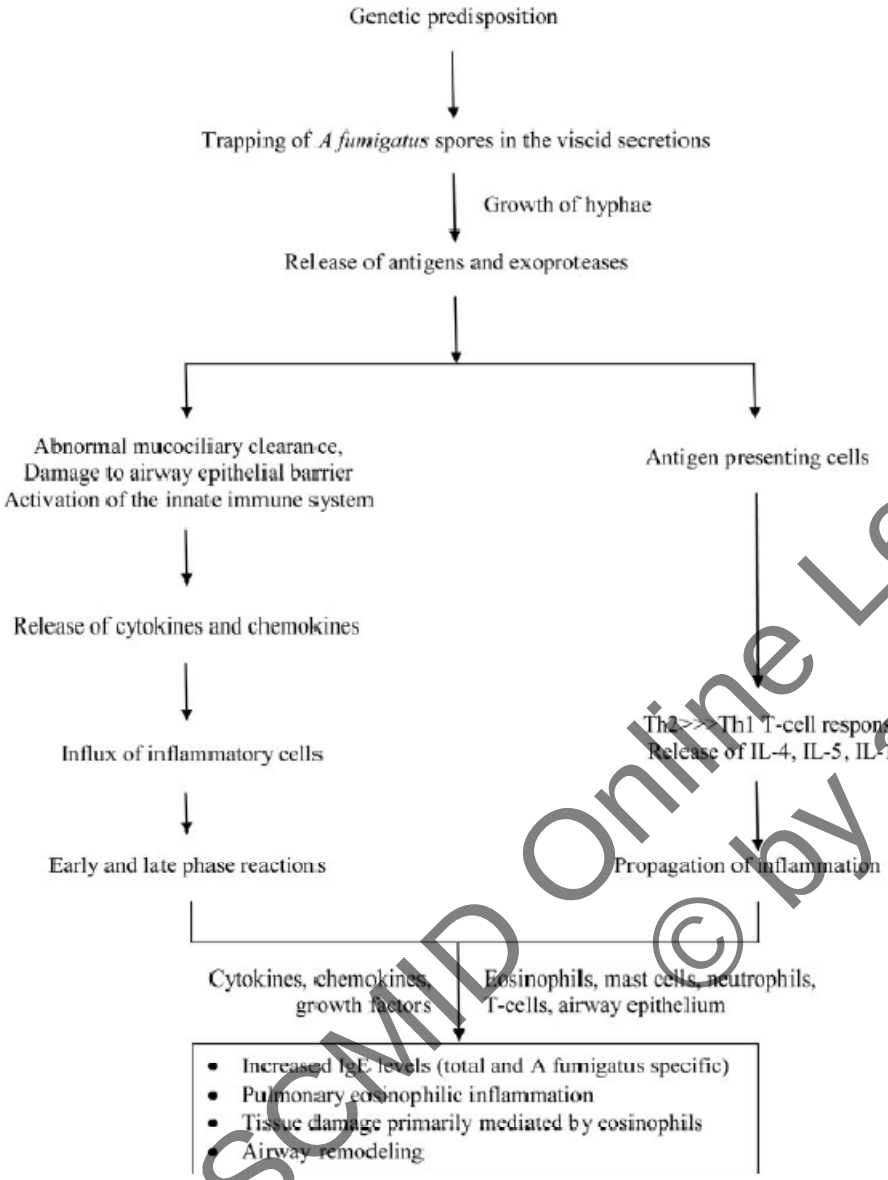
Allergic Bronchopulmonary Aspergillosis Immunologic Classification

- immediate hypersensitivity (type I)
- antigen-antibody complexes (type III)
- eosinophil-rich inflammatory cell responses (type IVb)

