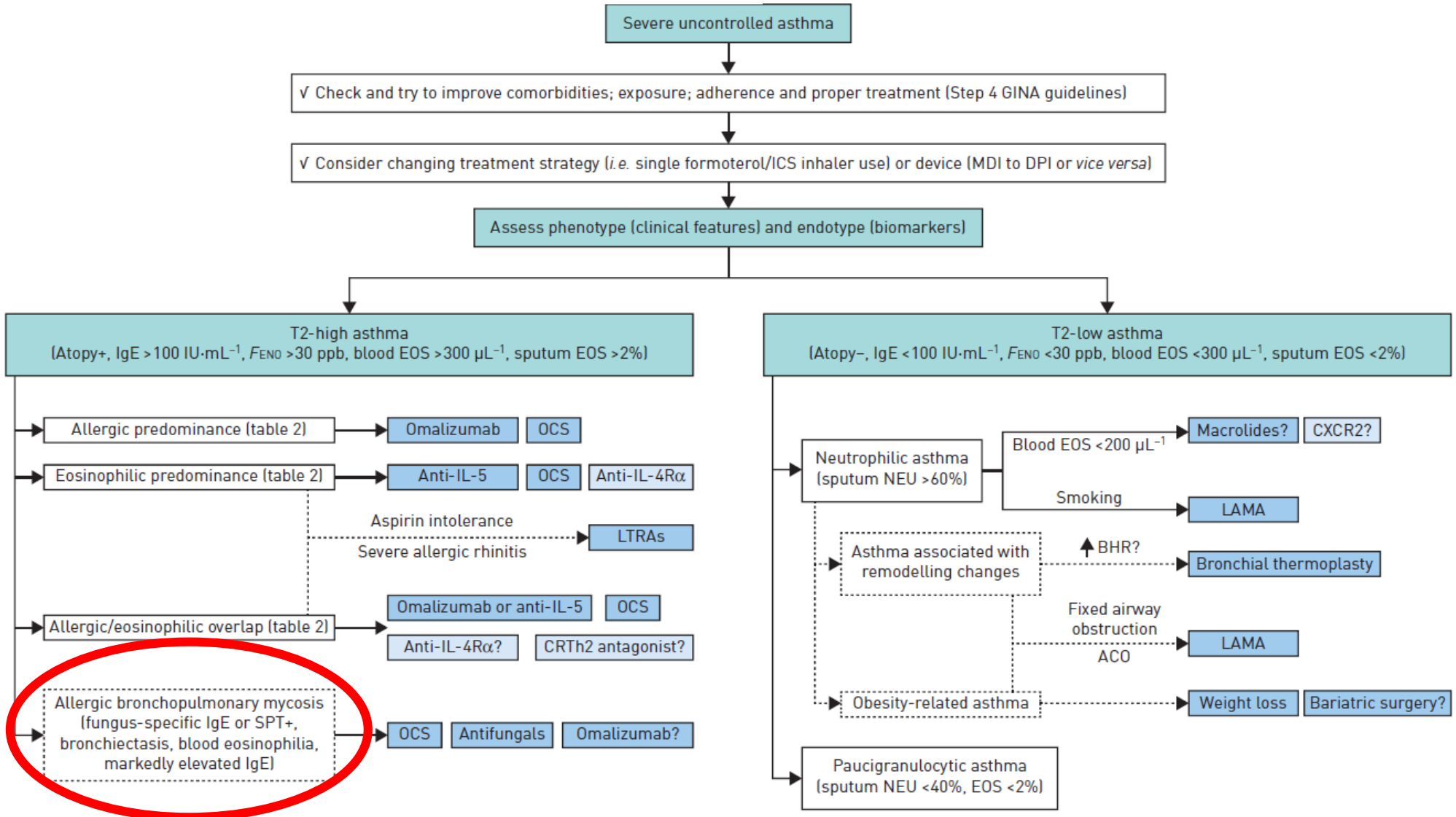
ΕΛΛΗΝΙΚΗ ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC THORACIC SOCIETY
ΟΜΑΔΑ ΑΣΘΜΑΤΟΣ
ASTHMA WORKING GROUP

Σοβαρό άσθμα και Αλλεργική Βρογχοπνευμονική Μυκητίαση

Βιττωράκης Στυλιανός

An algorithmic approach for the treatment of severe uncontrolled asthma

Eleftherios Zervas[1], Konstantinos Samitas[1], Andriana I. Papaioannou[2], Petros Bakakos[3], Stelios Loukides[2] and Mina Gaga[1]



Thorax (1952), 7, 317.

BRONCHO-PULMONARY ASPERGILLOSIS*

A REVIEW AND A REPORT OF EIGHT NEW CASES

BY

K. F. W. HINSON, A. J. MOON, AND N. S. PLUMMER

From the London Chest Hospital

(RECEIVED FOR PUBLICATION APRIL 4, 1952)

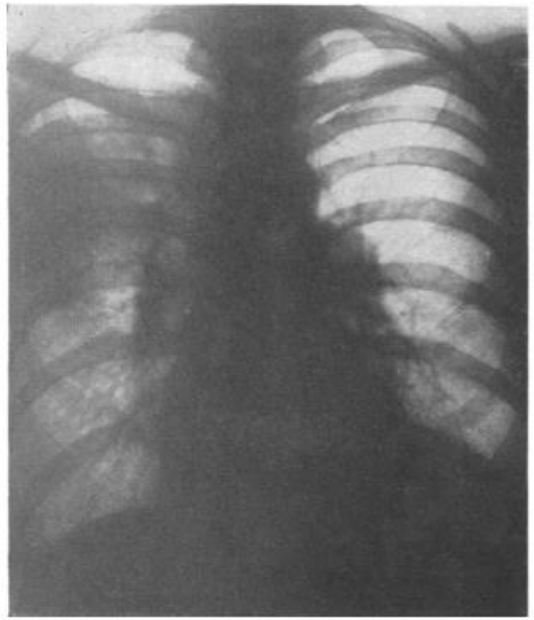


FIG. 13.—Case 6: consolidation in the right upper lobe (20.10.47).

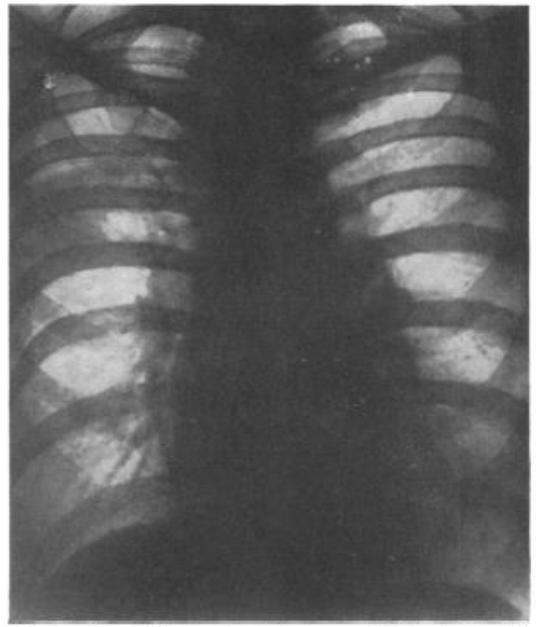


FIG. 14.—Case 6: three weeks later the consolidation has almost resolved (12.11.47).

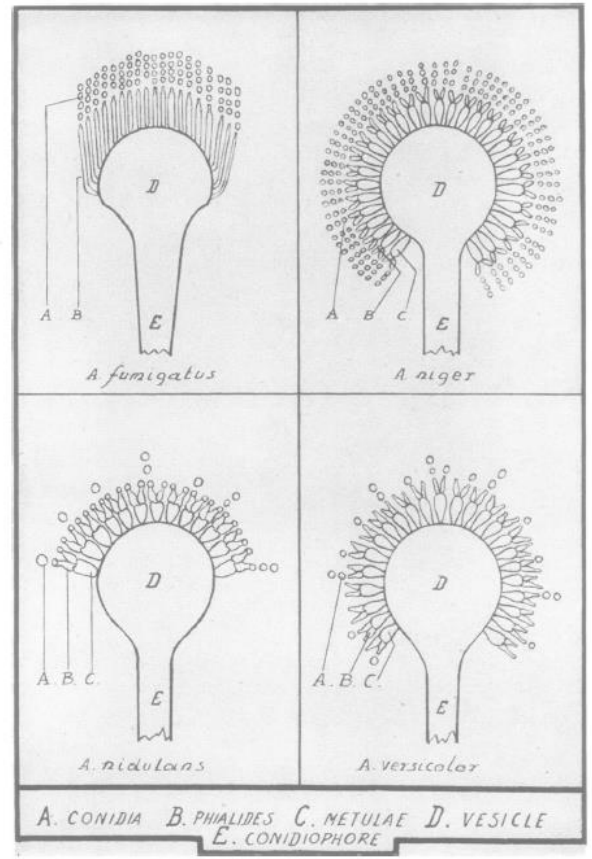


FIG. 1.—Diagram showing morphological differences between strains of the fungus *Aspergillus*.

FIG. 2.—A sputum plug from Case 7 separated for display.

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Aspergillus fumigatus

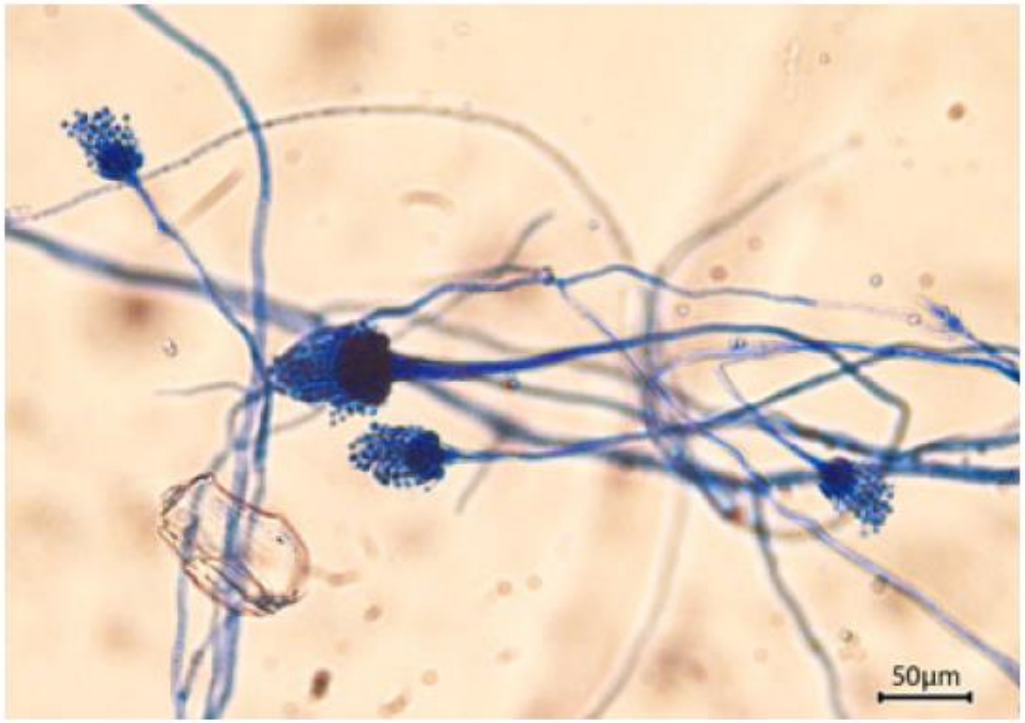


Fig. 1. Photomicrograph of *Aspergillus fumigatus* under lactophenol cotton blue mount (100×).

- Spore forming fungi
- Thermophilic, survival at temperatures up to 70°C
- Soil, compost, garbage collection, water damaged structures, damp basements, barns, sewage treatment facilities
- The spores are dispersed by wind in the atmosphere
- Inhalation is unavoidable
- Size of spores: 3-5µm (reach lower airways)

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013

Aspergillus associated respiratory disorders

Table 1. *Aspergillus*-associated respiratory disorders[1,2]

I. Upper respiratory tract
- 1. Allergic aspergillosis
  - Allergic *Aspergillus* sinusitis (AAS)
- 2. Saprophytic colonisation
  - Sinus fungal balls
- 3. Invasive disease
  - Acute fulminant invasive sinusitis
  - Chronic invasive sinusitis
  - Granulomatous invasive sinusitis

II. Lower respiratory tract
- 1. Allergic aspergillosis
  - (IgE mediated) *Aspergillus* induced asthma (AIA)
  - Allergic bronchopulmonary aspergillosis (ABPA)
  - Hypersensitvity pneumonitis
- 2. Saprophytic colonisation
  - Aspergilloma
    - simple
    - complex (chronic cavitary pulmonary aspergillosis)
- 3. Invasive disease
  - Invasive pulmonary aspergillosis
    - acute
    - subacute (chronic necrotising pulmonary aspergillosis)

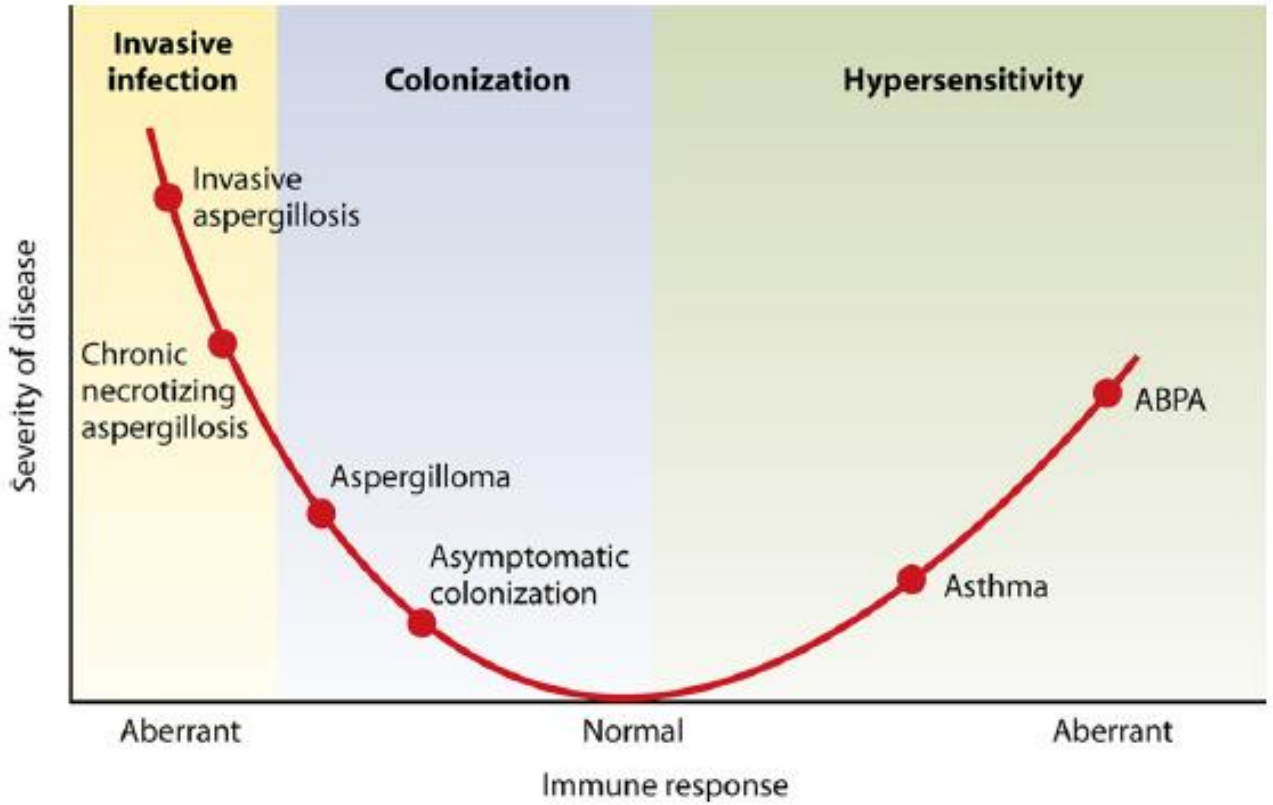


FIG. 1. Diagrammatic representation of diseases attributed to *Aspergillus* species as a function of the host's immune response. ABPA, allergic bronchopulmonary aspergillosis.

Park, Mehrad CLINICAL MICROBIOLOGY REVIEWS 2009,A.Shah Allergy Asthma Immunol Res 2016

Aspergillus Induced Asthma-AIA

- ✓**Asthma** + **hypersensitivity to Aspergillus** *(*Aspergillus Sensitization-AS)
- ✓SPTs or elevated s.IgE levels
- ✓Exclusion of ABPA
- ✓16% to 38% in different geographical regions -pooled prevalence **of 25%**

- ➢identification of Aspergillus Sensitization (AS) is important as it is associated with higher rates of bronchiectasis and severe asthma

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013

Aspergillus Induced Asthma-AIA

Table 4—*Comparison of Specific Investigations of All Groups

Variables	Group A (n = 26)	Group B (n = 26)	Group C (n = 49)	Group D (n = 22)	Group E (n = 8)	p Value
TLC, cells/μL						E vs B, < 0.005; E vs C, < 0.05; E vs D, < 0.0168
Range	5,900–9,900	4,400–12,600	3,500–13,100	6,500–13,000	5,800–19,000	
Mean ± SD	7,300 ± 1,400	7,870 ± 1,948	8,154 ± 1,951	8,500 ± 1,400	1,000 ± 4,100	
AEC, cells/μL						E vs B, E vs C, E vs D, < 0.05; D vs B, D vs C, < 0.0001
Range	80–300	190–2,210	110–3,720	240–1,900	800–2,300	
Mean ± SD	250 ± 61	1,500 ± 690	2,599 ± 895	11,300 ± 450	1,400 ± 595	
PFT						
Disease, No. (%)						E vs BCD, < 0.05
Mild		18 (69.2%)	28 (57.1%)	11 (50%)	3 (38%)	
Moderate		6 (23%)	12 (24.4%)	8 (36.3%)	1 (12.5%)	
Severe		2 (7.69%)	9 (18.3%)	3 (13.7%)	4 (50%)	
FEV_1, L						
Range	2.8–4.4	1.12–4.0	0.56–4.3	1.4–4.6	0.89–4.6	
Mean ± SD	3.6 ± 0.54	2.46 ± 0.73	2.4 ± 0.8	2.6 ± 0.97	2.1 ± 0.87	
FVC, L						
Range	3.3–4.9	2.14–4.46	1.49–4.9	2.2–5.0	2.4–4.4	
Mean ± SD	4.2 ± 0.57	3.23 ± 0.7	3.2 ± 0.8	3.5 ± 0.89	3.2 ± 0.72	
PEFR, L/s						
Range	7.6–12	2.61–10.4	1.58–12.12	3.5–10	1.4–8.4	
Mean ± SD	11 ± 1.6	6.19 ± 2.1	5.8 ± 2.4	6.2 ± 1.8	5.3 ± 2.6	
Serum total IgE, IU/mL						E vs B, E vs C, E vs D, < 0.05; D vs B, D vs C, < 0.05
Range	17.27–155.50	17.27–2,195	17.27–2,057	17.27–2,471.83	1,676.62–2,489.11	
Mean ± SD	72.55 ± 51.38	1,063.56 ± 585.63	1,052 ± 580.30	1,532 ± 432.56	1,987.78 ± 319.42	

*PFT, pulmonary function test; PEFR = peak expiratory flow rate.

