Need for Revised Criteria for ABPA and Indian scenario

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Diagnostic criteria and staging

Diagnostic criteria (Rosenberg-Patterson)

Major Criteria

- **A**sthma
- **R**adiological opacities
- **T**ype 1 *Aspergillus* skin-test positive
- **S**pecific *Aspergillus* IgE/IgG elevated
- **P**recipitins (*Af*) in serum
- **I**gE levels elevated in serum
- **C**entral bronchiectasis
- **E**osinophilia

Minor Criteria

- Presence of *Aspergillus* in sputum
- Expectoration of brownish-black mucus plugs
- Delayed type III skin reaction to *Aspergillus* antigen

Rosenberg M, et al. Ann Intern Med 1977; 86: 405-14
Patterson R, et al. Arch Intern Med 1986; 146: 916-18

Problems with Patterson criteria

No agreement on the number of criteria that should be present to make the diagnosis

Lays equal weightage on all the components, while some may be more important than others

Lack of consensus on the specific cutoff value for IgE levels and eosinophil counts

Agarwal R. Int J Respir Care 2010; 6: 53-4, 56-63
Agarwal R, et al. Future Microbiol 2013;8: 1463-74

New criteria

ISHAM INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY — ABPA complicating asthma working group

doi: 10.1111/cea.12141

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*

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Agarwal R, et al. Clin Exp Allergy 2013; 43: 850-73

New diagnostic criteria for ABPA

Predisposing conditions

Bronchial asthma, cystic fibrosis

Obligatory criteria (both should be present)

Type I *Af* skin test positive or elevated *Af* IgE (>0.35 kUA/L)

Elevated total IgE levels (>1000 IU/mL)*

Other criteria (at least two of three)

Presence of *Af* precipitating (or IgG) antibodies 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

†Chest radiographic features consistent with ABPA may be transient or permanent

Agarwal R, et al. Clin Exp Allergy 2013; 43: 850-73




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Agarwal R, et al. Expert Rev Respir Med 2016; 10: 1317-1334

Why not skin testing?

	Sensitivity	Specificity
Type 1 *Aspergillus* skin test positive	94.7% (87.7–100)	79.7% (72.6–88.6)
IgE levels>1000 IU/mL	97.1% (90.7–100)	37.7% (31.6–44.2)
A.fumigatus specific IgE levels>0.35 kUA/L	100% (100–100)	69.3% (61.8–79.2)
A.fumigatus precipitins	42.7% (27.8–59.2)	97.1% (94.8–98.9)
Total eosinophil count>1000 cells/μL	36.1% (24.1–49.0)	92.5% (89.1–95.6)
HRCT evidence of bronchiectasis	91.9% (72.7–100)	80.9% (75.2–85.7)
Chest radiographic transient opacities	28.3% (16.9–41.7)	96.8% (94.5–98.8)
HRCT evidence of high-attenuation mucus	39.7% (23.9–58.4)	100% (100–100)

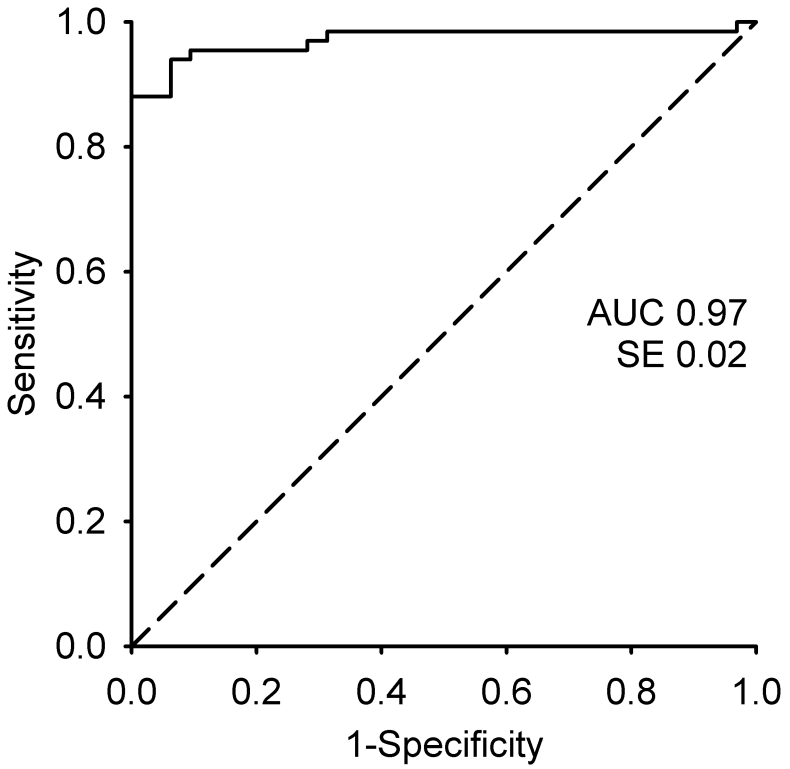
The values in parenthesis represent 2.5–97.5% bootstrap confidence intervals obtained by bootstrapping 5000 samples.

