Recent advances in diagnosis and management of ABPA

Arindam
SR(Pulmonary Medicine)

Conventional diagnostic criteria for ABPA

Primary

- Episodic bronchial obstruction (asthma)
- Peripheral blood eosinophilia
- Immediate skin reactivity to *Aspergillus* antigen
- Precipitating antibodies against *Aspergillus* antigen
- Elevated serum immunoglobulin E concentrations
- History of pulmonary infiltrates (transient or fixed)
- Central bronchiectasis

Secondary

- *Aspergillus* fumigatus in sputum (by repeated culture or microscopic examination)
- History of expectoration of brown plugs or flecks
- Arthus reactivity (late skin reactivity) to aspergillus fumigatus antigen

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- Original study by : **MICHAEL ROSENBERG, M.D.; ROY PATTERSON, M.D published in** annals of internal medicine in 1986.
- It was originally a report of 20 patients with high probability of ABPA and postulated that if 6 of the 7 criteria are present disease is highly likely and disease is certain if it is a full house.
- They also recommended that any patient with allergic asthma and pulmonary infiltrate should be investigated for ABPA.

Why need for a new criteria

- Due to lack of gold standard the criteria could not be validated.
- Cut off values for different serological tests was not defined.
- It imparted same importance to all of 7 features whereas subsequent research has shown few of them are clinically more relevant than others.

R. Agarwa A. Chakrabarti, A. Shah, D. Gupta,J. F. Meis, R. Guleria, R. Moss, D. W.Denning and For the ABPAcomplicating asthma ISHAM working group, Clinical & Experimental Allergy,2013 (43) 850–873

New diagnostic criteria

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)

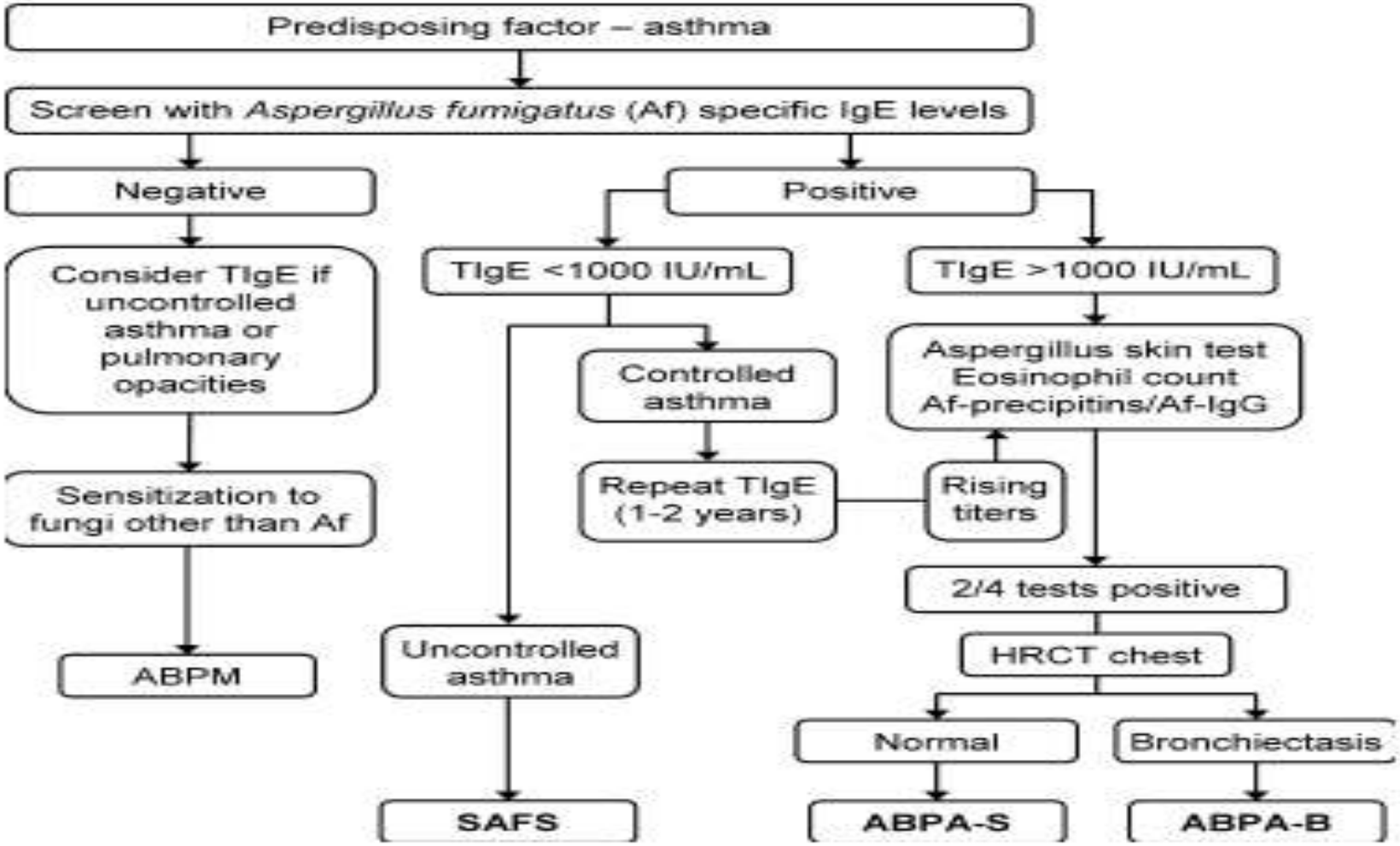
Presence of precipitating or IgG antibodies against A. fumigatus in serum