105 asthmatic patients

- B: asthmatic subjects, SPTs-
- C: asthmatic subjects , SPTs +, Aspergillus Ag –
- D: SPTs +, Aspergillus Ag +
- E: ABPA (Aspergillus Ag +)

105 patients with bronchial asthma:

28.5% (30) sensitized to Aspergillus antigens = more severe form of asthma

- Higher mean duration of illness (p,0.001),
- Higher mean eosinophil count (p,0.0001),
- Higher mean total IgE (p,0.05)
- More usage of oral corticosteroids per year (p,0.004).
- increased incidence of bronchiectasis

Maurya et al, Chest 2015

Sensitization to moulds and asthma severity

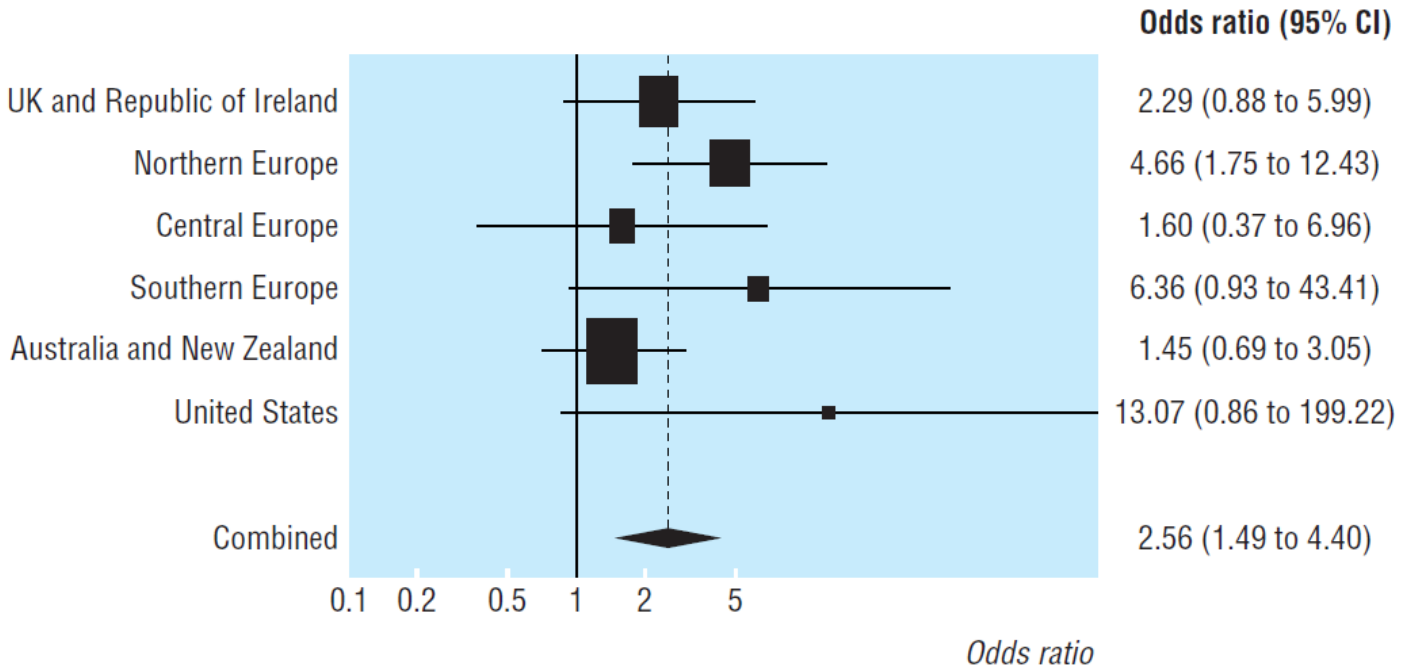


Fig 2 Multivariable adjusted odds ratios (95% confidence interval) for association of severe versus mild asthma with sensitisation to moulds (either *Alternaria alternata* or *Cladosporium herbarum*, or both) by region (adjusted within region for age, sex, smoking habits, passive smoking, and parental history of asthma) with combined odds ratio from model with region included as random effect

Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey

Mahmoud Zureik, Catherine Neukirch, Bénédicte Leynaert, Renata Liard, Jean Bousquet, Françoise Neukirch, on behalf of the European Community Respiratory Health Survey

- ✓ The frequency of sensitisation to moulds (Alternaria alternata or Cladosporium herbarum or both) increased significantly with increasing asthma severity
- ✓ odds ratio 2.56 for severe vs mild asthma

Mahmoud Zureik et al, BMJ 2002

Severe asthma with fungal sensitization (SAFS) – Diagnostic Criteria

TABLE 2 Definition of allergic bronchopulmonary aspergillosis (ABPA) and proposed definition of severe asthma with fungal sensitisation (SAFS), with some additional features

Feature	ABPA[#]	SAFS (proposed)
Clinical features		
Asthma	Any severity	Severe[¶]
Pulmonary infiltrates (history)	Yes, which resolve with corticosteroids	No
Eosinophilia	Yes, if not on systemic corticosteroids	Not studied, but not required
Central bronchiectasis	Yes, but many patients with early disease do not have this feature	No
Thick mucous plugs	Yes, usually	Unknown
Chronic rhinosinusitis, with or without nasal polyps	Occasional	Sometimes
Fungal features		
Aspergillus precipitins positive (2× asthma control)	Yes (almost all cases)	No
Aspergillus IgG test positive (2× asthma control)	Yes	No
Aspergillus prick test positive (>3 mm)	Yes	Yes or no[+]
Other fungal skin tests positive (>3 mm)	No[§]	Yes or no[+]
Serum IgE elevated (>1000 IU·mL^{-1})	Yes (may be only >500 IU·mL^{-1}, especially if on corticosteroids)	No (<1000 IU·mL^{-1})
Aspergillus-specific RAST test positive (2× asthma control)	Yes	Yes or no[+]
Other fungal RAST test positive	No[§]	Yes or no[+]
Airways colonised by *Aspergillus fumigatus*	Yes	Unknown

Ig: immunoglobulin; RAST: radioallergosorbent test. [#]: as defined by RICKETTI *et al*. [126] and PATTERSON *et al*. [127]; [¶]: typically British Thoracic Society level 4 or equivalent; [+]: at least one fungal skin or RAST test positive (better and more specific tests may emerge in the future); [§]: there are rare instances of bronchopulmonary mycosis due to other fungi, with typical clinical features.

1) severe (poorly controlled) asthma

2) a positive skin-prick test result for fungi or antifungal IgE>0.4 kU/L(not necessarily to Aspergillus species)

3) a total IgE <1000 kU/L , no bronchiectasis, no mucous plugging (exclusion of ABPA)

D.W. Denning et al, Eur Respir J 2006

Allergic Bronchopulmonary Aspergillosis (ABPA)- Pathogenesis

- Predominantly affects patients with asthma and cystic fibrosis
- airway colonisation in susceptible hosts that elicits an allergic response.
  - Mainly type I (IgE-mediated hypersensitivity)
  - **Tissue invasion does not occur**

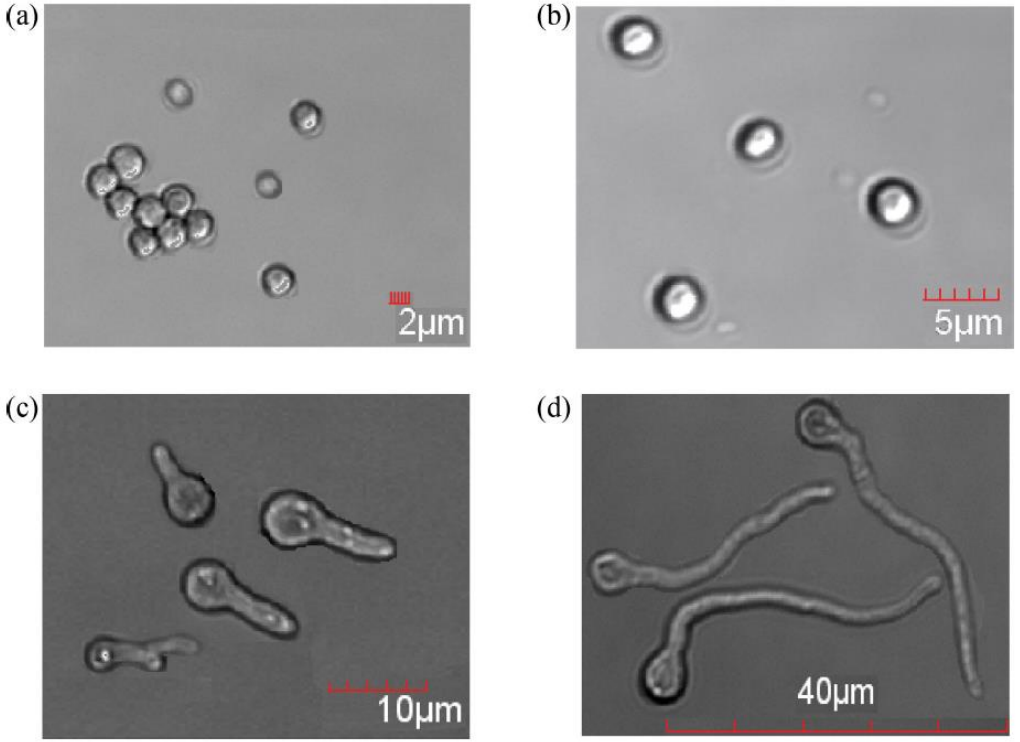


Figure 3. The differing morphological stages of *A. fumigatus* growth; as time proceeds, resting conidia (3a) begin to swell (3b) and germinate (3c), eventually forming hyphae (3d). [*A. fumigatus* conidia (1×10^7 ml) were added to minimal essential medium (Sigma) supplemented with 5% fetal calf serum and incubated at 37°C. A 1 ml aliquot was withdrawn at the times indicated, diluted in ice cold PBS to halt any further development and representative images were captured using an Olympus BX51 Colorview sodt imaging system].

a) Resting conidia

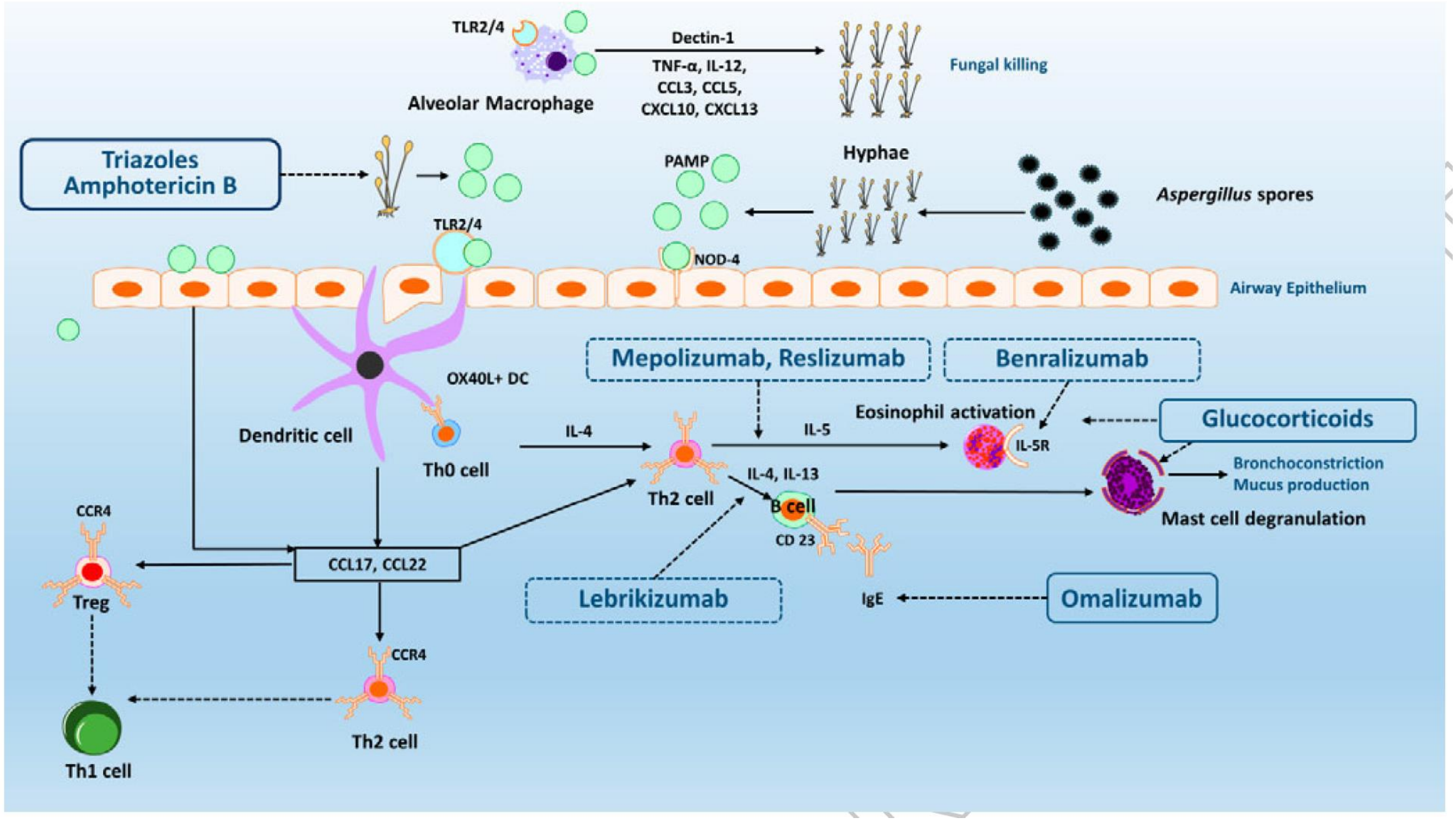
b) Swelling of conidia

c) Germination

d) Hyphae formation

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013

Allergic Bronchopulmonary Aspergillosis (ABPA)- Immune response



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Allergic Bronchopulmonary Aspergillosis (ABPA)- Pathogenesis

HLA/DR

MBL

SPA2

TLR-9

IL-4Ra/10

TGF-β

Table 2. Genetic susceptibility in allergic bronchopulmonary aspergillosis (ABPA) complicating asthma and cystic fibrosis (CF)