Rajan TV. Trends Immunol 2003; 24: 376–379



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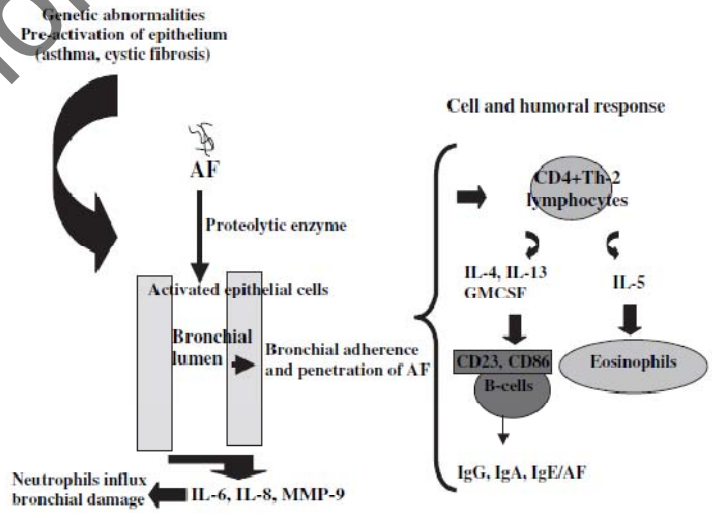

I. Tillie-Leblond I et al.. Allergy 2005: 60: 1004–1013

Allergic Bronchopulmonary Aspergillosis Epidemiology

- **Prevalence of ABPA**
  - **1 to 2% in patients with asthma**
  - **2 to 15% in patients with cystic fibrosis (CF)**

- **The condition remains underdiagnosed with reports of mean diagnostic latency of even 10 years between the occurrence of symptoms and the diagnosis**

- **There has been an increase in the number of cases of ABPA due to the heightened physician awareness and the widespread availability of serologic assays**

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Allergic Bronchopulmonary Aspergillosis Prevalence in Asthma

Study/Year	Type of Study	Type of Skin Test	Type of Antigen	Criteria Used for Diagnosis of ABPA	Prevalence of AH in Asthma (n/N)	Prevalence of ABPA in Asthma (n/N)
Attapattu[31]/1991	Prospective	Intradermal	Commercial (Bencard Allergie; Munich, Germany)	Major (A/R/T/E/P) Minor (C)	58/134	8/134
Eaton et al[33]/2000	Prospective	Prick	Commercial (Hollister-Stier Laboratories)	Major (A/R/T/E/P/I/C/S)	47/255	9/35
Kumar and Gaur[34]/2000	Prospective	Intradermal	Locally prepared	Major (A/R/T/E/P/I/C/S) Minor (C/S/B)	47/200	32/200
Al-Mobeireek et al[20]/2001	Prospective	Prick	Commercial (Soluprick; ALK Laboratories; Wallingford, CT)		12/53	
Maurya et al[35]/2005	Prospective	Intradermal	Locally prepared	Major (A/R/T/E/P/I/C/S) Minor (C/S)	30/105	8/105
Agarwal et al[23]/2007	Prospective	Intradermal	Commercial (Hollister-Stier Laboratories)	Major (A/R/T/E/P/I/C/S) Minor (S/B)	291/755	155/755
Prasad et al[36]/2008	Prospective	Intradermal	Not available	Major (A/R/T/E/P/I/C/S) Minor (C/S/B)	74/244	18/244

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Allergic Bronchopulmonary Aspergillosis Prevalence in CF