Radiographic pulmonary opacities consistent with ABPA†

Total eosinophil count > 500 cells/lL in steroid naıve patients (may be historical)

R.Agarwal etal journal of clinical and experimental alergy 2013

Algorithm to diagnose ABPA based on this criteria



Cut-off values of serum IgE (total and *A. fumigatus* -specific) and eosinophil count in differentiating allergic bronchopulmonary aspergillosis from asthma

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	ABPA (n = 76)	Asthma (n = 296)	P value
Age, in years	34.5 (13.1)	36.2 (13.6)	0.41
Male gender	40 (52.6%)	139 (47%)	0.37
Duration of asthma, in months	120 (51–180)	60 (24–141)	**0.0001**
History of atopy	7 (9.2%)	80 (27%)	**0.001**
Symptoms			
Cough	74 (97.4%)	277 (93.6%)	0.2
Breathlessness	74 (97.4%)	265 (89.8%)	0.04
Wheeze	72 (94.7%)	279 (94.3%)	0.87
Chest tightness	58 (76.3%)	238 (80.4%)	0.43
Two or more exacerbations in last year requiring steroids	44 (57.9%)	108 (36.5%)	**0.001**
Hospitalisation for asthma in last year	10 (13.2%)	15 (5.1%)	0.038
Lung function test			
FEV_1, % predicted	64.7 (23.3)	74.5 (4.03)	**0.001**
FVC, % predicted	75.2 (19.9)	84.4 (20.2)	**0.0001**
Bronchodilator reversibility	40 (53.3%)	152 (52.8%)	0.93
Severity of obstruction			
Normal	18 (24%)	129 (44.7%)	0.01
Mild	26 (34.7%)	74 (25.7%)	
Moderate	19 (25.3%)	58 (20.1%)	
Severe	12 (16%)	27 (9.4%)	
Investigations for ABPA			
Type 1 *Af* skin test positive	72 (94.7)	69 (23.3%)	**0.0001**
IgE levels, IU ml^{-1}	8243.8 (3028.8–14 000)	1191.3 (590.3–1900)	**0.0001**
Af-specific IgE levels, kUA l^{-1}	30.3 (15.58–49.4)	0.2 (0.1–0.71)	**0.0001**
Af precipitins	37 (48.7%)	10 (3.4%)	**0.0001**
Total eosinophil count, cells per μl	1190.4 (542.5–1455)	298 (174.5–500)	**0.0001**
Chest radiographic transient opacities	26 (34.2%)	9 (3%)	**0.0001**
HRCT chest evidence of bronchiectasis	64 (84.2%)	73 (24.7%)	**0.0001**