Mutations/ polymorphisms	Population	Number of patients	Control population	Significance OR (95% confidence intervals)	Author/reference
HLA (6p21.3)					
DR4	Caucasian	16 ABPA (asthma)	56 allergy; 39 controls	Allergy: 0.9 (0.3–2.9), $P = 0.9$; Control: 22.8 (2.5–211.8), $P = 0.002$	Aron et al. [49]
DR5	Caucasian	16 ABPA (asthma)	56 allergy; 39 controls	Control: 5.3 (1.4–20.7), $P = 0.02$	Aron et al. [49]
	Caucasian	35 ABPA (asthma and CF)	50 Af sensitized asthma/CF; 98 controls	Asthma: 1.8 (0.7–4.9), $P = 0.2$; Control: 2.8 (1.1–6.8), $P = 0.03$	Chauhan et al. [50]
DR7	Caucasian	16 ABPA (asthma)	56 allergy; 39 controls	Allergy: 1.7 (0.5–5.7), $P = 0.4$; Control: 35 (1.8–691.4), $P = 0.004$	Aron et al. [49]
DR2	Caucasian	35 ABPA (both asthma and CF related)	50 Af sensitized asthma or CF; 98 controls	Asthma: 4.9 (1.8–13.6), $P = 0.001$ Control: 3.7 (1.6–8.4), $P = 0.001$	Chauhan et al. [50]
DR2/DR5	Caucasian	35 ABPA (both asthma and CF related)	50 Af sensitized asthma or CF; 98 controls	Asthma: 5.1 (1.9–13.3), $P = 0.0005$; Control: 5.4 (2.3–12.9), $P < 0.0001$	Chauhan et al. [50]
DRB1*1501	Caucasian	35 ABPA (both asthma and CF related)	50 Af sensitized asthma or CF; 98 controls	Asthma: 3.1 (0.9–10.3), $P = 0.05$ Control: 4.5 (2.1–9.7), $P = 0.0001$	Chauhan et al. [50]
DRB1*1503	Caucasian	35 ABPA (both asthma and CF related)	50 Af sensitized asthma or CF; 98 controls	Asthma: 24.8 (1.4–452.7), $P = 0.008$ Control: 37.5 (4.4–316.8), $P < 0.0001$	Chauhan et al. [50]
DRB1*0701, DRB1*1501, DQB1*0602, DQB1*0201	Caucasian	38 ABPA (CF)	46 CF, 306 asthma, 176 controls	DRB1*0701, DRB1*1501, DQB1*0602 associated with ABPA susceptibility, while DQB1*0201 associated with possible protection	Muro et al. [64]
Mannose-binding lectin (10q11.2–q21)					
G1011A in intron 1	Indian	11 ABPA (asthma)	49 allergic individuals; 84 controls	Allergy: 1.2 (0.5–3.3), $P = 0.7$ Control: 8.2 (2.8–23.4), $P < 0.0001$	Kaur et al. [60]
Exon 1 (R52C, G54D, G57E), Promoter (H/L -550, Y/X -221, P/Q + 4)	Caucasian	38 allergic fungal disease (28 ABPA, 7 SAFS, 3 NOS)	Historical controls	No significant relationship, $P > 0.05$	Harrison et al. [61]
Surfactant Protein A2 (10q22.3)					
G1649C in exon 4	Indian	32 ABPA (asthma)	34 controls	2.6 (1.2–5.7), $P = 0.01$	Saxena (2003)[53]
	Caucasian	7 ABPA (asthma)	46 controls	2.7 (0.3–21.9), $P = 0.6$	Vaid (2007)[58]
T1492C in intron 3	Indian	32 ABPA (asthma)	34 controls	4.8 (1.1–21.6), $P = 0.03$	Saxena (2003)[53]
	Caucasian	7 ABPA (asthma)	46 controls	3.5 (0.7–16.7), $P = 0.2$	Vaid (2007)[58]
A1660G in exon 4	Indian	27 ABPA, 119 Af colonizers	–	5.3 (1.7–16.9), 0.002	Saxena et al. [53]
Toll-like receptor 9 (3p21.3)					
T1237C in 5′ promoter	Caucasian	22 ABPA (asthma)	14 SAFS, 80 controls	SAFS: 6.9 (0.8–58.2), $P = 0.09$; Control:2.5 (1.01–6.1), $P = 0.04$	Carvalho et al. [59]

(continued)

Table 2 (continued)

Mutations/ polymorphisms	Population	Number of patients	Control population	Significance OR (95% confidence intervals)	Author/reference
IL-4Rα (16p12.1–p11.2)					
−4G>A (Ile75val) in promoter	Caucasian	40 ABPA (14 asthma, 26 CF)	56 non-ABPA (23 asthma, 33 CF)	3.3 (1.8–6.1), $P = 0.008$	Knutsen et al. [56]
IL-10 (13q13)					
−1082 G>A in promoter	Caucasian	27 ABPA (CF)	351 CF	GG genotype: 1.67 (0.64–4.36); AG genotype: 0.43 (0.15–1.18)	Brouard et al. [54]
	Caucasian	9 ABPA	24 CCPA	0.38 (0.21–0.67), $P = 0.0006$	Sambatakou (2006) [57]
TGF-β (19q13.1, 13.2)					
T869C in exon 1	Caucasian	9 ABPA	24 CCPA	0.42 (0.24–0.75), $P = 0.003$	Sambatakou et al. [57]
CFTR mutations (7q31.2)					
	Caucasian	79 ABPA in asthma	268 controls 94 asthmatics	Control: 10.4 (4.4–24.8) Asthma: 5.5 (1.6–18.8)	Miller et al., Aron et al., Marchand et al., Eaton et al., Agarwal et al. [48, 49, 51, 52, 62]
CHIT1 gene (1q31–32)					
24 bp duplication in exon 10	NA	6 ABPA	–	All six children had 24 bp duplication	Vicencio et al. [63]

Af, *Aspergillus fumigatus*; CCPA, chronic cavitary pulmonary aspergillosis; CFTR, CF transmembrane conductance regulator; HLA, human leucocyte antigen; IL, interleukin; MBL, mannose-binding lectin; NOS, not otherwise specified; OR, odds ratio; SAFS, severe asthma with fungal sensitization; SNP, single nucleotide polymorphism; SP, surfactant protein; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumour necrosis factor.

Genetic susceptibility in ABPA complicating asthma and CF

(mutations/polymorphisms HLA/DR, MBL, SPA2, TLR-9, IL-4Ra, IL-10, TGF-β)

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013

Allergic Bronchopulmonary Aspergillosis (ABPA)- Epidemiology

Table 1. Prevalence of *Aspergillus* sensitization (AS) and allergic bronchopulmonary aspergillosis (ABPA) complicating asthma in studies conducted in this millennium

Study	Country	Type of study	Skin test/antigen	Prevalence of AS, n/N (%; 95% CI)	Prevalence of ABPA, n/N (%; 95% CI)
Eaton et al. [25]	New Zealand	Prospective	SPT/commercial (Hollister-Stier, USA)	47/255 (18.4; 14.1–23.7)	12/243 (4.9; 2.8–8.5)
Kumar et al. [30]	India	Prospective	Intradermal/indigenous	47/200 (23.5; 18.1–29.9)	32/200 (16; 11.5–21.8)
Al-Mobeireek et al. [26]	Saudi Arabia	Prospective	SPT/commercial (SoluPrick, ALK labs)	12/53 (22.6; 13.3–35.8)	7/264 (2.7; 1.3–5.5)*
Maurya et al. [31]	India	Prospective	Intradermal/indigenous	30/105 (28.6; 20.8–37.9)	8/105 (7.6; 3.9–14.5)
Agarwal et al. [32]	India	Prospective	Intradermal/commercial (Hollister-Stier)	291/755 (38.5; 35.1–42.1)	155/755 (20.5; 17.8–23.6)
Prasad et al. [33]	India	Prospective	Intradermal/not available	74/244 (30.3; 24.9–36.4)	18/244 (7.4; 4.7–11.4)
Agarwal et al. [34]	India	Prospective	Intradermal/indigenous	87/242 (35.9; 30.2–42.2)	54/242 (22.3; 17.5–28)
Ghosh et al. [35]	India	Prospective	Intradermal/indigenous	54/215 (25.1; 19.8–31.3)	15/215 (6.9; 4.2–11.2)
Sarkar et al. [36]	India	Prospective	SPT/commercial (Creative Drug Industries, India)	40/126 (31.7; 24.2–40.4)	10/126 (7.9; 4.3–14.1)*
Ma et al. [27]	China	Prospective	–	11/200 (5.5; 3.1–9.7)	5/200 (2.5; 1.0–5.9)
Pooled prevalence				25.1 (19.6–31.6)	8.4 (5.3–13.1)

*Allergic bronchopulmonary mycosis

- AS complicating asthma (AIA): 5.5% to 38.5% with a pooled prevalence **of 25%**
- ABPA in asthma ranges between 2.5 and 22.3% with a pooled prevalence **of 8.4%**

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013

Allergic Bronchopulmonary Aspergillosis (ABPA)- Clinical Features

- ✓ poorly controlled asthma
- ✓ golden-brown sputum (56%),
- ✓ peripheral eosinophilia

1/3 relatively asymptomatic despite extensive radiological lesions

<u>113 patients with ABPA</u>

mean age: 32 years,

mean age of onset of asthma :21 years.

- ✓ Cough (99%)
- ✓ Breathlessness (99%)
- ✓ Expectoration (98%)
- ✓ Wheezing (97%)
- ✓ Haemoptysis (41%)
- ✓ Nasal symptoms 45%
- ✓ Expectoration of sputum plugs 37%
- ✓ Nasal plugs by 6%

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013

Allergic Bronchopulmonary Aspergillosis (ABPA)- Clinical Features

Clinical features	Behera et al/1994	Chakrabati et al/2002	Agarwal et al/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%
Absolute EOS count>500/µL	12/28 (43%)	100%	76.1%
Fleeting shadows	77%	74%	40%
Skin test against Asp (type I)	51%	85%	100%
Elevated IgE levels			100%
Serum precipitins against Aspergillus	77%	71.9%	85.6%
Central bronchiectasis	71%	69%	76.1%

Agarwal, CHEST /135/3/ MARCH, 2009

Allergic Bronchopulmonary Aspergillosis (ABPA)- Diagnostic tests

- **Aspergillus Skin test:** is a surrogate marker for ABPA - was regarded as hallmark of ABPA
  - Sensitivity 88- 94%
  - *Should be replaced by Aspergillus s.IgE*

- **A.Fumigatus specific IgE:** are considered to be a hallmark of ABPA
  - level > 0.35 kUA/L sensitivity 100% (must be used as screening test) - specificity 66.2%
  - Unreliable for follow up of ABPA

- **Total Serum IgE:** diagnosis and follow up of ABPA
  - A normal serum IgE generally excludes active ABPA
  - The cut-off value remains speculative and needs validation
  - level > 1000IU/mL (2400ng/ml) (classic ABPA): sensitivity 39% - specificity 100%
  - The lowest value after treatment (clinical and radiological improvement) is a 'new' baseline for an individual.
  - An increasing level (>50% of the 'new' baseline) of total IgE along with clinical and radiological worsening =exacerbation of ABPA

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013/R.Agarwal Expert Review of Respiratory Medicine 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- Diagnostic tests

- **Serum precipitins or specific IgG to A.Fumigatus:**
  - 10% of asthmatics with or without SAFS
  - A.fumigatus-specific IgG (>27 mgA/L) is far more sensitive (89%) than Aspergillus precipitins (27%)

- **Peripheral eosinophilia:**
  - > 500 cells/µL – criterion for diagnosis of ABPA
  - only 40% of patients with ABPA > 1000 cells/lL at diagnosis
  - a low eosinophil count does not exclude ABPA

- **Sputum cultures for A. Fumigatus:**
  - supportive but not diagnostic of ABPA
  - 39 to 60% depending on the number of specimens examined
  - vast majority of culture-negative ABPA patients have detectable A. fumigatus DNA in their sputum
  - Susceptibility to antifungal agents

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013/R.Agarwal Expert Review of Respiratory Medicine 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- Diagnostic tests

- **Pulmonary function tests:**
  - helpful in categorizing the severity of asthma and the underlying lung disease.
  - can be normal in ABPA
  - normal spirometry should not exclude ABPA

- **Recombinant Aspergillus antigens:**
  - Asp f1,3 in AS and ABPA, Asp f3,4,6 in ABPA
  - 36-68% specificity

- **Galactomannan detection:**
  - Polysaccharide component of aspergillus cell wall
  - Sensitivity 25,7%
  - Specificity 82%

A.Shah, C. Panjabi, Eur Respir Rev 2014/ R.Agarwal et al Clin. Exp. All. 2013/R.Agarwal Expert Review of Respiratory Medicine 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation – Plain Chest Radiology

Plain chest radiology

Transient changes

- Perihilar infiltrates simulating adenopathy
- Air-fluid levels from dilated central bronchi filled with fluid and debris
- Massive consolidation-unilateral or bilateral
- Radiologic infiltrates
- 'Toothpaste' shadows due to mucoid impaction in damaged bronchi
- 'Gloved finger' shadows from distally occluded bronchi filled with secretions
- 'Tramline' shadows representing oedema of the bronchial walls
- Collapse-lobar or segmental

Permanent changes

- Central bronchiectasis with normal peripheral bronchi
- Parallel-line shadows representing bronchial widening
- Ring-shadows 1-2 cm in diameter representing dilated bronchi *en face*
- Pulmonary fibrosis
- Late changes-cavitation, contracted upper lobes and localised emphysema

R.Agarwal et al , Indian Journal of Radiology and Imaging / November 2011, Shah et al, Allergy Asthma Immunology Res 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation-Plain Chest Radiology

Consolidation
(transient patchy-91%)

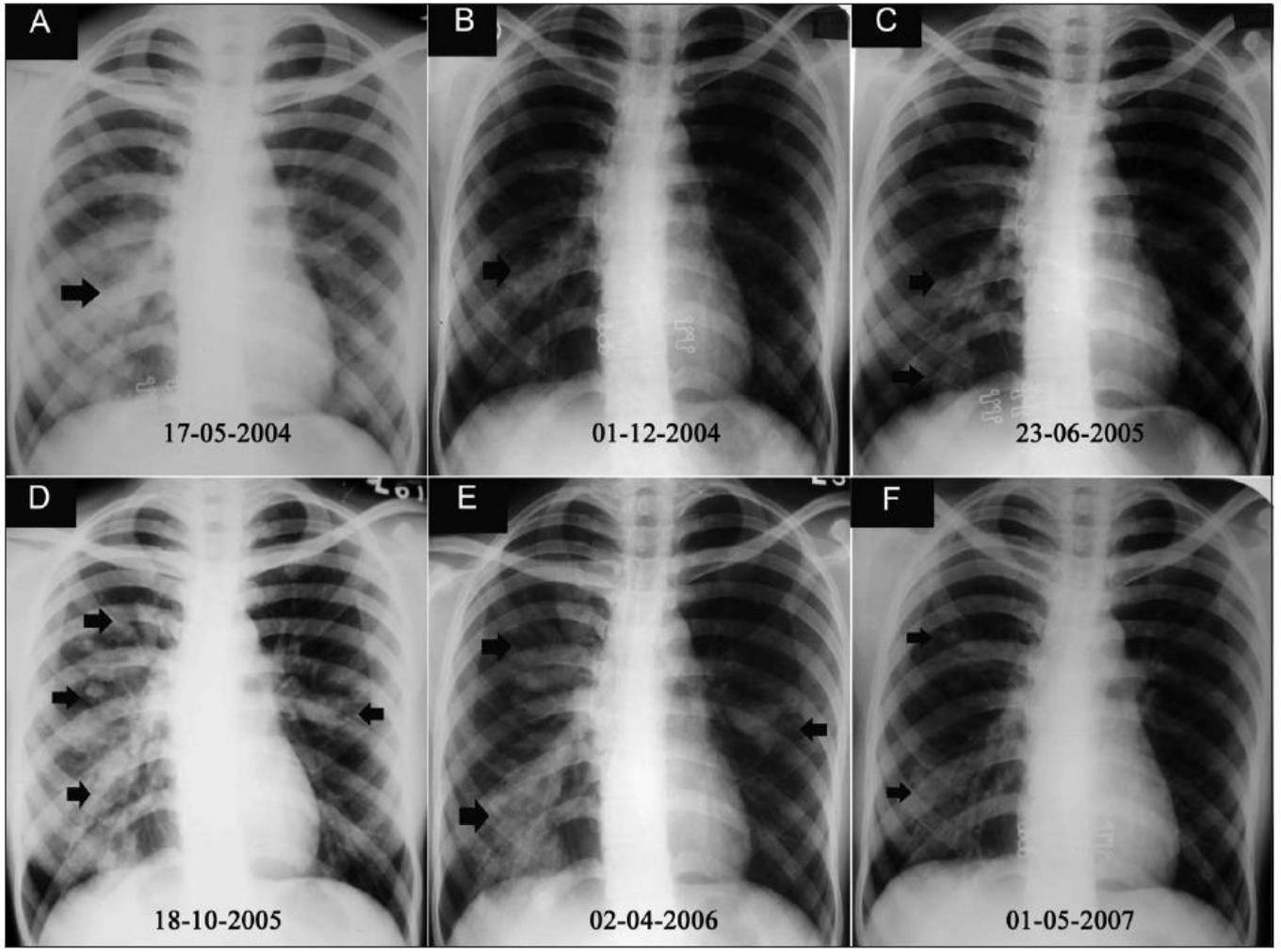

Figure 1 (A-F): Serial chest radiographs over 3 years in a patient of ABPA show typical fleeting opacities (arrows) involving different areas of the lung. The patient received multiple courses of antituberculous therapy without any relief of symptoms

R.Agarwal et al , Indian Journal of Radiology and Imaging / November 2011

Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation-Plain Chest Radiology

Y-shape and Finger-in-glove opacities (Mucoid impaction)

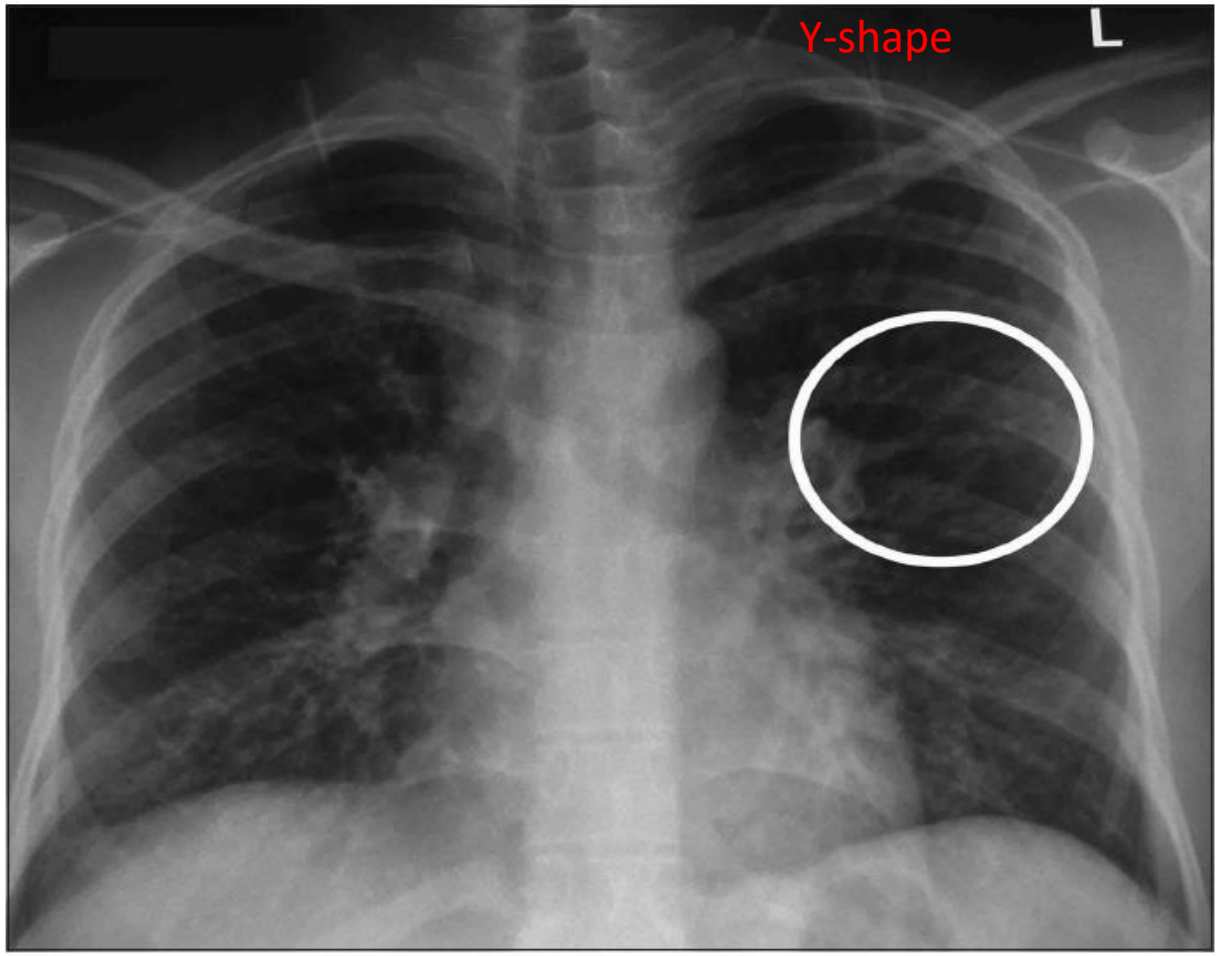

Figure 3: Chest radiograph shows a "Y-shaped" opacity (circle) that represent mucus-filled bronchi