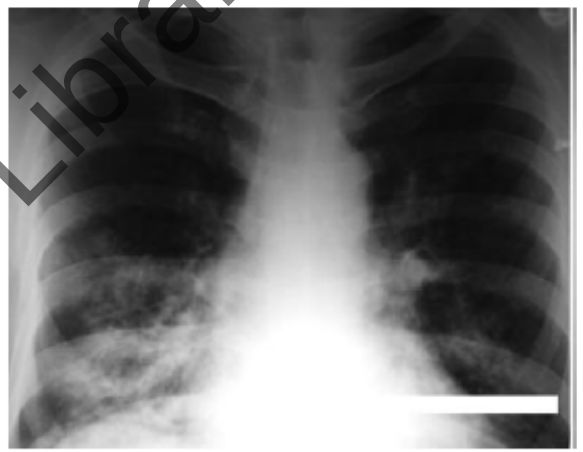
Study	Year	Nature of Study	Patients, No.	AH in CF	ABPA* in CF	Diagnosis of AH†
Mearns et al[184]	1967	Prospective	86	28/86		Skin test
Allan et al[185]	1975	Prospective	30	11/30		Skin test
Silvernan et al[186]	1978	Prospective	46	17		Skin test
Nelson et al[187]	1979	Prospective	46	13/46	5/46	Skin test
Laufer et al[177]	1984	Prospective	100	33/100	10/100	Skin test
Feanny et al[188]	1988	Prospective	117	18/117	12/117	Skin test
Schonheyder et al[189]	1988	Prospective	200		10/200	
Zeaske et al[190]	1988	Prospective	75	44/75	10/75	Skin test
Knutsen et al[176]	1990	Prospective	73	18/73	9/73	Skin test
Nicolai et al[179]	1990	Prospective	148	58/148		Serology
Simmonds et al[191]	1990	Prospective	137		8/137	
Hutcheson et al[192]	1991	Prospective	79	24/79		Skin test
el-Dahr et al[193]	1994	Prospective	147	30/147	22/147	Serology
Marchant et al[194]	1994	Retrospective	160		16/160	Skin test
Mroueh and Spock[178]	1994	Retrospective	236	38/87	15/236	Skin test
Becker et al[181]	1996	Prospective	53	15/51	1/53	Skin test
Hutcheson et al[195]	1996	Prospective	118	47/112	6/118	Skin test
Geller et al[182]	1999	Prospective	14,210		281/14,210	
Nepomuceno et al[183]	1999	Retrospective	172		16/172	
Cimon et al[196]	2000	Prospective	128		5/128	
Mastella et al[174]	2000	Prospective	12,447		967/12,447	
Taccetti et al[197]	2000	Prospective	3,089		191/3,089	
Ritz et al[180]	2005	Prospective	160	20/160	11/160	Serology
Skov et al[198]	2005	Retrospective	277		13/277	
Almeida et al[199]	2006	Prospective	32	11/32	2/32	Skin test
Kraemer et al[173]	2006	Prospective	122		16/122	
Chotirmall et al[190]	2008	Prospective	50		6/50	
Rapaka and Kolls[200]	2008	Retrospective	440		31/440	

Allergic Bronchopulmonary Aspergillosis
Clinical Features

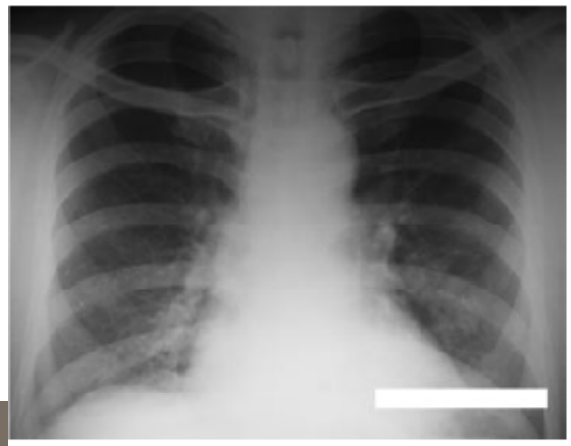
Clinical Features	Behera et al[19]/1994	Chakrabarti et al[21]/2002	Agarwal et al[23]/2007
Patients, No.	35	89	155
Male/female gender, No.	14/21	53/35	79/76
Mean age, yr	34.3	36.4	33.4
Mean duration of asthma, yr	11.1	12.1	8.9
History of asthma	94%	90%	100%
Expectoration of sputum plugs	Not available	69%	46.5%
Mean eosinophil count, per μL			1,264
AEC > 500/μL, %	12/28 (43%)	100%	76.1%
Fleeting shadows	77%	74%	40%
History of intake of antituberculous drugs	34%	29%	44.5%
Skin test against Aspergillus			
Type I	51%	85%	100%
Type III	25.7%	16.9%	83.2%
Mean IgE levels	Not done	Not done	6,434
Elevated IgE levels, %			100%
Aspergillus-specific IgE/IgG	Not done	Not done	100%
Serum precipitins against Aspergillus	57%	71.9%	86.5%
Central bronchiectasis	71%	69%	76.1%