Agarwal R, et al. PLoS One 2013; 8: e61105

Why Af IgG and not precipitins

Af IgG cutoff: ≥27 mg_A/L (Phadia platform)

Sensitivity of *Af* IgG: 89% (compared to 27% for *Aspergillus* precipitins)



Agarwal R, et al. Mycoses 2017; 60: 33-39

Staging

Stage	Description
I	Acute phase
II	Remission
III	Exacerbation
IV	Glucocorticoid-dependent ABPA
V	End-stage (Fibrotic) ABPA

Patterson R, et al. Ann Intern Med 1982;96:286-91

Staging

Stage	Definition	Features
0	Asymptomatic	Never diagnosed to have ABPA in the past; presentation with controlled asthma (according to GINA guidelines), and meeting the diagnostic criteria of ABPA (Table 1)
1	Acute	Never diagnosed to have ABPA in the past; presentation with uncontrolled asthma/constitutional symptoms, and meeting the diagnostic criteria of ABPA
1a	With mucoid impaction	Presence of mucoid impaction on thoracic imaging or bronchoscopy
1b	Without mucoid impaction	No mucoid impaction on thoracic imaging or bronchoscopy
2	Response	Clinical and/or radiological improvement AND fall in IgE by ≥25% of baseline at eight weeks
3	Exacerbation	Clinical and/or radiological worsening accompanied by an increase in IgE by ≥50% from the previous baseline
4	Remission	Sustained clinicoradiological improvement with IgE levels remaining at or below baseline (or increase by <50%) for ≥6 months off therapy
5a	Treatment-dependent ABPA	Two or more relapses within six months of stopping treatment OR deterioration in clinical and/or radiological condition and/or immunological worsening on tapering oral steroids/azoles
5b	Glucocorticoid-dependent asthma	Systemic corticosteroids required for asthma control while the ABPA activity is controlled (as indicated by IgE levels and thoracic imaging)
6	Advanced ABPA	Presence of complications (cor pulmonale and/or chronic type II respiratory failure) along with presence of extensive bronchiectasis consistent with

Agarwal R, et al. Clin Exp Allergy 2013;43:850-73

Radiological classification

Patterson et al.
- ABPA-S
- ABPA-CB

Kumar et al.
- ABPA-S
- ABPA-CB
- ABPA-CB-ORF

Long-term clinical significance of these classifications remains unknown

Patterson R, et al. Arch Intern Med 1986; 146: 916-8
Greenberger PA, et al. Ann Allergy 1993; 70: 333-338
Kumar R. Chest 2003;124: 890-892

New radiological classification

ABPA-S (Serological ABPA)

ABPA-B (ABPA with bronchiectasis)

ABPA-HAM (ABPA with high-attenuation mucus)

ABPA-CPF (ABPA with chronic pleuropulmonary fibrosis)

Agarwal R, et al. Clin Exp Allergy 2013;43:850-73

Indian scenario

First description

UK - Hinson KFW et al- [Thorax 1952; 7: 317-33]

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

US - Patterson R et al- [Univ Mich Med Cent J 1968; 34: 8-11]

India - Shah JR et al- [J Assoc Physicians India **1971**; 19: 835-41]

Burden of the disease

Scoping review

193 million adults with asthma worldwide using GINA estimates

4,837,000 patients (range 1,354,000-6,772,000) develop ABPA assuming overall prevalence of ABPA as 2.1% (range, 0.7-3.5%)

Denning DW, et al. Med Mycol 2013; 51: 361-370

Studies in this millennium

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.