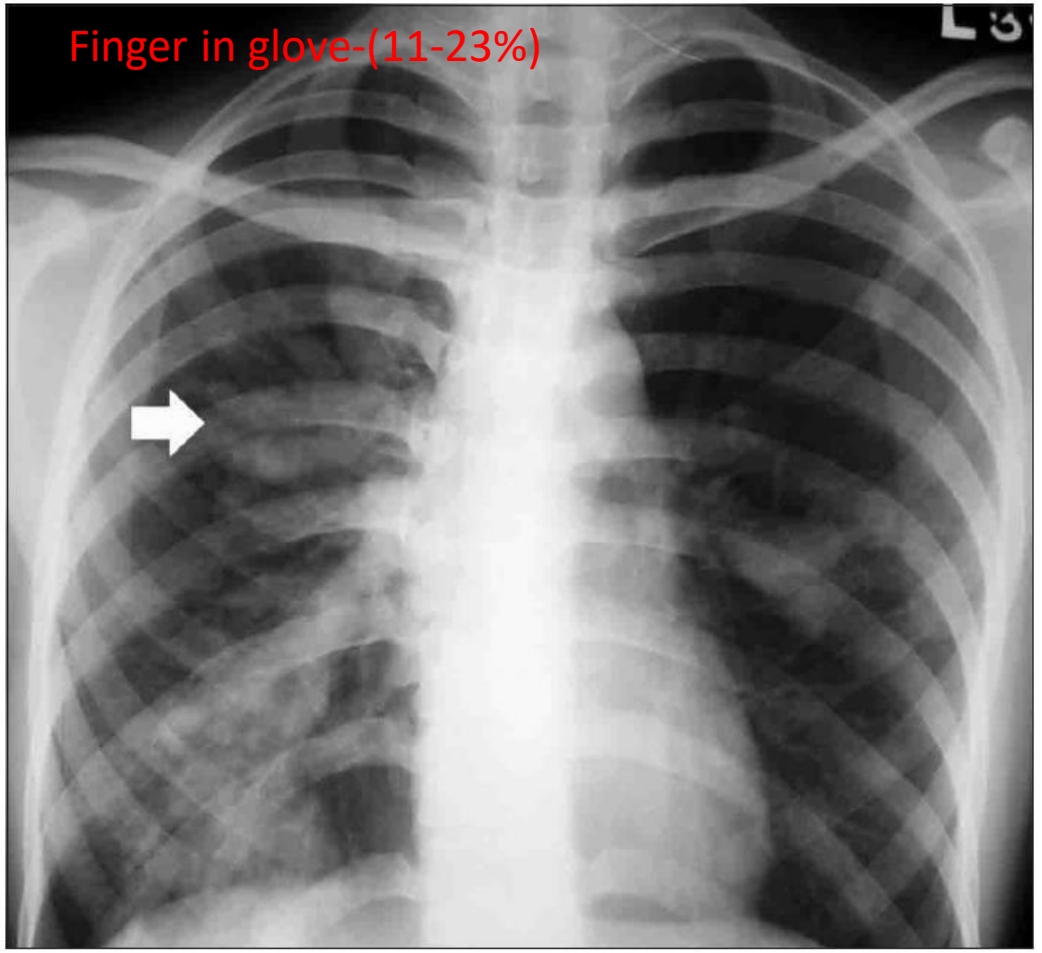

Figure 4: Chest radiograph shows mucoid impaction with the classic finger-in-glove pattern (arrow)

R.Agarwal et al , Indian Journal of Radiology and Imaging / November 2011

Allergic Bronchopulmonary Aspergillosis (ABPA)- **Radiological investigation**-Plain Chest Radiology

Atelectasis (14-39%)

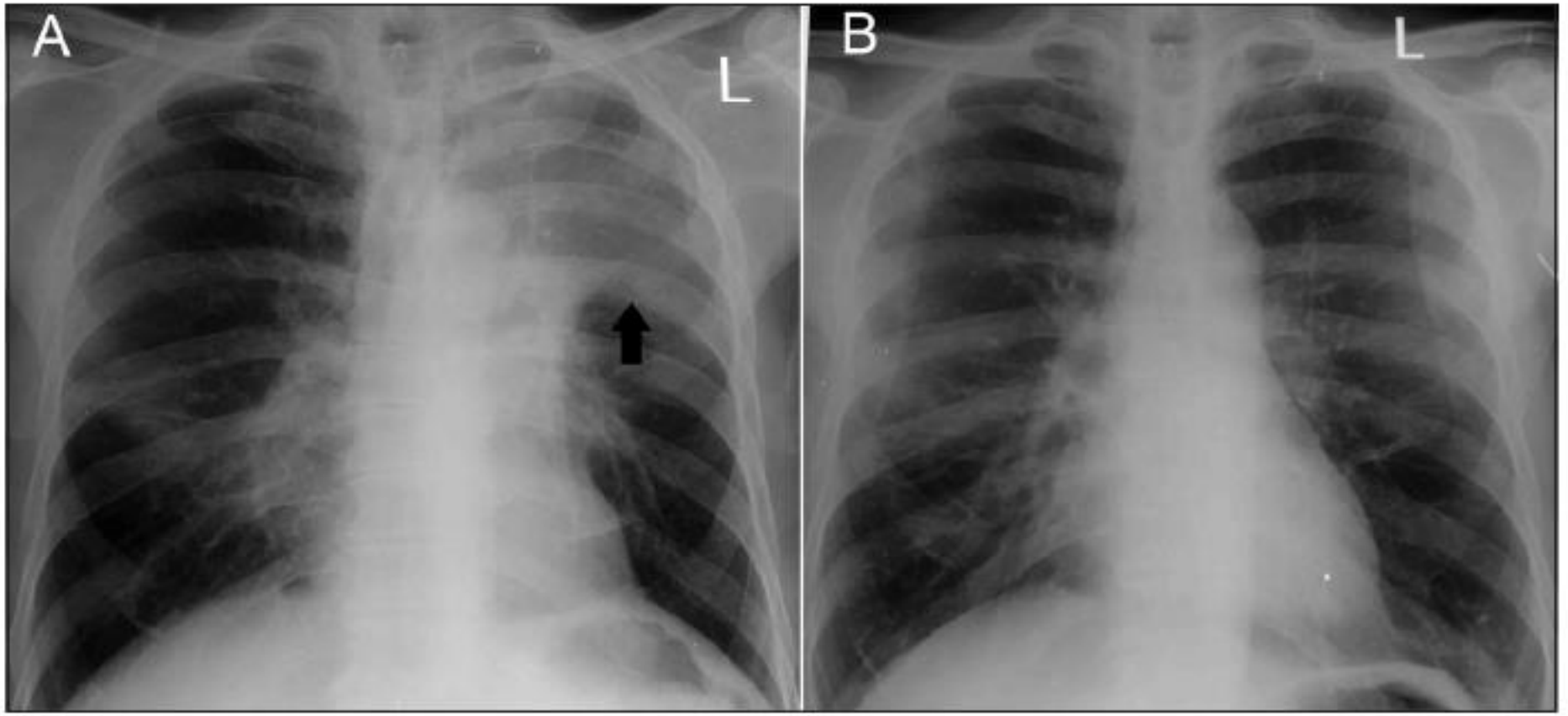

Figure 5 (A, B): Chest radiograph at presentation (A) shows left upper lobe collapse (arrow) that cleared (B) after treatment with glucocorticoids

R.Agarwal et al , Indian Journal of Radiology and Imaging / November 2011, Shah et al, Allergy Asthma Immunology Res 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- **Radiological investigation**-Plain Chest Radiology

Tram-line shadows (edema of the bronchial walls (45-92%)

Parallel lines (65-70%) - bronchial widening = permanent change

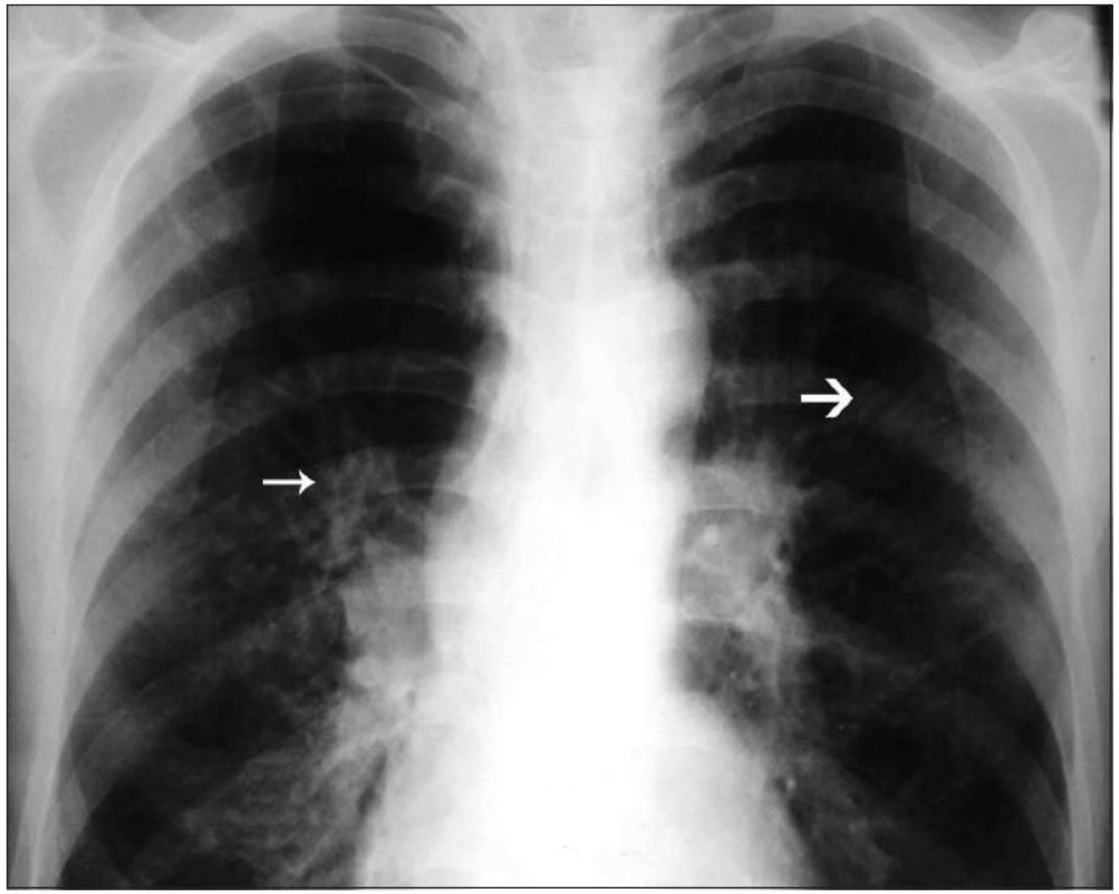

Figure 7: Chest radiograph shows the presence of tram-line (thick arrow) and parallel-line (thin arrow) shadows

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Allergic Bronchopulmonary Aspergillosis (ABPA)- **Radiological investigation**-Plain Chest Radiology

Bronchiectasis , Fibrosis

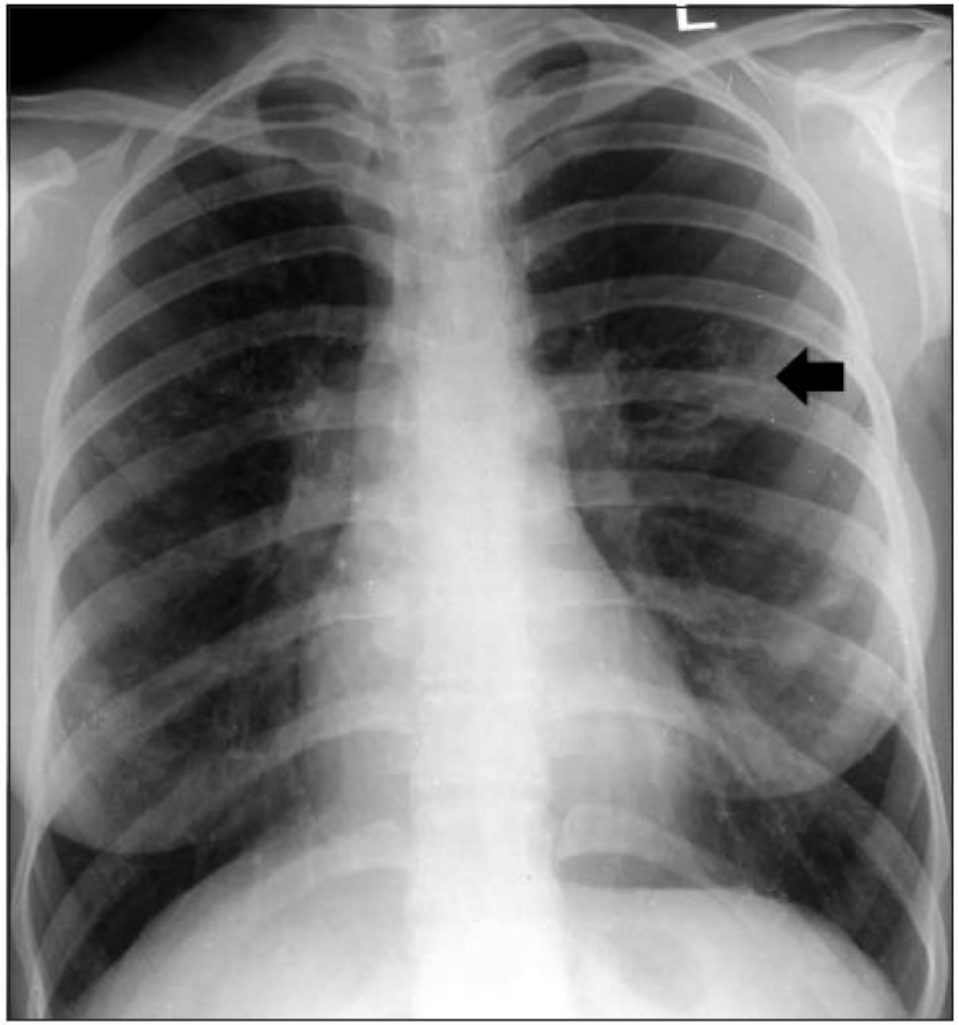

Figure 8: Chest radiograph shows central bronchiectasis (arrow) in the left mid-zone

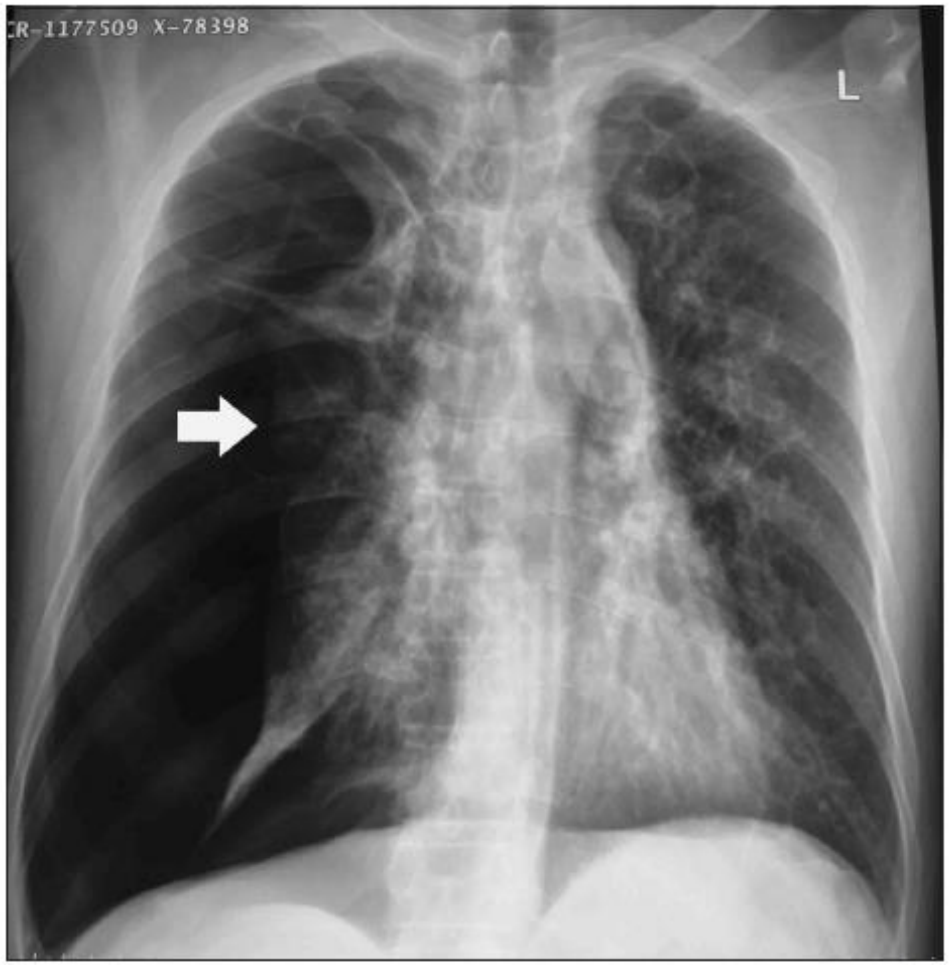

Figure 9: Chest radiograph of a patient with end-stage fibrotic ABPA who presented with a right-sided spontaneous pneumothorax (arrow)