Behera D et al. Indian J Chest Dis Allied Sci 1994; 36:173–179
Chakrabarti A et al. Mycoses 2002; 45:295–299
Agarwal R et al. Chest 2007; 132:1183–1190

1. Chest radiographic findings
   - Transient changes
     - Common
       - Patchy areas of consolidation
       - Radiologic infiltrates: toothpaste and gloved finger shadows due to mucoid impaction in dilated bronchi
       - Collapse: lobar or segmental
     - Uncommon
       - Bronchial wall thickening: tramline shadows
       - Air-fluid levels from dilated central bronchi filled with fluid
       - Perihilar infiltrates simulating adenopathy
       - Massive consolidation: unilateral or bilateral
       - Small nodules
       - Pleural effusions
   - Permanent changes
     - Common
       - Parallel-line shadows representing bronchial widening
       - Ring-shadows 1–2 cm in diameter representing dilated bronchi en face
       - Pulmonary fibrosis: fibrotic scarred upper lobes with cavitation
     - Uncommon
       - Pleural thickening
       - Mycetoma formation
       - Linear scars



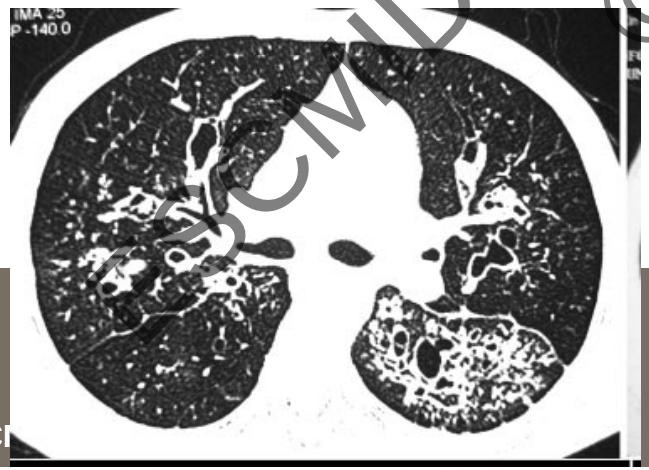
transient pulmonary opacities
in the right lower lobe
before and after treatment

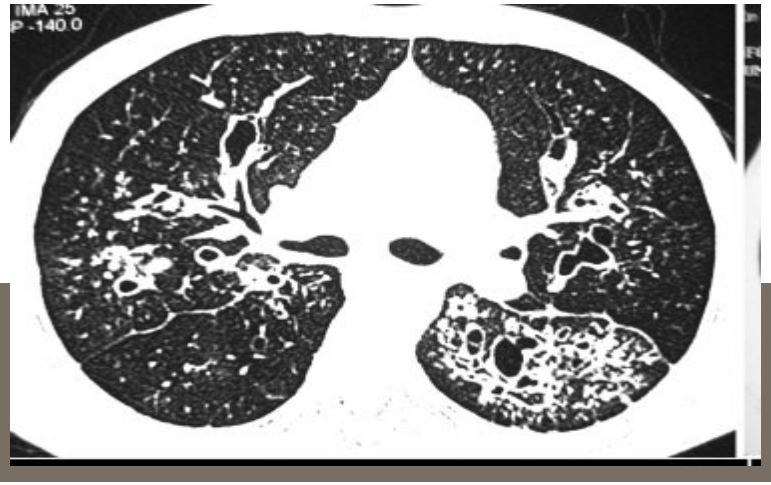


Allergic Bronchopulmonary Aspergillosis
HRCT Findings

Common
- Central bronchiectasis
- Mucus plugging with bronchoceles
- Consolidation
- Centrilobular nodules with tree-in-bud opacities
- Bronchial wall thickening
- Areas of atelectasis
- Mosaic perfusion with air trapping on expiration

Uncommon
- High-attenuation mucus (finding most helpful in differential diagnosis)
- Pleural involvement
- Randomly scattered nodular opacities