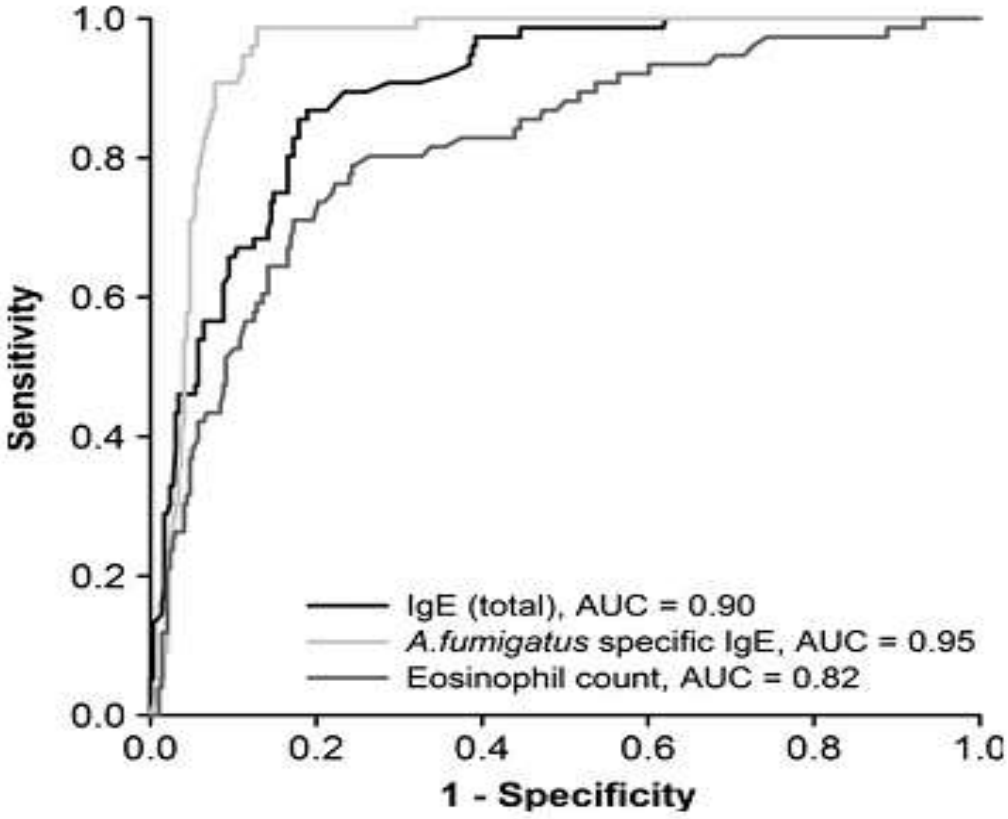
Table 3 Sensitivity and specificity of various cut-offs of the immunological tests used for differentiating ABPA from asthma