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Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation - CT scan findings

Computed tomography findings

Bronchial abnormalities

- Bronchiectasis, usually central, as characterised by the 'signet ring' and 'string of pearls' appearances
- Dilated bronchi with or without air-fluid levels
- Totally occluded bronchi
- Bronchial wall thickening
- Parallel-line opacities extending to the periphery
- High attenuation mucous plugs

Parenchymal changes

- Consolidation
- Non-homogeneous patchy opacities
- Parenchymal scarring of varying extent
- Segmental or lobar collapse
- Cavitation
- Emphysematous bullae

Pleural involvement

- Pleural effusions
- Spontaneous pneumothorax
- Bronchopleural fistula
- Pleural fibrosis
- Pleural thickening

R.Agarwal et al , Indian Journal of Radiology and Imaging / November 2011

Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation - CT scan findings

Central Bronchiectasis (CB-ABPA)

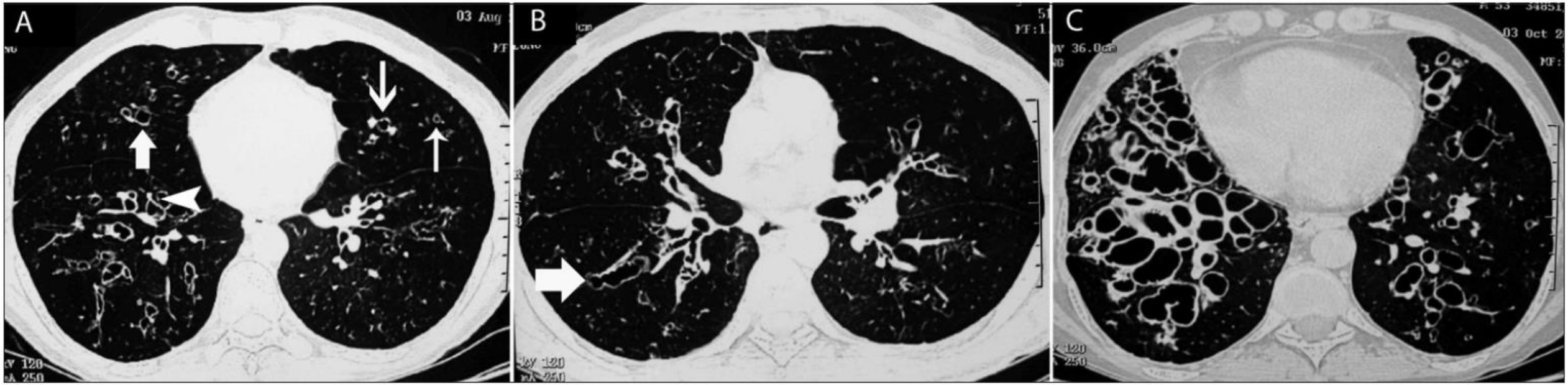


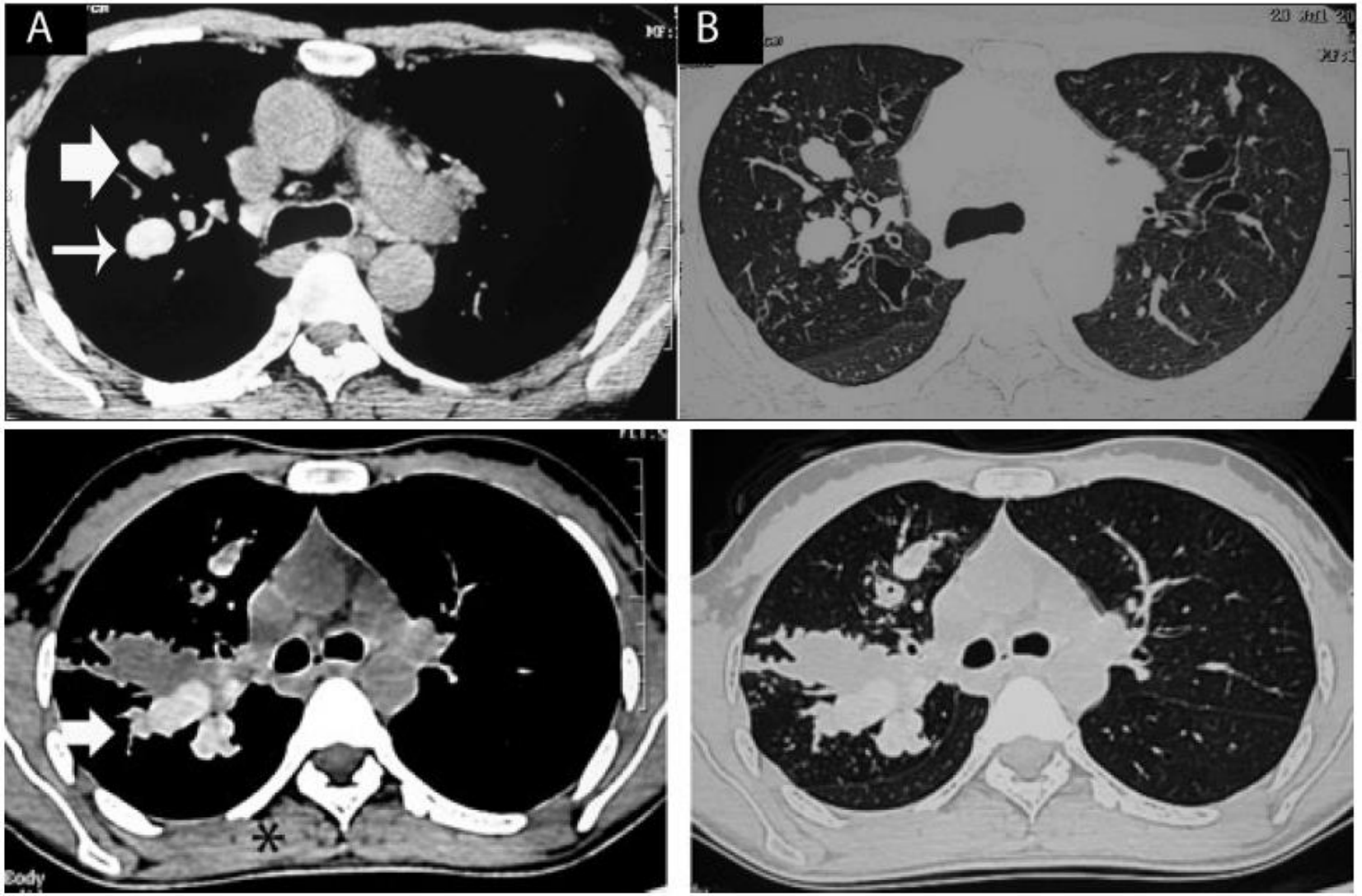
Figure 10 (A-C): Axial HRCTs (lung window) show the various types of bronchiectasis in three different patients with ABPA: cylindrical bronchiectatic cavities (thin arrow) of various sizes with the characteristic signet-ring appearance (thick arrow) (A), varicose bronchiectasis (arrows in B), and cystic bronchiectasis

- ✓ 26%–39% are associated with peripheral bronchiectasis
- ✓ usually upper lobes
- ✓ Cylindrical, varicose, cystic
- ✓ Central bronchiectasis (CB) is a sine qua non for the diagnosis of ABPA

R.Agarwal et al , Indian Journal of Radiology and Imaging / November 2011

Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation - CT scan findings

Atelectasis and mucoid impaction



- filling of the airways by mucoid secretions
- generally hypodense
- may also have high CT attenuation values (HAM)- 20%
- pathognomonic of ABPA

specificity of 100%
sensitivity 19-32%
should be considered as a radiological criteria separate from other findings.

HAM (High Attenuation Mucus): denser than the paraspinal skeletal muscle

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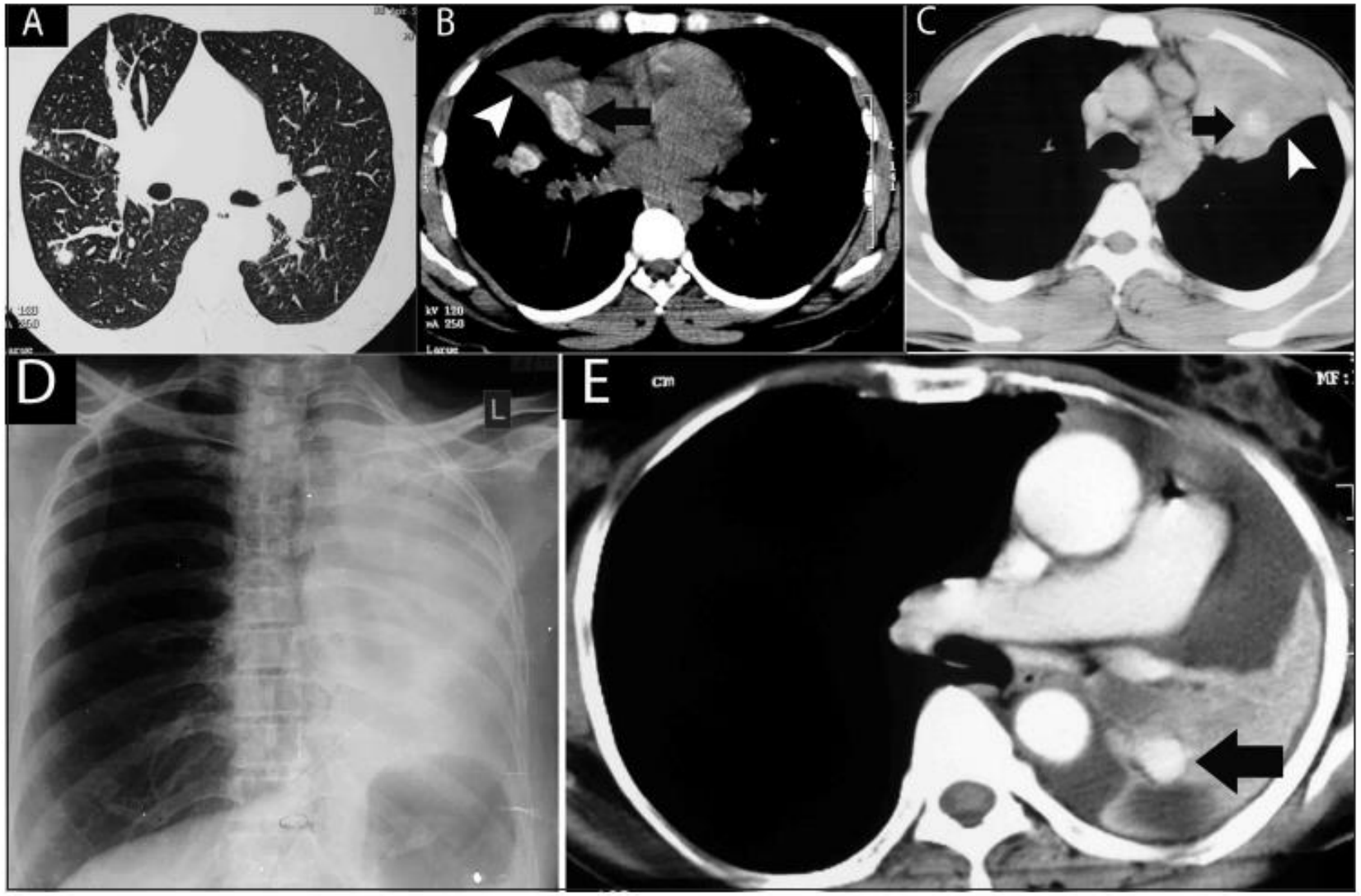
Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation - CT scan findings

Atelectasis and mucoid impaction



A. Subsegmental atelectasis.
B. Hyperattenuated mucus (arrow) with segmental collapse (arrowhead).
C. High attenuation mucus (arrow) within a collapsed left upper lobe and lingual (arrowhead).
D. E. left lung collapse which is due to hyperdense mucus (arrow) within the collapsed lung

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Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation - CT scan findings

Centrilobular nodules- tree-in-bud –mosaic pattern

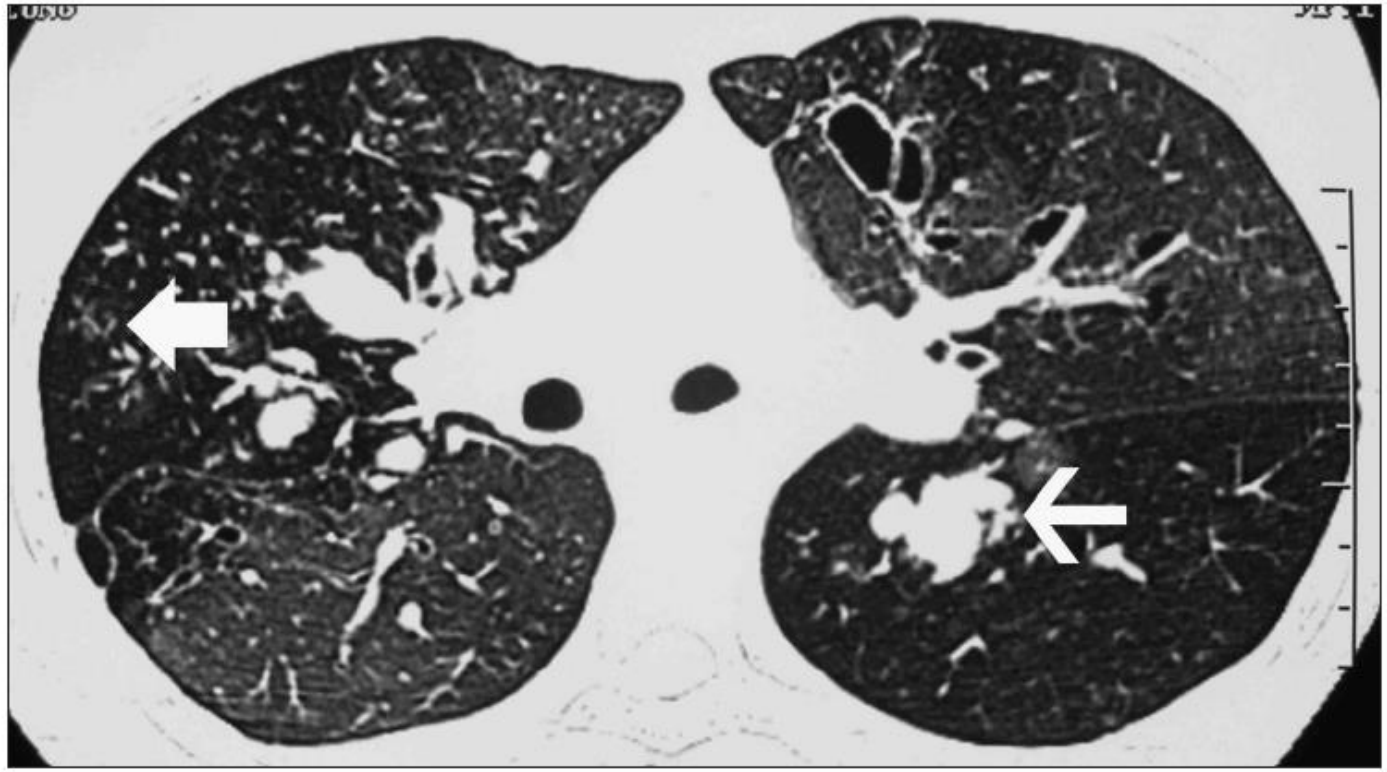

Figure 16: Axial HRCT (lung window) shows a mosaic pattern. There is central bronchiectasis with mucoid impaction in many of the bronchiectatic cavities (thin arrow). Also seen are centrilobular nodules in a tree-in-bud pattern (bold arrow)

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Allergic Bronchopulmonary Aspergillosis (ABPA)- Radiological investigation - CT scan findings