SPT, skin prick test.

Prevalence is higher in the Indian population compared to other populations

Agarwal R, et al. Clin Exp Allergy 2013; 43:850-873

Burden in India

Total population (2011 Indian census)	1,210,569,573		
Adult Indian population (>=15y)	838,218,964		
	INSEARCH	GINA	WHS
Asthma prevalence adults >=15y	17,183,489	30,462,016	27,661,226
ABPA prevalence			
0.70%	120,284	213,234	193,629
2.50%	429,587	761,550	691,531
3.50%	601,422	1,066,170	968,143
5%	859,174	1,523,101	1,383,061
10%	1,718,349	3,046,202	2,766,123
20%	3,436,698	6,092,403	5,532,245

Agarwal R, et al. PLoS One 2014; 9: e114745

ABPA in COPD

In India, ABPA has been identified in conditions other than asthma and cystic fibrosis

Medical Mycology November 2010, **48**, 988–994

informa
healthcare

Aspergillus hypersensitivity in patients with chronic obstructive pulmonary disease: COPD as a risk factor for ABPA?

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Agarwal R, et al. Med Mycol 2010; 48: 988-994

ABPA in pulmonary tuberculosis-related fibrocavitary disease

Case-control study

50 consecutive symptomatic new referrals with PTB-related fibrocavitary disease and 50 controls

AS was present in 16 (32%) cases and two (4%) controls

Fourteen cases (one control) had IgE values >1000 IU/mL while two cases manifested eosinophilia

Aspergillus precipitins were positive in 13 cases (two controls); eight of these 13 cases did not have AS

Dhooria S, et al. Int J Tuberc Lung Dis 2014; 18: 850-855

Environmental factors in ABPA

Prospective case-control questionnaire based study

202 subjects of asthma (103 and 99 *Aspergillus* unsensitized and sensitized asthma respectively) and 101 ABPA

Living conditions (home environment, presence of moisture in the walls, details of house type, presence of separate kitchen), use of water coolers, type of fuel, contact with farms, cattle and pets

No significant differences in environmental factors were noted in ABPA population compared to asthmatic patients except for a higher rural residence in ABPA (47% vs. 66%, p=0.007)

Agarwal R, et al. Lung India 2014; 31: 232-236

Genetic predisposition

Innate immunity
Surfactant protein A2 gene polymorphisms
Mannose-binding lectin gene polymorphisms
Toll-like receptor 9 gene polymorphisms
Adaptive immunity
HLA associations
Interleukin 4 receptor alpha polymorphisms
Interleukin 13 polymorphisms

Interleukin 10 promoter polymorphisms
Interleukin 15 polymorphisms
Tumor necrosis factor-α polymorphisms
Transforming growth factor-β polymorphisms
Others
CFTR gene mutation
CHIT1 gene mutations

Agarwal R, et al. Clin Exp Allergy 2013;43:850-73

Genetic predisposition

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Surfactant protein A2 gene polymorphisms
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Interleukin 4 receptor alpha polymorphisms
Interleukin 13 polymorphisms

Interleukin 10 promoter polymorphisms
Interleukin 15 polymorphisms
CFTR gene mutation
CHIT1 gene mutations

Not studied well in the Indian Population

Agarwal R, et al. Clin Exp Allergy 2013;43:850-73

Sensitization to *A.flavus* in ABPA

53 subjects with a mean (SD) age of 34.2 (12.8) years were included

Sensitization to *A.flavus* was seen in 51 (96.2%) subjects; 49 (92.5%) instances on fungal-specific IgE

Sputum culture was positive in 18 (33.9%; *A.flavus* [n=12], *A.fumigatus* [n=6]) subjects

ABPM due to *A.flavus* was diagnosed in 16 (30.2%) subjects

More likely to have high-attenuation mucus and a trend towards higher occurrence of sinusitis, compared to ABPA

Sehgal IS et al. Med Mycol 2018; In press

Clinical presentation

Poorly controlled asthma

Low grade fever, hemoptysis, productive cough, weight loss and malaise

Routine screening of asthmatics - In our series of 155 cases of ABPA - 19% had well controlled asthma

- In India, almost 1/3rd of the patients are still misdiagnosed as pulmonary tuberculosis
- Need for better training of physicians and pulmonary physicians