	Sensitivity	Specificity
IgE (total)		
>417 IU ml	100 (95.3–100)	17.9 (13.7–22.8)
>1000 IU ml	100 (95.3–100)	36.8 (31.3–42.6)
>2500 IU ml	84.2 (74.04–91.6)	82.1 (77.2–86.3)
>5000 IU ml	67.1 (55.4–77.5)	89.5 (85.5–92.8)
>10 000 IU ml	44.7 (33.3–56.6)	96.6 (93.9–98.4)
>20 000 IU ml	7.9 (2.9–16.4)	99.7 (98.1–99.9)
Aspergillus fumigatus-specific IgE		
>0.35 kUA l^{-1}	100 (95.3–100)	66.2 (60.5–71.6)
>1 kUA l^{-1}	98.7 (92.9–99.9)	78.4 (73.3–82.9)
>2 kUA l^{-1}	96.1 (88.9–99.2)	87.5 (83.2–91.04)
>5 kUA l^{-1}	90.8 (81.9–96.2)	92.2 (88.6–95.01)
>10 kUA l^{-1}	82.9 (72.5–90.6)	93.6 (90.2–96.1)
>15 kUA l^{-1}	76.3 (65.2–85.3)	94.6 (91.4–96.9)
>20 kUA l^{-1}	64.5 (52.7–75.1)	95.3 (92.2–97.4)
>50 kUA l^{-1}	23.7 (14.7–34.8)	97.6 (95.2–99.04)
>90 kUA l^{-1}	2.6 (0.3–9.2)	99.3 (97.6–99.9)
Total eosinophil count		
>500 cells per μl	78.9 (68.1–87.5)	75.3 (70.02–80.1)
>1000 cells per μl	43.4 (32.1–55.3)	93.2 (89.8–95.8)
>1500 cells per μl	22.4 (13.6–33.4)	97.6 (95.2–99.04)
>2500 cells per μl	7.9 (2.9–16.4)	98.7 (96.6–99.6)

Table 2 Performance characteristics of the best cut-off of various immunological tests used in the diagnosis of allergic aspergillosis determined using the Youden statistic.

	IgE (total)	*Aspergillus fumigatus* -specific IgE	Total eosinophil count
Best cut-off value	2347 IU ml^{-1}	1.91 kUA l^{-1}	507 cells per µl
Sensitivity	86.8 (77.1–93.5)	98.7 (92.9–99.9)	78.9 (68.1–87.5)
Specificity	81.1 (76.2–85.4)	87.2 (82.8–90.8)	75.7 (70.4–80.5)
Predictive value of a positive test	54.1 (44.8–63.2)	66.4 (56.9–74.9)	45.5 (36.8–54.4)
Predictive value of a negative test	96.0 (92.8–98.1)	99.6 (97.9–99.9)	93.3 (89.4–96.1)

All values are expressed as percentage with 95% confidence intervals.


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
IgE (total), AUC = 0.90
A.fumigatus specific IgE, AUC = 0.95
Eosinophil count, AUC = 0.82

Diagnostic Performance of Various Tests and Criteria Employed in Allergic Bronchopulmonary Aspergillosis: A Latent Class Analysis

Ritesh Agarwal[1*], Dipesh Maskey[1], Ashutosh Nath Aggarwal[1], Biman Saikia[2], Mandeep Garg[3], Dheeraj Gupta[1], Arunaloke Chakrabarti[4]

PLoS ONE 8(4): e61105. doi:10.1371/journal.pone.0061105

- The sensitivity and specificity of different tests were as following
  - ❑ aspergillus skin test positivity 94.7% & 79.7%.
  - ❑IgE >1000IU/ml 97.1 %& 37.7%.
  - ❑A fumigatus specific IgE level >.35kUA/L 100% & 69.3%.
  - ❑Eosinophil count >1000cells/cc 29.5%&93.1%
  - ❑Bronchiectasis 91.9 and 80.9%
  - ❑HAM 39.7% &100%

	No. of patients	Sensitivity	Specificity
Patterson criteria [9]			
At least 5 criteria	97	100% (100–100)	87% (83.2–90.6)
At least 6 criteria	56	100% (100–100)	100% (100–100)
At least 7 criteria	22	39.3% (26.4–52.1)	100% (100–100)
All 8 major criteria	07	12.5% (4.2–21.7)	100% (100–100)
Agarwal criteria [11]	55	96.4% (94.2–100)	100% (100–100)