Laboratory and Pulmonary Function Tests

- ***Serum Precipitins Against* A fumigatus**
  - **The precipitating IgG antibodies are elicited from crude extracts of *A fumigatus* and can be demonstrated using the double gel diffusion technique**
  - **Problem: Also be present in other pulmonary disorders and thus represent supportive not diagnostic evidence forABPA**
- ***Peripheral Eosinophilia***
  - **A blood absolute eosinophil count > 1,000 cells/L is a major criterion for the diagnosis of ABPA.**
  - **Problem: Half of the patients without eosinophilia. A low eosinophil count does not exclude the diagnosis of ABPA**
- ***Sputum Cultures for* A fumigatus**
  - **Problem: A. fumigatus can also be grown in patients with other pulmonary diseases due to the ubiquitous nature of the fungi**
- ***Role of Specific Aspergillus Antigens***
  - **Problem: Lack of reproducibility and consistency and cross-reactivity with other antigens.**
  - **Recombinant allergens Asp f1, Asp f2, Asp f3, Asp f4, and Asp f6 may be promising in the diagnosis of ABPA**
- ***Pulmonary Function Test:***
  - **Help to categorize the severity of the lung disease but have no diagnostic value in ABPA**
  - **Usual finding is an obstructive defect of varying severity**

Allergic Bronchopulmonary Aspergillosis Rosenberg-Patterson Diagnostic Criteria

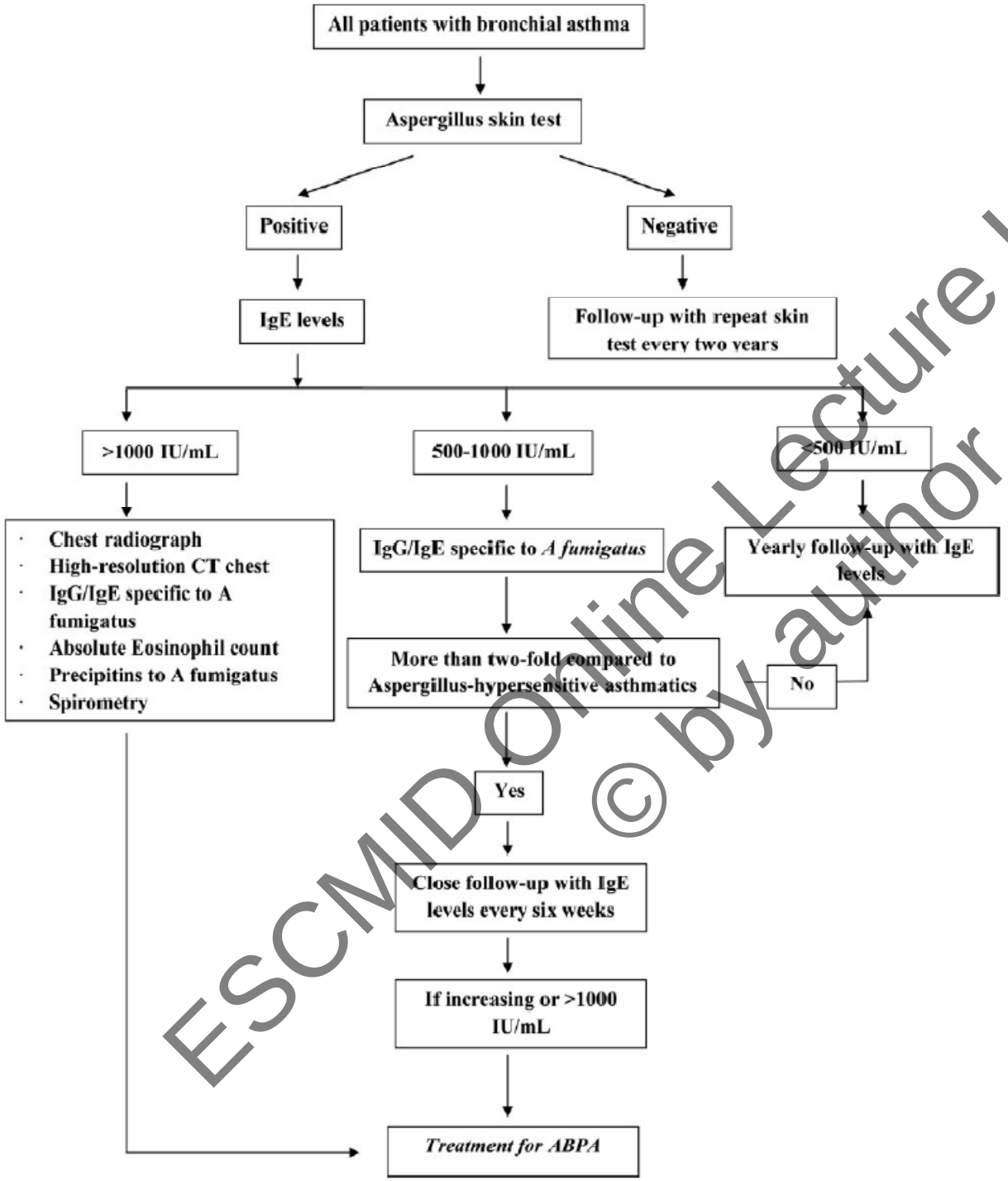
- **Major criteria (ARTEPICS)**
  - **A Asthma**
  - **R Roentgenographic fleeting pulmonary opacities**
  - **T Skin test positive for Aspergillus (type I reaction, immediate cutaneous hyperreactivity)**
  - **E Eosinophilia**
  - **P Precipitating antibodies (IgG) in serum**
  - **I IgE in serum elevated (1,000 IU/mL)**
  - **C Central bronchiectasis**
  - **S Serums *A fumigatus*-specific IgG and IgE (more than twice the value of pooled serum samples from patients with asthma who have Aspergillus hypersensitivity)**
- **Minor criteria**
  - **Presence of Aspergillus in sputum**
  - **Expectoration of brownish black mucus plugs**
  - **Delayed skin reaction to Aspergillus antigen (type III reaction)**
- **Six of eight major criteria makes the diagnosis almost certain**
- **ABPA-S or**
  - **the absence of central bronchiectasis**
- **ABPA-CB**
  - **The presence of central bronchiectasis**