Spontaneous pneumothorax, Fibrocavitary disease

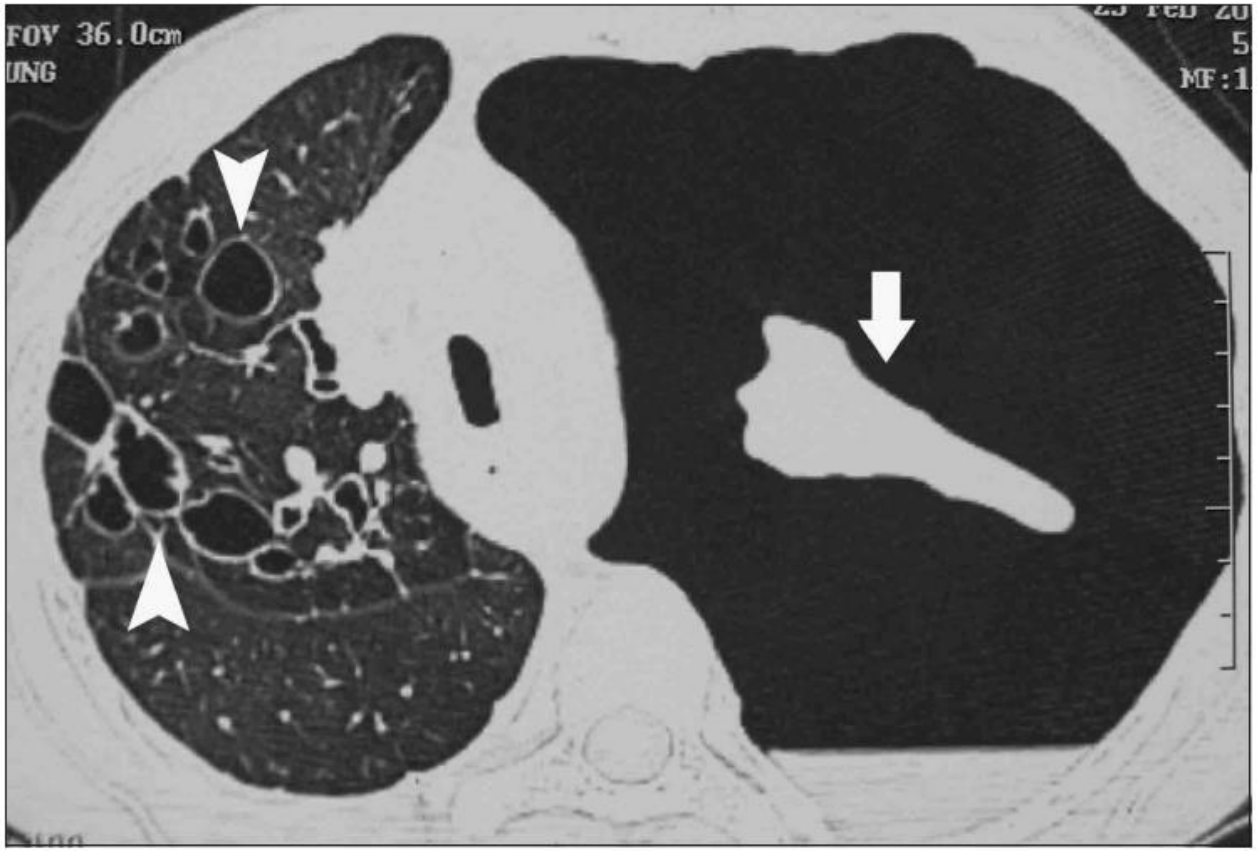

Figure 17: Axial HRCT (lung window) in a patient of ABPA who presented with a left-sided spontaneous pneumothorax (arrow). Extensive central and peripheral bronchiectasis is seen involving the right lung (arrowheads)

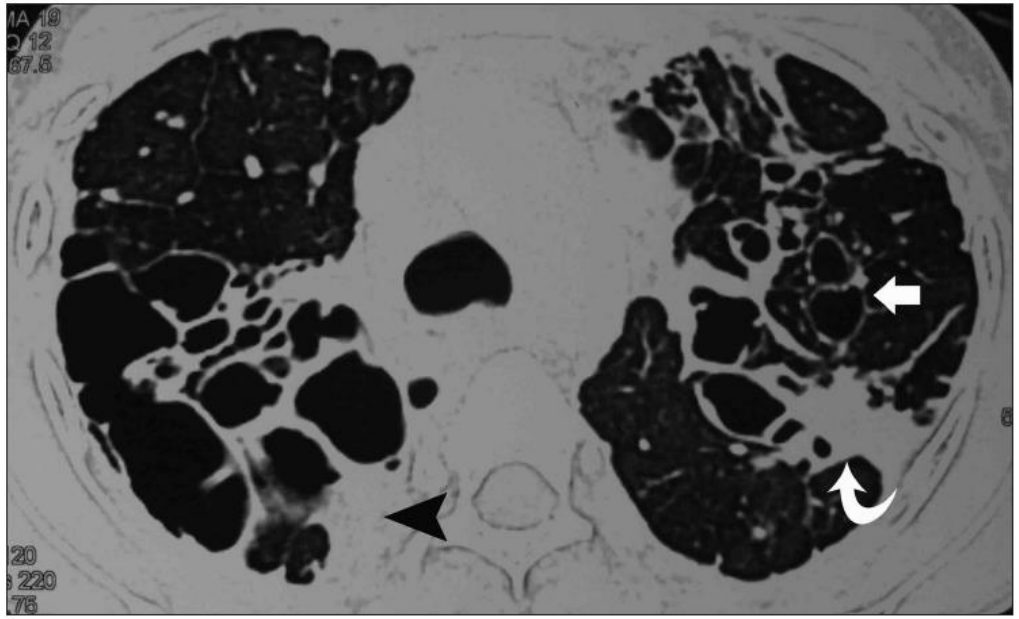

Figure 18: Axial HRCT (lung window) shows extensive bronchiectatic cavities (arrows), with pleural (arrowhead) and pulmonary fibrosis (curved arrow)

R.Agarwal et al , Indian Journal of Radiology and Imaging / November 2011

Allergic Bronchopulmonary Aspergillosis (ABPA)- Diagnosis and diagnostic criteria

Greenberger

1952 First Case Series (79)	1977 Diagnostic Criteria (43)	1986 Rosenberg-Patterson criteria[46,47]	1991-2002 1991 Diagnostic Criteria: Revised (44)	1991-2002 'Truly minimal' criteria[7]	2013 ISHAM Working Group[29]	1999 ABPA in CF[55]
Clinical features described	Asthma Total IgE elevated Immediate skin test positive Serum eosinophilia Precipitins Parenchymal infiltrates Central bronchiectasis	***Major criteria*** 1. Asthma 2. Presence of transient pulmonary infiltrates (fleeting shadows) 3. Immediate cutaneous reactivity to *Af* 4. Elevated total serum IgE >1000IU/ml 5. Precipitating antibodies against *Af* 6. Peripheral blood eosinophilia 7. Elevated serum IgE and IgG to *Af* 8. Central/proximal bronchiectasis with normal tapering of distal bronchi ***Minor criteria*** 1. Expectoration of golden brownish sputum plugs 2. Positive sputum culture for *Aspergillus* species 3. Late (Arthus-type) skin reactivity to *Af*	ABPA-CB Asthma Immediate skin test positive Total IgE elevated Specific IgE and IgG elevated Central bronchiectasis ABPA-S Asthma Immediate skin test positive Total IgE elevated Specific IgE & IgG elevated Additional findings Mucus plugs Sputum + aspergillus Precipitins Parenchymal infiltrates Delayed skin test positive	1. Asthma 2. Immediate cutaneous reactivity to *Af* 3. Total serum IgE >1,000 ng/mL (417 kU/L) 4. CB in the absence of distal bronchiectasis	***Predisposing conditions*** 1. Bronchial asthma 2. Cystic fibrosis ***Obligatory criteria (both should be present)*** 1. Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Af* 2. Elevated total IgE levels (>1,000 IU/mL)* ***Other criteria (at least two of three)*** 1. Presence of precipitating or IgG antibodies against *Af* in serum 2. Radiographic pulmonary opacities consistent with ABPA 3. Total eosinophil count >500 cells/μL in steroid naïve patients (may be historical) (*If the patient meets all other criteria, an IgE value <1,000 IU/mL may be acceptable)	**Presence of two of the following three:** (i) Immediate skin reactivity to *Af* antigens, (ii) Precipitating antibodies to *Af* antigens, (iii) Total serum IgE >1,000 IU/mL; **and at least two of the following six:** (i) Bronchoconstriction, (ii) Peripheral blood eosinophilia >1,000/μL, (iii) History of pulmonary infiltrates, (iv) Elevated specific IgE-*Af*/IgG-*Af*, (v) *Af* in sputum by smear or culture, (vi) Response to steroids

ABPA, allergic bronchopulmonary asperillosis; *Af*, *Aspergillus fumigatus*; CB, central bronchiectasis; CF, cystic fibrosis; IgE, immunoglobulin E; IgG, immunoglobulin G; ISHAM, International Society for Human and Animal Mycology.

Peterson Proc Am Thorac Soc Vol 7. pp 237–244, 2010, Agarwal Chest 2009

Allergic Bronchopulmonary Aspergillosis (ABPA)- Proposed diagnostic criteria- criteria-ISHAM working group 2013

Table 4. Newly proposed diagnostic criteria for allergic bronchopulmonary aspergillosis

Predisposing conditions
Bronchial asthma, cystic fibrosis
Obligatory criteria (both should be present)
Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Aspergillus fumigatus*
Elevated total IgE levels (> 1000 IU/mL)*
Other criteria (at least two of three)
Presence of precipitating or IgG antibodies against *A. fumigatus* in serum
Radiographic pulmonary opacities consistent with ABPA†
Total eosinophil count > 500 cells/μL in steroid naïve patients (may be historical)

*If the patient meets all other criteria, an IgE value < 1000 IU/mL may be acceptable.

†The chest radiographic features consistent with ABPA may be transient (i.e. consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities) or permanent (i.e. parallel line and ring shadows, bronchiectasis and pleuropulmonary fibrosis).

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Clinical & Experimental Allergy, **43**, 850–873

OPINIONS IN ALLERGY

Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria

R. Agarwal[1], A. Chakrabarti[2], A. Shah[3], D. Gupta[4], J. F. Meis[5,6], R. Guleria[7], R. Moss[8], D. W. Denning[9] and For the ABPA complicating asthma ISHAM working group*

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

R.Agarwal et al Clinical and Experimental Allergy 2013

Allergic Bronchopulmonary Aspergillosis (ABPA)- Proposed diagnostic criteria-ISHAM working group 2016

A. Predisposing conditions

Bronchial asthma, cystic fibrosis, COPD, post-tuberculous fibrocavitary disease

B. Essential criteria (both must be met)

i. Serum *Aspergillus fumigatus*-specific IgE levels >0.35 KUA/L ‡

ii. Elevated serum total IgE levels >1000 IU/mL*

Additional criteria (at least two of three)

i. Serum *Aspergillus fumigatus*-specific IgG levels >27 mgA/L

ii. Thoracic imaging findings consistent with ABPA†

iii. Peripheral blood eosinophil count >500 cells/µL (may be historical)

**An IgE value <1000 IU/mL may be acceptable, if all other criteria are met (especially if the serum Aspergillus fumigatus-specific IgG levels >27 mgA/L)*

†Features on HRCT chest and/or chest radiograph consistent with ABPA include transient abnormalities (i.e. nodules, consolidation, mucoid impaction, hyperattenuating mucus, fleeting opacities, toothpaste/gloved finger opacities, tram-track opacities) or permanent (i.e. parallel lines, ring shadows, bronchiectasis and pleuropulmonary fibrosis).

‡A positive type I Aspergillus skin test may be considered as a criterion in the place of serum Aspergillus fumigatus-specific IgE levels only if the latter test is not available

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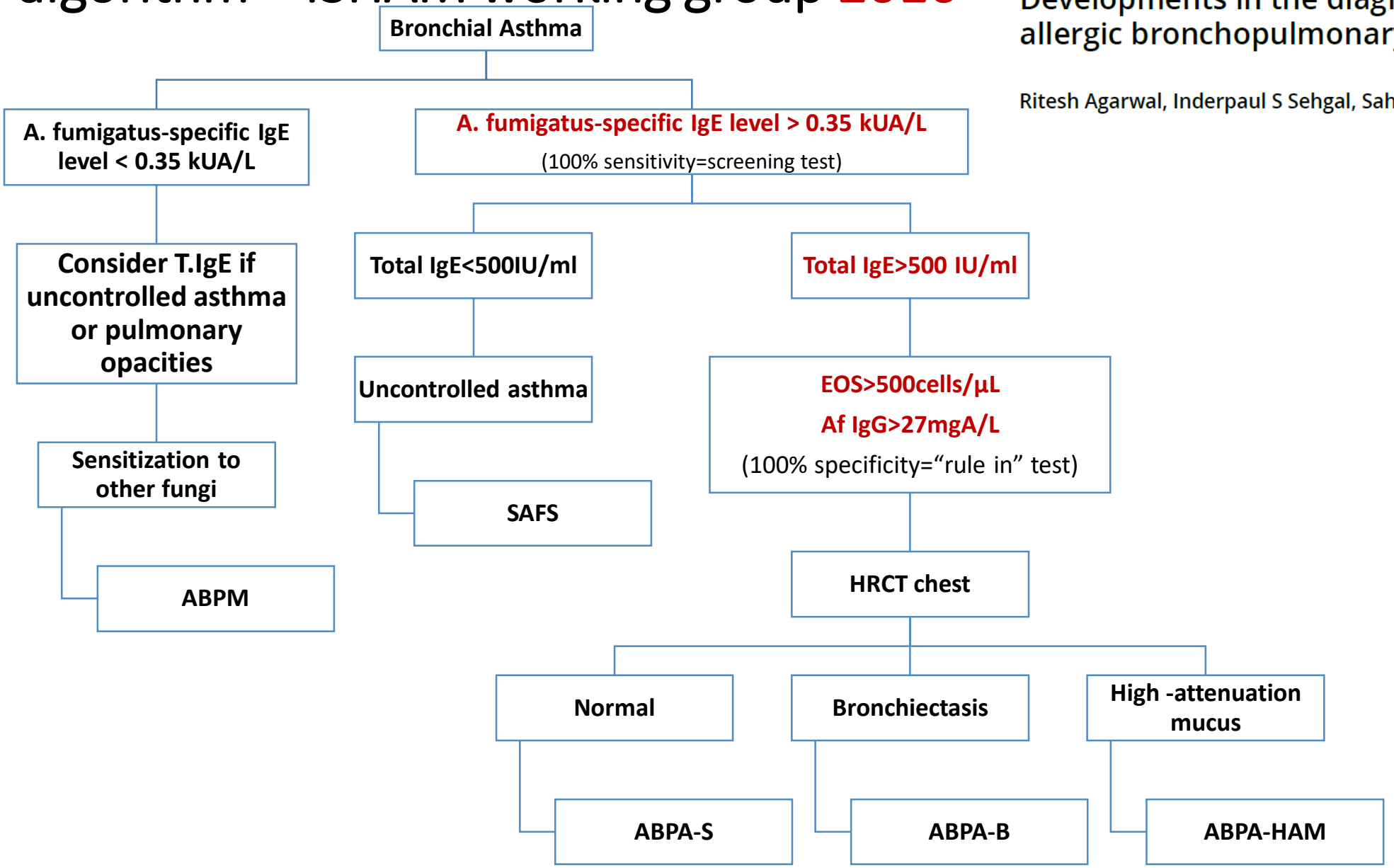
Allergic Bronchopulmonary Aspergillosis (ABPA)- Proposed Diagnostic algorithm – ISHAM working group 2016

Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis

Ritesh Agarwal, Inderpaul S Sehgal, Sahajal Dhooria & Ashutosh N Aggarwal



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Allergic Bronchopulmonary Aspergillosis (ABPA)- Proposed Clinical Staging/Course - ISHAM working group 2016

Clinical staging of allergic bronchopulmonary aspergillosis (ABPA) in patients with asthma		
Stage	Definition	**Features**
0	Asymptomatic	• **No previous diagnosis of ABPA** • **Controlled asthma (according to GINA/EPR-3 guidelines)** • **Fulfilling the diagnostic criteria of ABPA**
1	Acute	• **No previous diagnosis of ABPA** • **Uncontrolled asthma/symptoms consistent with ABPA** • **Meeting the diagnostic criteria of ABPA**
1a	With mucoid impaction	**Mucoid impaction observed on chest imaging or bronchoscopy**
1b	Without mucoid impaction	**Absence of mucoid impaction on chest imaging or bronchoscopy**
2	Response	• **Clinical and/or radiological improvement AND** • **Decline in IgE by ≥25% of baseline at 8 weeks**
3	Exacerbation	• **Clinical and/or radiological worsening AND** • **Increase in IgE by ≥50% from the baseline established during response/remission**
4	Remission	• **Sustained clinico-radiological improvement AND** • **IgE levels persisting at or below baseline (or increase by <50%) for≥6 months off treatment**
5a	Treatment-dependent ABPA	• **≥2 exacerbations within 6 months of stopping therapy OR** • **Worsening of clinical and/or radiological condition, along with immunological worsening (rise in IgE levels) on tapering oral steroids/azoles**
5b	Glucocorticoid -dependent asthma	**Systemic glucocorticoids required for control of asthma while the ABPA activity is controlled (as indicated by IgE levels and thoracic imaging**
6	Advanced ABPA	• **Extensive bronchiectasis due to ABPA on chest imaging AND** • **Complications (cor pulmonale and/or chronic type II respiratory failure)**

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Allergic Bronchopulmonary Aspergillosis (ABPA)- Proposed Radiological staging ISHAM

Table 6. Newly proposed radiological classification of ABPA based on computed tomographic (CT) chest findings

Classification	Features
ABPA-S (Serological ABPA)	All the diagnostic features of ABPA (Table 4) but no abnormality resulting from ABPA on HRCT chest*
ABPA-B (ABPA with bronchiectasis)	All the diagnostic features of ABPA including bronchiectasis on HRCT chest
ABPA-HAM (ABPA with high-attenuation mucus)	All the diagnostic features of ABPA including presence of high-attenuation mucus
ABPA-CPF (ABPA with chronic pleuropulmonary fibrosis)	ABPA with at least two to three other radiological features such as pulmonary fibrosis, parenchymal scarring, fibro-cavitary lesions, aspergilloma and pleural thickening without presence of mucoid impaction or high-attenuation mucus

*Findings resulting from co-existent disease, bullae from asthma, tracheomalacia, etc. should not be considered while labelling the patients as ABPA-S.