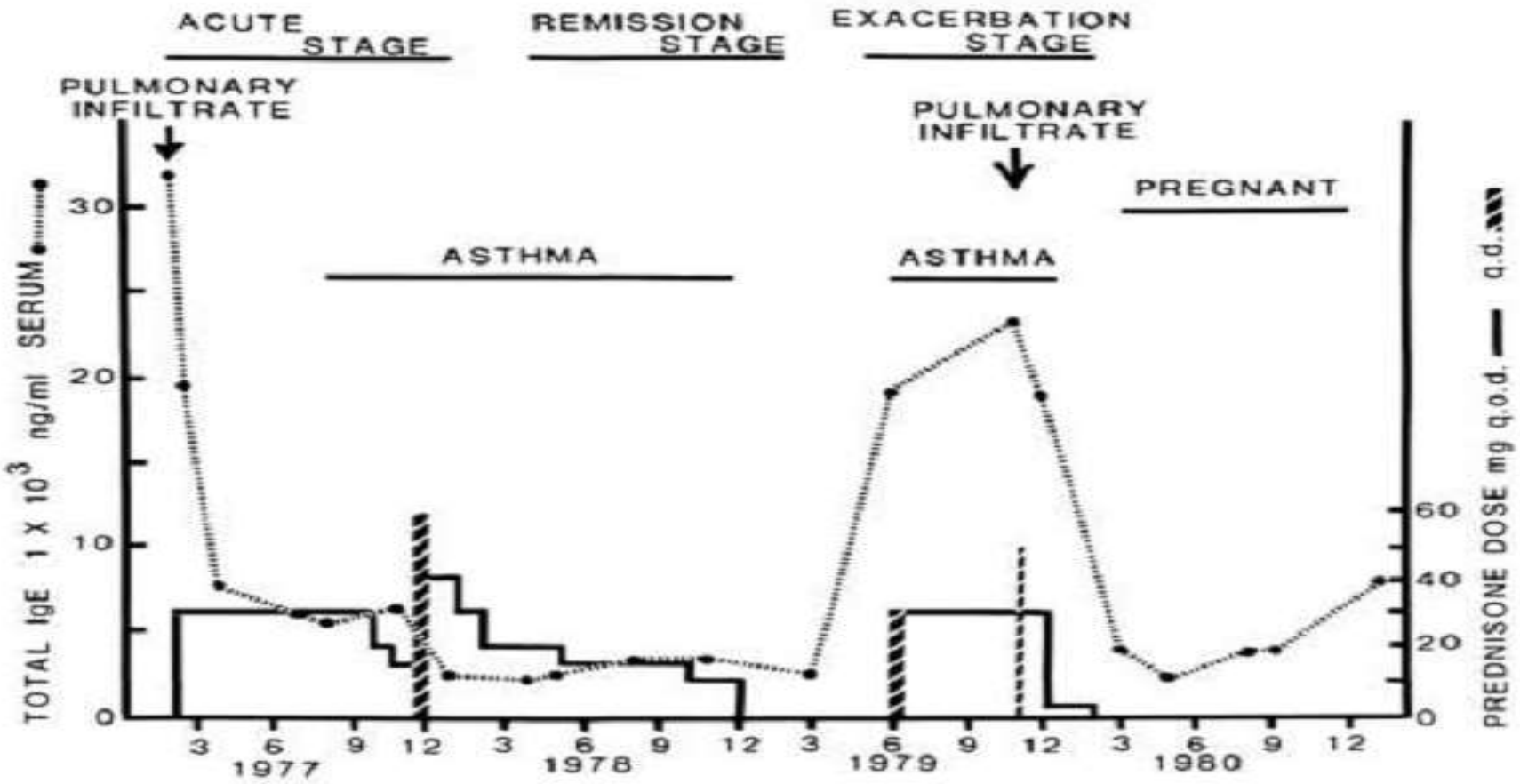
The values in parenthesis represent 2.5–97.5% bootstrap confidence intervals obtained by bootstrapping 5000 samples.
doi:10.1371/journal.pone.0061105.t004