Allergic Bronchopulmonary Aspergillosis Minimal Diagnostic Criteria

Rosenberg M, Patterson R et al. Ann Intern Med 1977; 86:405–414

- **Minimal ABPA-CB**
  - **Asthma**
  - **Immediate cutaneous hyperreactivity to Aspergillus antigens**
  - **Central bronchiectasis**
  - **Elevated IgE**
  - **Raised *A fumigatus*-specific IgG and IgE**
- **Minimal ABPA-S**
  - **Asthma**
  - **Immediate cutaneous hyperreactivity to Aspergillus antigens**
  - **Transient pulmonary infiltrates on chest radiograph**

Algorithm followed in the diagnostic workup for ABPA



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Allergic Bronchopulmonary Aspergillosis Diagnostic Criteria in CF

- **Classic Diagnostic Criteria**
  - **Acute or subacute clinical deterioration (cough, wheeze, and other pulmonary symptoms) not explained by another etiology**
  - **IgE in serum elevated (1,000 IU/mL)**
  - **Immediate cutaneous reactivity to Aspergillus or presence of serum IgE antibody to *A fumigatus***
  - **Precipitating antibodies to *A fumigatus* or serum IgG antibodyto *A fumigatus***
  - **New or recent abnormalities on chest radiograph or chest CT scan that have not cleared with antibiotics and standard physiotherapy Classic diagnostic criteria**

Stevens DA et al. Clin Infect Dis 2003; 37(suppl):S225–S264

Allergic Bronchopulmonary Aspergillosis Diagnostic Criteria in CF

- **Minimal diagnostic criteria**
  - **Acute or subacute clinical deterioration (cough, wheeze, andother pulmonary symptoms) not explained by another etiology**
  - **Total serum IgE levels 500 IU/mL. If total IgE level is 200–500 IU/mL, repeat testing in 1–3 mo is recommended**
  - **Immediate cutaneous reactivity to Aspergillus or presence of serum IgE antibody to *A fumigatus***
  - **One of the following:**
    - **precipitins to *A fumigatus* or demonstration of IgG antibody to *A fumigatus*; or**
    - **new or recent abnormalities on chest radiography (on chest radiography or chest CT scan that have not cleared with antibiotics and standard physiotherapy)**