HRCT, high-resolution CT; ABPA, allergic bronchopulmonary aspergillosis.

Agarwal et al Clinical and Experimental Allergy 2013

Allergic Bronchopulmonary Aspergillosis (ABPA)- Proposed Scoring System- ISHAM 2016

Table 2. Proposed scoring system for the diagnosis of allergic bronchopulmonary aspergillosis (ABPA)

Immunological score	Value/findings	Score
A. fumigatus-specific IgE	<0.35 kUA/L	-7
	0.35-1.9 kUA/L	+1
	>1.9 kUA/L	+3
Total IgE	<417 IU/mL	-3
	417-1000 IU/mL	+1
	1000-2300 IU/mL	+2
	>2300 IU/mL	+3
Peripheral blood eosinophil count	<500 cells/µL	0
	500-1000 cells/µL	+3
	>1000 cells/µL	+4
A. fumigatus-specific IgG	<27 mg_A/L	0
	>27 mg_A/L	+4
Radiological score		
HRCT chest*	Normal	0
	≥2 features of fibrosis	+2
	Bronchiectasis involving <3 lobes	+3
	Bronchiectasis involving ≥3 lobes	+4
	Extensive mucoid impaction	+4
	Hyperattenuating mucus	+5
Scoring		
Total score 8 with radiologic score 0	ABPA at risk	
Total score ≥9 with radiologic score of 0	ABPA-S (serological ABPA)	
Total score ≥9 with radiologic score of 2	ABPA-CPF (ABPA with chronic pleuropulmonary fibrosis)	
Total score ≥9 with radiologic score of 3 or 4	ABPA-B (ABPA with bronchiectasis)	
Total score ≥9 with radiologic score of 5	ABPA-HAM (ABPA with high attenuation mucus)	

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Allergic Bronchopulmonary Aspergillosis (ABPA)- Treatment of ABPA ISHAM

1. Glucocorticoids

A) Oral corticosteroids

- Treatment of choice for ABPA

Regimen 1 (low dose)

Prednisolone 0.5 mg/kg/day for one to two weeks,
then on alternate days for six to eight weeks
Then taper by 5–10 mg every 2 weeks and discontinue

Regimen 2 (medium dose)

Prednisolone, 0.75 mg/kg for 6 weeks, 0.5 mg/kg for 6 weeks,
then tapered by 5 mg every 6 weeks to continue for a total
duration of at least 6–12 months

- 13% may not respond and may require escalation of steroid dose or other therapies
- 50% of patients relapse when they are tapered
- 20–45% glucocorticoid dependent (stage 5b)
- After discontinuation of prednisolone –monitoring every 6-8 weeks to ensure remission is maintained

R.Agarwal Expert Review of Respiratory Medicine 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- Treatment of ABPA ISHAM

1. Glucocorticoids

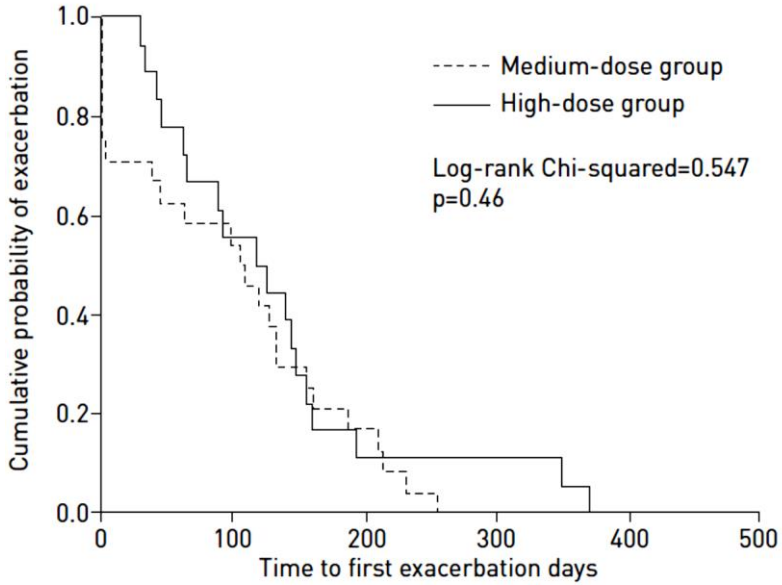
A) Oral corticosteroids

A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma

Ritesh Agarwal[1], Ashutosh N. Aggarwal[1], Sahajal Dhooria[1], Inderpaul Singh Sehgal[1], Mandeep Garg[2], Biman Saikia[3], Digambar Behera[1] and Arunaloke Chakrabarti[4]

92 subjects (high-dose n=44, medium-dose n=48) were included in the study. The numbers of subjects with exacerbation after 1 year (high-dose 40.9% *versus* medium-dose 50%, p=0.59) and glucocorticoid-dependent ABPA after 2 years (high-dose 11.4% *versus* medium-dose 14.6%, p=0.88) were similar in the two groups. Although composite response rates were significantly higher in the high-dose group, improvement in lung function and time to first exacerbation were similar in the two groups. Cumulative glucocorticoid dose and side-effects were significantly higher in the high-dose group.

Medium-dose oral glucocorticoids are as effective and safer than high-dose in treatment of ABPA.



Low-dose oral glucocorticoids are as effective and safer than medium-dose in treatment of ABPA.

Agarwal et al ERJ 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- Treatment of ABPA ISHAM

1. Glucocorticoids

B) Inhaled clucocorticoids

- High doses of ICS alone have a little role in the management of ABPA
- They can be used for asthma control

C) Intravenous pulse doses of glucocorticoids

- 15mg/kg methylprednisolone- max=1gr intravenously for 3 consecutive days
- Pediatric patients (steroid-sparing modality)
- Refractory asthma exacerbations

Tracy et al, J.Fungi 2016, R.Agarwal Expert Review of Respiratory Medicine 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- Treatment of ABPA ISHAM

2. Antifungal agents

- steroid-sparing agents

A) Itraconazole

- The most widely used
- Poor bioavailability, interactions with several drugs (+glucocorticoids)
- *200 mg twice a day, with therapeutic drug monitoring for at least 16 weeks.*
- *Response often takes longer than 16 weeks*
- *Tapered after 4-6 months (over 4 to 6 months)*

B) Nebulized amphotericin B

- No systemic absorption - adverse events
- Limited efficacy
- Use when alternative options have been exhausted
- May prevent ABPA exacerbations

Nebulized amphotericin B
Amphotericin B deoxycholate
Daily: 5-40 mg twice daily
Intermittent: 20 mg (10 mg twice daily) thrice weekly
Liposomal amphotericin B
Intermittent: 25 mg twice weekly
Amphotericin B lipid complex
Intermittent: 50 mg twice weekly

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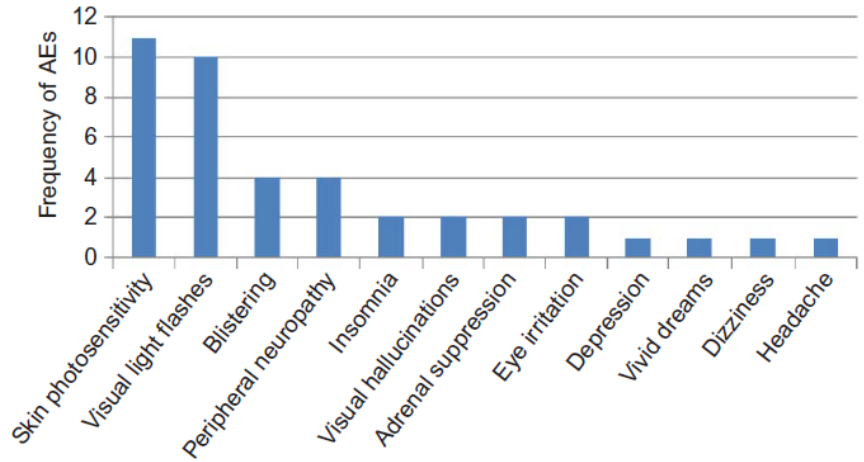
Allergic Bronchopulmonary Aspergillosis (ABPA)- Treatment of ABPA ISHAM

2. Antifungal agents

C) Newer Azoles (Voriconazole, Posaconazole)

- Few studies
- Clinical improvement in 70-75%
- Better bioavailibity, less adverse reactions
- Reduction in OCS, improvement in asthma control, decline in IgE
- Symptomatic patients despite treatment, adverse effects to itraconazole



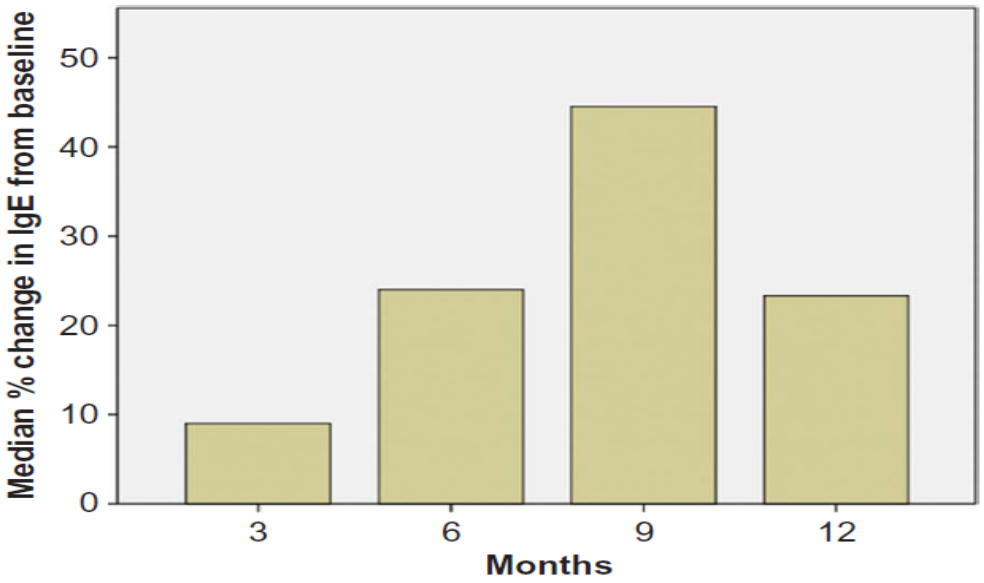


TABLE 3.—Improvements in clinical parameters during voriconazole therapy at 3, 6, and 12 months (ABPA and SAFS patients combined).

Clinical or health-care utilization feature		3 months (%)		6 months (%)		12 months (%)	
		Vori ($n = 25$)	Posa ($n = 9$)	Vori ($n = 19$)	Posa ($n = 9$)	Vori ($n = 17$)	Posa ($n = 9$)
Symptoms	Reduction in cough frequency (%)	17/24 (70)	7/9 (78)	15/19 (78)	6/9 (67)	7/17 (41)	8/9 (89)
	Reduction in breathlessness (%)	10/24 (41)	5/9 (56)	12/19 (63)	4/9 (44)	7/17 (41)	4/9 (44)
	Increased energy (%)	8/24 (33)	4/9 (44)	8/19 (42)	4/9 (44)	7/17 (41)	5/9 (56)
	Reduced chest infections (%)	17/24 (70)	7/9 (78)	9/19 (47)	7/9 (78)	9/17 (53)	7/9 (78)
Medication use	Reduction in oral antibiotics use (%)	16/24 (67)	7/9 (78)	11/19 (58)	7/9 (78)	11/17 (64)	6/9 (78)
	Reduction in OCS use (%)	4/18 (22)	2/9 (29)	5/18 (28)	2/7 (29)	5/17 (29)	2/7 (29)
	Discontinuation of OCS (%)	8/18 (33)	4/7 (57)	12/18 (67)	4/7 (57)	15/17 (88)	3/7 (43)
	Reduction in SABA use (%)	12/25 (48)	6/9 (67)	8/19 (42)	5/9 (56)	10/17 (58)	7/9 (78)
Health-care service use	Reduction in hospital admissions (%)	9/10 (90)	1/2 (50)	9/10 (90)	1/2 (50)	9/10 (90)	2/2 (100)
	Reduction in GP/emergency visits (%)	13/25 (52)	6/9 (67)	11/19 (58)	8/9 (89)	12/17 (71)	6/9 (67)
Quality of life	Reduction in patients' overall symptoms (%)	18/25 (72)	7/9 (78)	13/19 (68)	7/9 (78)	10/17 (58)	7/9 (78)
	Increased exercise tolerance (%)	7/25 (28)	4/9 (44)	6/19 (31)	5/9 (56)	5/17 (29)	4/9 (44)
	Increased QOL (%)	18/25 (72)	7/9 (78)	13/19 (68)	7/9 (78)	10/17 (58)	7/9 (78)

Notes: OCS, oral corticosteroid; SABA, short-acting beta-2 agonist; QOL, quality of life; GP, general practice; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitization; Vori, voriconazole; posa, posaconazole. () indicates %.

voriconazole and posaconazole can be alternative antifungal therapy in patients with ABPA

R.Agarwal Expert Review of Respiratory Medicine 2016, Tracy et al, J.Fungi 2016

Allergic Bronchopulmonary Aspergillosis (ABPA)- Treatment of ABPA ISHAM

2. Antifungal agents

A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma

CHEST

Ritesh Agarwal, MD, DM; Sahajal Dhooria, MD, DM; Inderpaul Singh Sehgal, MD, DM; Ashutosh N. Aggarwal, MD, DM; Mandeep Garg, MD; Biman Saikia, MD; Digambar Behera, MD; and Arunaloke Chakrabarti, MD

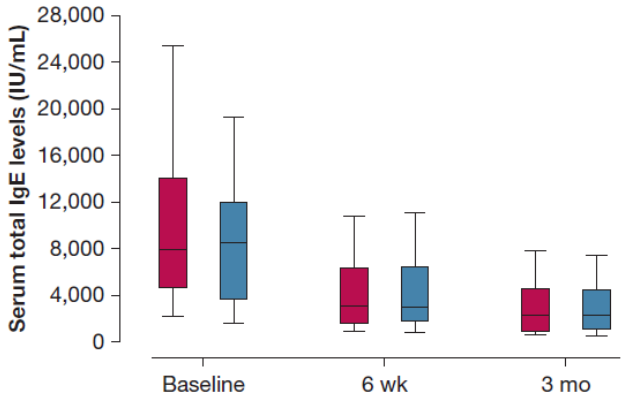
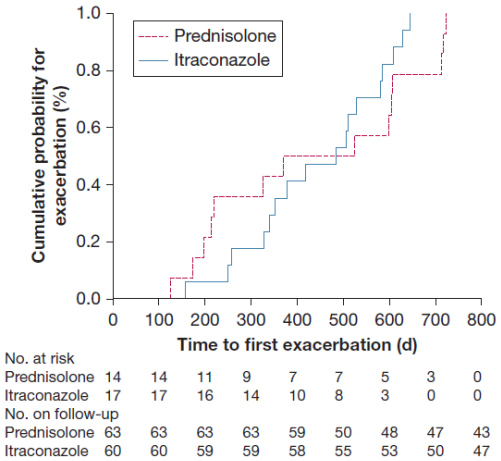


Figure 2 – *Box and whisker plots showing the IgE levels at baseline, 6 weeks, and 3 months in the two groups (prednisolone: red plots; itraconazole: blue plots). Box plots represent the 25th and 75th per-*



CONCLUSIONS: Prednisolone was more effective in inducing response than itraconazole in acute-stage ABPA. However, itraconazole was also effective in a considerable number and, with fewer side effects compared with prednisolone, remains an attractive alternative in the initial treatment of ABPA.

TABLE 2] Outcomes of Study Subjects Treated With Prednisolone or Itraconazole (N = 131)

Outcome	Prednisolone Group (n = 63)	Itraconazole Group (n = 68)	Estimated Difference (95% CI)	*P* Value
Primary outcomes				
Subjects with response following 6 wk of treatment[a]	63 (100%)	60 (88.2%)	−11.8 (−21.5 to −3.7)	.007
Subjects with response following 3 mo of treatment	63 (100%)	60 (100%)	0 (−0.06 to 0.06)	...

TABLE 3] Adverse Reactions Noted in Study Subjects Treated With Prednisolone or Itraconazole (n = 123)

Adverse Reaction	Prednisolone Group (n = 63)	Itraconazole Group (n = 60)[a]	Estimated Difference (95% CI)	*P* Value
Discontinuation of study drug	0	0	...	...
Cushingoid habitus	52 (82.5%)	0	82.5 (69.9 to 89.9)	.0001
Hypertension	0	0	...	...
Hyperglycemia	2 (3.2%)	0	3.2 (−3.3 to 10.9)	.50
Hypertrichosis	12 (19.1%)	0	19.1 (9.2 to 30.4)	.002
Acne	11 (17.5%)	0	17.5 (7.9 to 28.6)	.002
Striae	8 (12.7%)	0	12.7 (4.1 to 23.1)	.003
Weight gain (> 10% of baseline) at 6 wk	37 (58.7%)	2 (3.3%)	55.4 (40.7 to 66.9)	.0001
Mood changes	3 (4.8%)	0	4.8 (−2.0 to 13.1)	.24
Fatigue	3 (4.8%)	8 (13.3%)	−8.6 (−19.9 to 1.9)	.26
Liver function test abnormalities	0	9 (15%)	−15 (−26.1 to −6.0)	.001
Nausea	0	2 (3.3%)	−3.3 (−11.4 to 2.9)	.24

- ✓ Prednisolone more effective in inducing response
- ✓ No difference in Serum IgE / exacerbations
- ✓ Iitraconazole less AR

Agarwal et al Chest 2018

Allergic Bronchopulmonary Aspergillosis (ABPA)- Treatment of ABPA

ISHAM

3. Other agents

A. Omalizumab (375mg sc /2w)

102 ABPA patients
1091 IU/ml mean IgE
99% treatment failure to steroids/itraconazole
83% intravenous/16,67% sc Omalizumab
Dose: 225 mg to 750 mg, most commonly used dose was 375 mg every two weeks

Table 3
Baseline characteristics of 102 individuals.