Agarwal R, et al. Chest 2006; 130: 442-8

Agarwal R, et al. In: Aspergillosis: From Diagnosis to Prevention. New York: Springer; 2009. p. 707-24

Immunologic findings

Total serum IgE levels

- IgE levels are significantly raised in the Indian asthmatic population even without ABPA due to worm infestations, other allergies
- In one study, almost 70% of asthmatics in our Chest clinic had IgE >1000 IU/mL (? Referral bias)
- Elevations in IgE levels always have to be correlated with radiological and/or clinical manifestations

Agarwal R, et al. PLoS One 2013; 8:e61105

Immunologic findings

Peripheral eosinophilia

- Eosinophil count >1000 cells/µL is a major criterion for diagnosis of ABPA
- In a study involving 209 ABPA patients
  - Median eosinophil count at diagnosis was 850 cells/µL
  - 60% had an eosinophil count <1000 cells/µL
- In India, eosinophil count is used to screen asthmatic patients for ABPA and is one important cause for missed diagnosis

Agarwal R. Textbook of Pulmonary and Critical Care Medicine. New Delhi: Jaypee Publications, 2010; 947-970
Agarwal R, et al. J Infect Public Health 2011; 4:235-243

Central bronchiectasis

Central bronchiectasis (CB) with peripheral tapering of bronchi – believed to be *sine qua non* for ABPA

Arbitrarily defined if bronchiectasis confined to medial 2/3rd or half of lung

Bronchiectasis can extend to the periphery in 26-39% of the lobes involved depending on the definition used

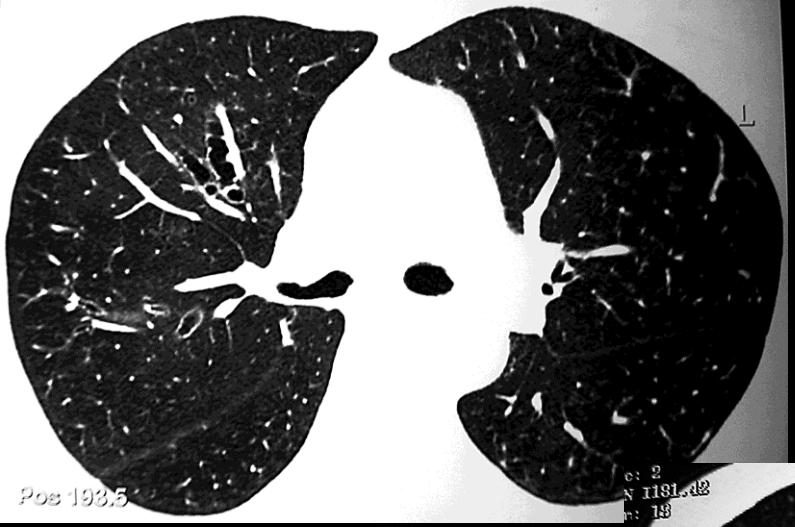
No longer considered a specific criteria for ABPA

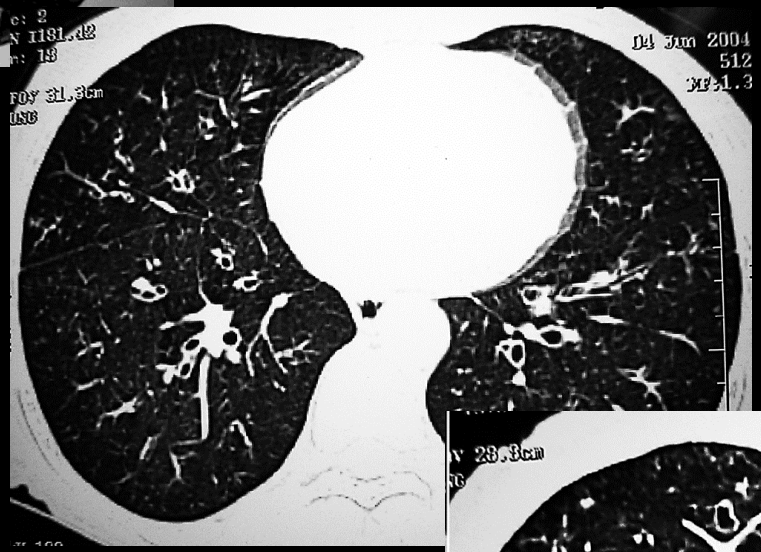
Aim is to diagnose ABPA before development of bronchiectasis i.e. in the serological stage