Stevens DA et al. Clin Infect Dis 2003; 37(suppl):S225–S264

Allergic Bronchopulmonary Aspergillosis Staging

Stage	Description	Clinical Picture	Radiologic Findings	Immunologic Features
I	Acute phase	Usually symptomatic, fever, weight loss, wheeze	Normal or presence of radiologic opacities	IgE > 1,000 IU/mL, raised specific IgG/IgE and precipitins to *A fumigatus*
II	Remission	Asymptomatic	Generally normal or significant resolution of radiologic opacities from the acute phase	Usually 35–50% decline in IgE levels by 6 wk to 3 mo; we give additional label of "complete remission" if the patient did not have any additional ABPA exacerbations over the next 3 mo after stopping steroid therapy
III	Exacerbation	Symptomatic as in acute phase	Transient or fixed pulmonary opacities	Doubling of IgE levels from baseline
IV	Glucocorticoid-dependent ABPA	Symptomatic	Transient or fixed pulmonary opacities	Two groups can be identified: one in whom IgE levels do not rise but require steroids for asthma control (glucocorticoid-dependent asthma); the other in whom steroids are required to continually suppress the disease activity (glucocorticoid-dependent ABPA)
V	End-stage (fibrotic) ABPA	Symptomatic, findings of fixed airway obstruction, severe pulmonary dysfunction, type II respiratory failure, cor pulmonale	Evidence of bronchiectasis, pulmonary fibrosis, pulmonary hypertension	Serum IgE levels and specific immunoglobulins do not become normal in most patients, and even these patients can have frequent exacerbations

Agarwal R et al. Chest 2006; 130:442–448

Allergic Bronchopulmonary Aspergillosis Therapy

- **Oral glucocorticoids**
  - **Regime 1 (Greenberger PA. J Allergy Clin Immunol 2002; 110:685– 692)**
    - **Prednisolone, 0.5 mg/kg/d, for 1–2 wk, then on alternate days for 6–8 wk**
    - **Taper by 5–10 mg every 2 wk and discontinue**
    - **Repeat the total serum IgE concentration and chest radiograph in 6 to 8 wk**
  - **Regime 2 (Agarwal R et al. Chest 2006; 130:442–448)**
    - **Prednisolone, 0.75 mg/kg, for 6 wk, 0.5 mg/kg for 6 wk**
    - **Taper by 5 mg every 6 wk to continue for a total duration of at least 6 to 12 mo**
    - **Total IgE levels are repeated every 6 to 8 wk for 1 yr to determine the baseline IgE concentrations**

- **Follow-up and monitoring**
  - **Medical history and physical examination, chest radiograph, and measurement of total IgE levels every 6 wk**
    - **A 35% decline in IgE level signifies satisfactory response to therapy**
    - **Doubling of the baseline IgE value can signify a silent ABPA exacerbation**

- **If the patient cannot be tapered off prednisolone, the disease has evolved into stage IV.**
  - **Management should be attempted with alternate-day prednisone with the least possible dose**
  - **Prophylaxis for osteoporosis: oral calcium and bisphosphonates**
  - **Oral itraconazole**
    - **Dose: 200 mg bid for 16 wk then once a day for 16 wk**

Allergic Bronchopulmonary Aspergillosis Therapy

- ***Inhaled Corticosteroids (ICS)***
  - **Small case studies suggest some benefit of ICS**
  - **a double-blind multicenter placebo-controlled trial in 32 patients suggested no superiority over placebo**
  - **use ICS only for the control of asthma once the oral prednisolone dose is reduced to 10 mg/day**

Report to the Research Committee of the British Thoracic Association. Br J Dis Chest 1979; 73:349–356

Allergic Bronchopulmonary Aspergillosis
Alternative Therapies

- **Antifungal Therapy**
  - **Inhaled amphotericin**
  - **Voriconazole**
- **Anti IgE Therapy**
  - **Omalizumab**