Baseline characteristics	No of data gained	
Age (years)	N = 102 (100)	
Mean (SD)		41 (19)
Median (range)		41 (7, 76)
Gender n (%)		
Male		48 (47.1)
Female		54 (52.9)
Race n (%)		
Caucasian		98 (96.07)
Melanoderm		3 (2.94)
Xanthoderm		1 (0.98)
Clinical history n (%)		
with TB		2 (1.96)
with Asthma		17 (16.67)
with CF		40 (39.21)
ABPA duration prior to Anti-IgE(yrs)	N = 59 (57.8)	
Mean (SD)		5.4 (4.26)
Anti-fungal treatment		47 (46.08)
Treatment failure with systemic steroids or itraconazole prior to treatment n (%)		101 (99.03)
Total eosinophil count	N = 22 (21.57)	
Mean (SD)		676.36 (190.16)
Median (range)		676 (317, 1100)
Total IgE (IU/ml)	N = 97 (95.1)	
Mean (SD)		1901 (1971.67)
Median (range)		1901 (131, 10,200)
Specific IgE for A.f (IU/ml)	N = 48 (47.05)	
Mean (SD)		31.72 (24.16)
FEV1 of predicted (%)	N = 93 (91.17)	
Mean (SD)		59.63 (19.34)
Median (range)		60 (21, 115)
FVC of predicted (%)	N = 24 (23.5)	
Mean (SD)		83.4 (21.6)
Median (range)		83 (45, 95)
FEV1/FVC	N = 31 (30.39)	
Mean (SD)		56.93 (14.16)
Median (range)		57 (41, 85)
Exacerbations prior	N = 98 (96.07)	
Mean (SD)		2.74 (2.31)
Median (range)		3 (0, 10)

Table 4
Effect of omalizumab on ABPA patients.

	prior			poster			*P* value
	Mean	SD	N	Mean	SD	N	
Total IgE (IU/ml)	1901	1971.67		804.5	514.7		<0.001
Exacerbation rate (per year per patient)	2.7404	2.3117		0.38	0.698		<0.001
FEV1 of predicted (%)	59.63	19.34		72.21	19		<0.001
FVC%	83.4	21.6		94.83	22.11		0.0767
FENO(ppm)	31.4	24.36		17.66	11.24		0.0713
ACT score	11.367	6.2		18.53	9.5		0.0099
Prednisone dosage (mg/d)	16.39	13.47		1.63	2.25		<0.001
No.of PSL use			96			67	<0.001

86% decrease in exacerbations
30% discontinuation of steroids
70% reduction of steroids to <90% initial dose

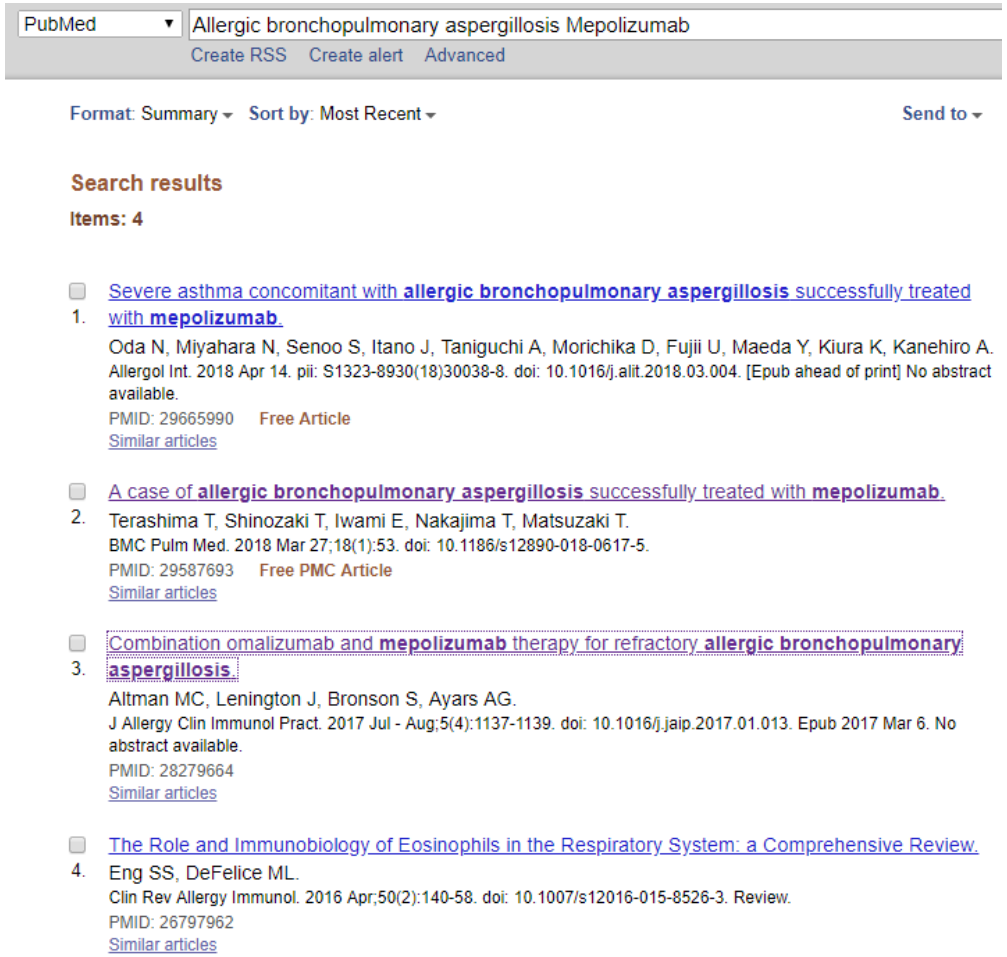
Jian-Xiong Li et al, Respiratory Medicine 2017

Allergic Bronchopulmonary Aspergillosis (ABPA)- Treatment of ABPA

ISHAM

3. Other agents

B. Mepolizumab



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3. Combination omalizumab and **mepolizumab** therapy for refractory **allergic bronchopulmonary aspergillosis**.
   Altman MC, Lenington J, Bronson S, Ayars AG.
   J Allergy Clin Immunol Pract. 2017 Jul - Aug;5(4):1137-1139. doi: 10.1016/j.jaip.2017.01.013. Epub 2017 Mar 6. No abstract available.
   PMID: 28279664
   Similar articles

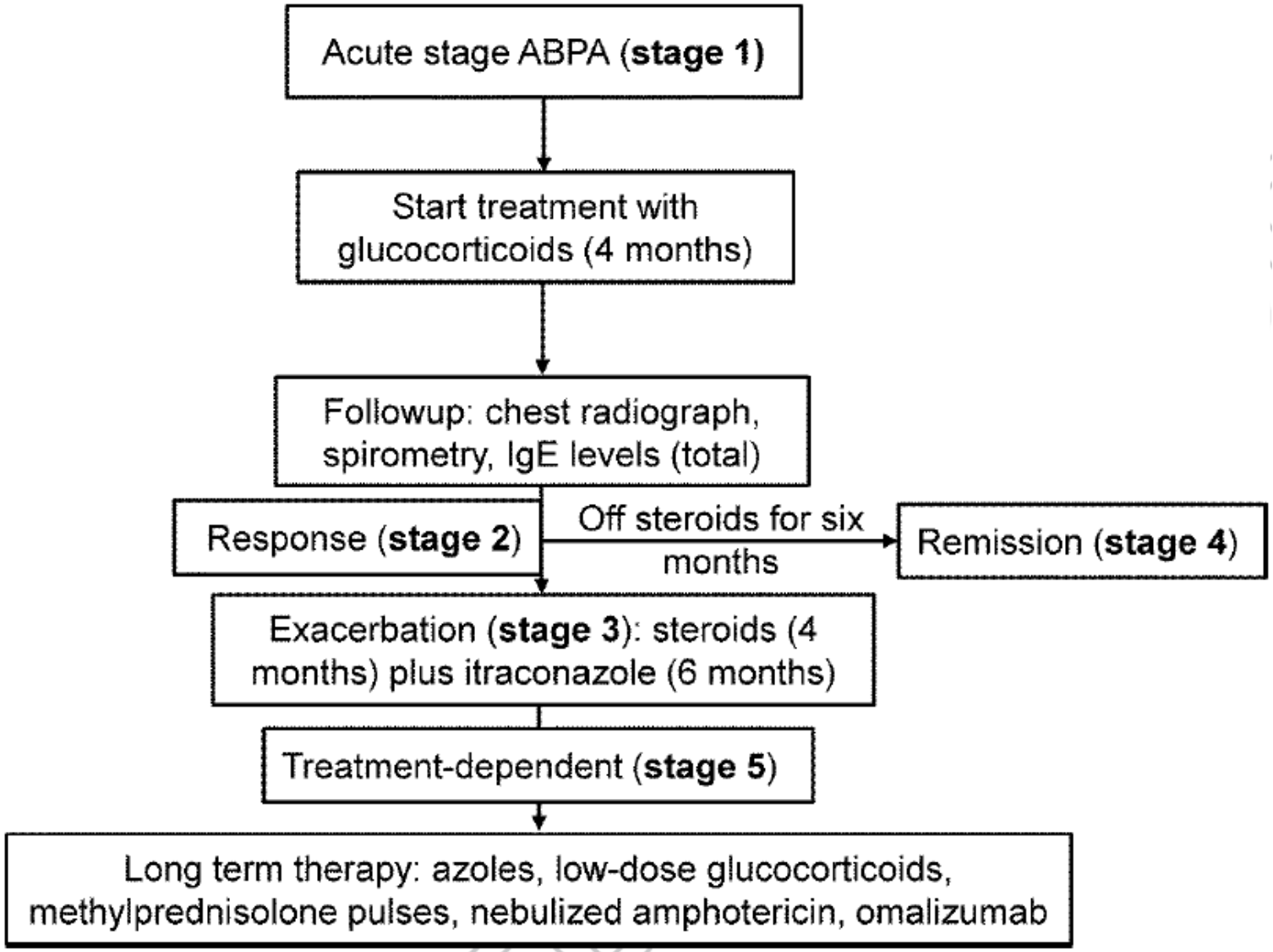
4. The Role and Immunobiology of Eosinophils in the Respiratory System: a Comprehensive Review.
   Eng SS, DeFelice ML.
   Clin Rev Allergy Immunol. 2016 Apr;50(2):140-58. doi: 10.1007/s12016-015-8526-3. Review.
   PMID: 26797962
   Similar articles

C. Therapeutic Bronchoscopy: When atelectasis persists after 4 weeks of OCS treatment

D. Enviromental Control: avoidance of gardening, farm related activities, renovations, compost, use of a mask

Jian-Xiong Li et al, Respiratory Medicine 2017

Allergic Bronchopulmonary Aspergillosis (ABPA)- Practical approach to treatment - ISHAM



- ✓ Well controlled asthma, no radiographic abnormalities **(stage 0)-- follow up- no treatment**
- ✓ Monitor clinical symptoms, chest radiograph and total IgE levels, every eight weeks

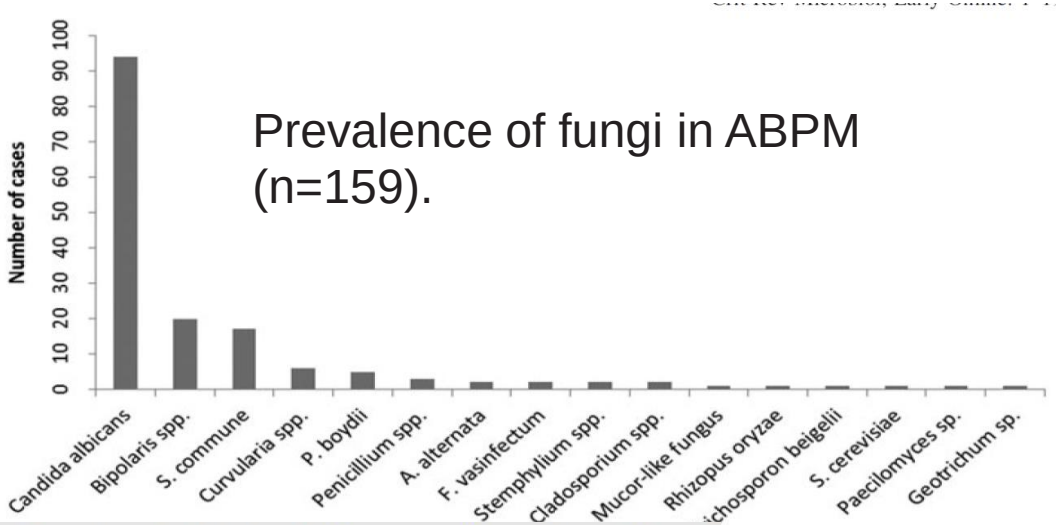
- ✓ **Response (stage 2)** = clinical and/or radiological improvement with at least 25% decline in IgE levels
- ✓ Monitor IgE frequently to establish the 'new' baseline level for an individual patient
- ✓ **Exacerbation (Stage 3)=** • Clinical and/or radiological worsening along with 50% increase in IgE

R.Agarwal Expert Review of Respiratory Medicine 2016

Allergic Bronchopulmonary Mucosis (ABPM)

- ABPA-like syndrome caused by fungi other than fumigatus (Candida albicans most often)
- Less than 150 cases reported globally
- Diagnostic criteria similar to ABPA (sensitization to the specific fungi)
- Clinical and lab findings similar to ABPA

Treatment similar to ABPA (antifungals according to their efficacy against a particular etiologic agent)



Prevalence of fungi in ABPM (n=159).

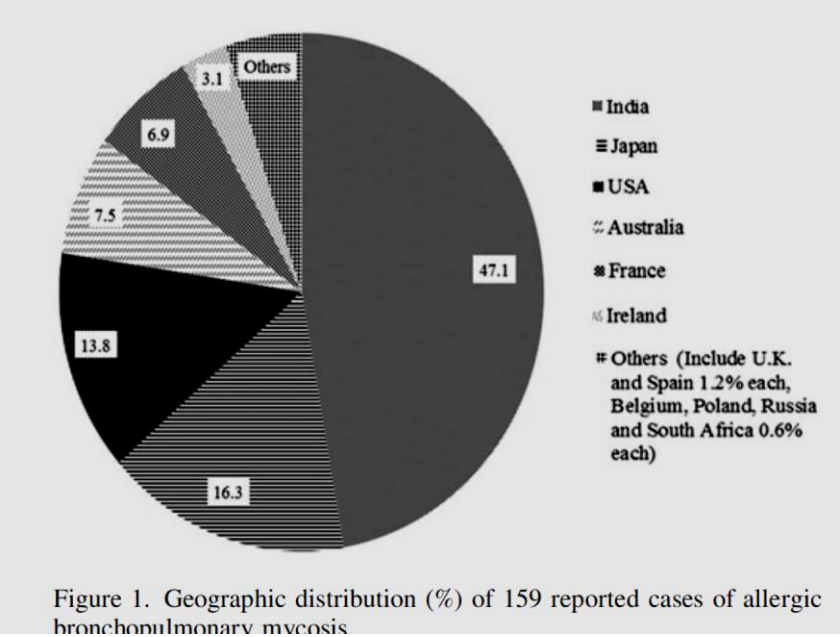


Figure 1. Geographic distribution (%) of 159 reported cases of allergic bronchopulmonary mycosis

Table 6. Synopsis of clinical and laboratory diagnostic profiles of allergic bronchopulmonary mycosis cases reported in English ($n = 143$).

Characteristics investigated	Results
Mean age ± SD (years; range)	41.70 ± 18.97 (6–84, $n = 71$)
Sex distribution (male:female)	1.33:1
History of asthma	46/143* (32.1%)
History of allergic disorders	51/143 (35.6%)
Raised total IgE	100/116 (86.2%)
Median total IgE (IU/ml; range)	1400 (80–37, 530, $n = 63$)
Eosinophilia	62/67 (92.5%)
Precipitins	39/43 (90.6%)
Specific (IgE/IgG) antibodies	35/39 (89.7%)
Type I skin test	52/55 (94.5%)
Pulmonary infiltrates	43/65 (66.1%)
Central bronchiectasis	21/65 (32.3%)
Isolation of fungus	60/67 (89.5%)

*Numerator denotes the number positive and denominator the number reported.

A. Chowdhary et al., Crit Rev Microbiol, Early 2013

Allergic Bronchopulmonary Aspergillosis (ABPA)- CF

- Prevalence 2-15% in CF
- Prompt recognition is essential due to profound deterioration of lung function
- Wheezing, fleeting opacities, bronchiectasis, mucus plugging
- Similar treatment

Practice points

Diagnosis in CF

- Acute or subacute deterioration in respiratory symptoms or lung function.
- Total serum IgE greater than 400 IU/ml.
- Skin-prick test positive to *Af*, together with either
  - o Positive *Aspergillus precipitins*
  - o Radiographic features consistent with ABPA.

Stevens et al, Clinical Infectious Diseases 2003;

Allergic Bronchopulmonary Aspergillosis (ABPA)- Conclusions

- ABPA is a controllable, albeit chronic illness
- All asthmatic patients (regardless severity) should be routinely investigated for ABPA with A.Fumigatus specific IgE
- It is important to treat the disease aggressively during the early stages
- Glucocorticoids should be used as the first-line of therapy in ABPA, and itraconazole reserved in those with exacerbations and glucocorticoid-dependent disease.
- Newer therapies may be tried in those with recurrent exacerbations, glucocorticoid-dependent ABPA or in patients who develop treatment-related adverse reactions.
- ABPA without asthma. Dx: bronchogenic carcinoma, TB

The End

Ευχαριστώ για την προσοχή σας!