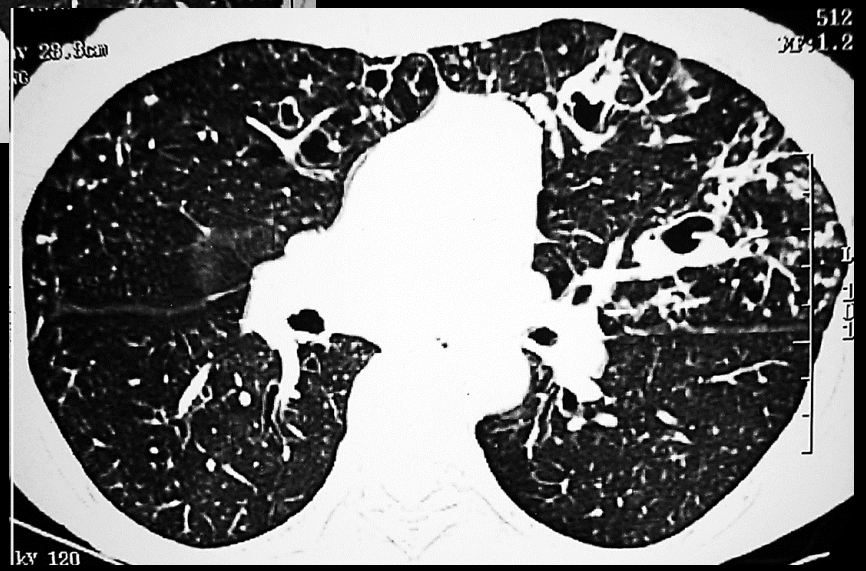
- Unfortunately, in India almost 75% of the patients are diagnosed with bronchiectasis

Agarwal R, et al. World J Radiol 2012; 4:141-150
Agarwal R, et al. Indian J Radiol Imaging 2011; 21:242-252

Central bronchiectasis

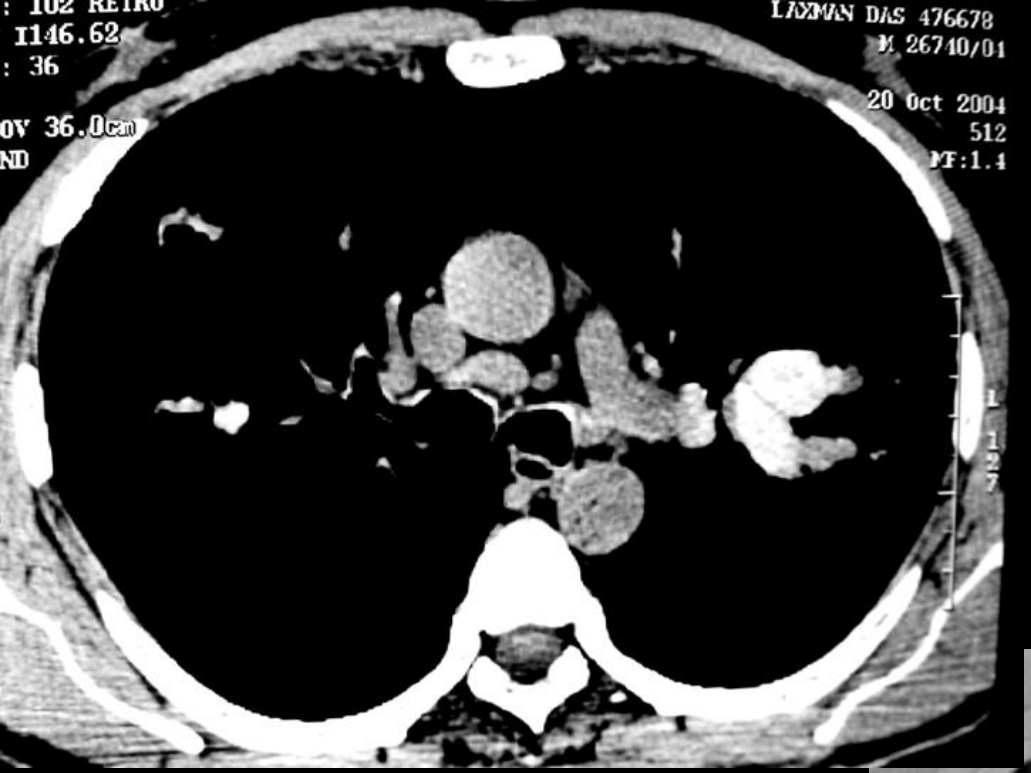


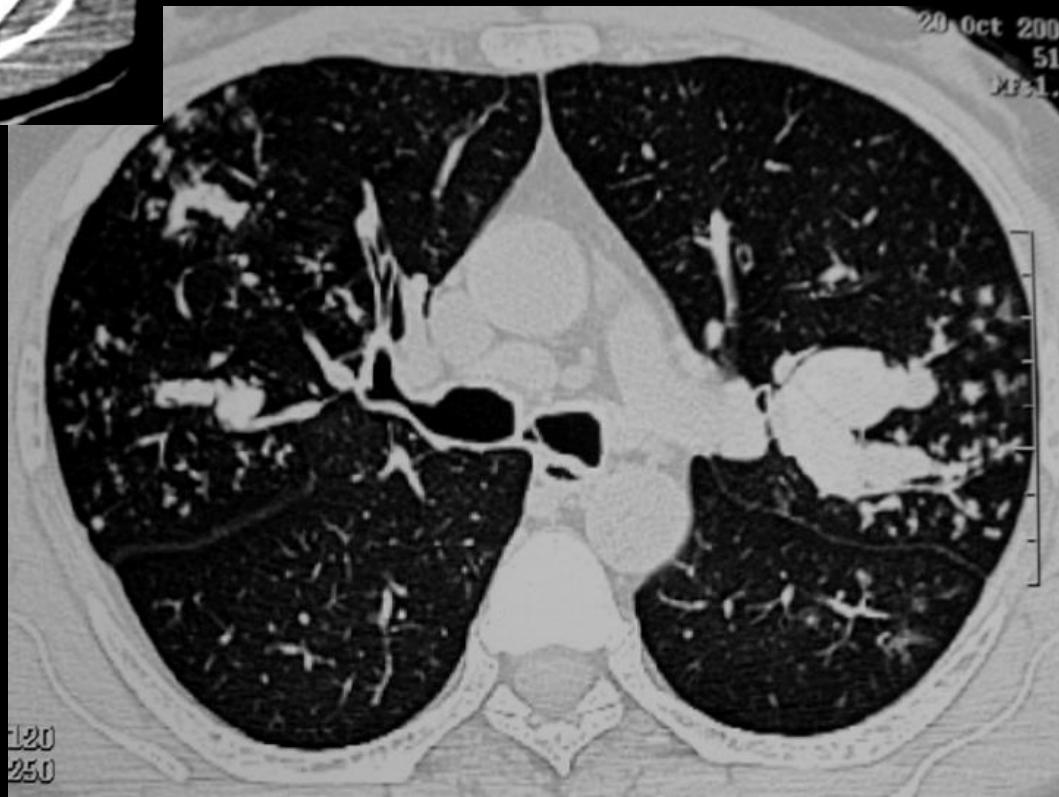




Agarwal R, et al. Chest 2006; 130: 442-8
Agarwal R, et al. Chest 2007; 132: 1183-90
Agarwal R, et al. Respir Med 2010; 104: 204-210
Agarwal R, et al. PLoS One 2010; 5:e15346

High-density mucus plugs





Agarwal R, et al. Am J Roentgenol 2006; 186: 904
Agarwal R, et al. PLoS One 2010; 5:e15346

High-attenuation mucus

Pathognomonic finding of ABPA

Uncommonly described from other centers

Seen in almost 20% of our patients

Could be recognition bias or could really represent a different spectrum of ABPA

We have found that patients with HAM have severer immunological findings compared to other patients and are prone for relapses

Agarwal R,et al. Chest 2007; 132:1183-1190
Agarwal R, et al. PLoS One 2010; 5:e15346

Future directions…

Why ABPA is so prevalent in Indian asthmatic patients?

Why there is higher prevalence of certain radiological findings in Indian patients?

Host susceptibility factors in ABPA

Working group on ABPA

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Join the ISHAM ABPA working group

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