Agarwal R, Maskey D, Aggarwal AN, Saikia B, Garg M, et al. (2013) Diagnostic Performance of Various Tests and Criteria Employed in Allergic Bronchopulmonary Aspergillosis: A Latent Class Analysis. PLoS ONE 8(4): e61105. doi:10.1371/journal.pone.006110

Staging

- Original study by: Patterson et al published in annals of internal medicine
- Prospective observational study over 10 years including 40 patients;
- Proposed stages were : acute/remission/exacerbation/corticosteroid dependent/fibrotic

Staging an aid to management



RECENT DEVELOPMENT IN STAGING

Table 5. Newly proposed clinical staging of ABPA in asthma

Stage	Definition	Features
0	Asymptomatic	• GINA definition of controlled asthma • On investigation fulfils the diagnostic criteria of ABPA (Table 4) • Has not been previously diagnosed to have ABPA
1	Acute	• Patient has uncontrolled asthma/constitutional symptoms • Fulfils diagnostic criteria for ABPA • Not previously diagnosed to have ABPA
1a	With mucoid impaction	Meets all the criteria and there is documented mucoid impaction on chest radiograph, CT chest or bronchoscopy
1b	Without mucoid impaction	Meets all the criteria and there is no documented mucoid impaction on CT chest or bronchoscopy
2	Response	• Clinical improvement (resolution of constitutional symptoms, improvement in asthma control) • Major radiological improvement* • IgE decline by ≥ 25% of baseline at 8 weeks
3	Exacerbation	Clinical and/or radiological deterioration associated with an increase in IgE by ≥ 50%
4	Remission	Sustained clinicoradiological improvement with IgE levels remaining at or below baseline (or increase by < 50%) for ≥ 6 months on or off therapy other than systemic glucocorticoids
5a	Treatment-dependent ABPA	If patient has relapse on two or more consecutive occasions within 6 months of stopping treatment or has worsening of clinical, radiological or immunological parameters on tapering oral steroids/azoles
5b	Glucocorticoid-dependent asthma	If the patient requires oral or parenteral glucocorticoids for control of asthma while the activity of ABPA is controlled as reflected by IgE levels and chest radiograph
6	Advanced ABPA	Presence of type II respiratory failure and/or cor pulmonale with radiological evidence of fibrotic findings consistent with ABPA on HRCT of the chest after excluding reversible causes of acute respiratory failure

EVIDENCES

Clinical Significance of Hyperattenuating Mucoid Impaction in Allergic Bronchopulmonary Aspergillosis*

An Analysis of 155 Patients

Ritesh Agarwal, MD, DM; Dheeraj Gupta, MD, DM, FCCP; Ashutosh N. Aggarwal, MD, DM, FCCP; Akshay K. Saxena, MD; Arunaloke Chakrabarti, MD; and Surinder K. Jindal, MD, FCCP

CHEST / 132 / 4 / OCTOBER, 2007

Table 3—*Factors Predicting Relapse in Patients With ABPA: Multivariate Analysis**

Variables	Patients With Relapse	Patients Without Relapse	Adjusted OR (95% CI)
Patients with ABPA-S (normal HRCT, n = 37) included	n = 35	n = 120	
Duration of asthma, yr	8.5 (5.1–11.9)	9 (7.7–10.3)	0.98 (0.92–1.04)
Lung function abnormality on spirometry	32 (78.3,70.1–84.8)	94 (91.4,77.6–97.0)	2.72 (0.66–11.18)
Absolute eosinophil count at presentation, /μL	1,454.2 (837–2,071.3)	1,208.5 (941.3–1,475.8)	1.0 (1.0–1.0)
IgE levels (total) at presentation, IU/mL	7,020.7 (5368.5–8,673)	6,263.2 (5180.8–7,345.5)	1.0 (1.0–1.0)
IgE levels (*A fumigatus*) at presentation, kU/L	7.6 (4.8–10.4)	8.6 (6.4–10.9)	0.99 (0.95–1.04)
Extent of bronchiectasis based on number of segments involved	8.6 (6.9–10.4)	4.7 (4–5.3)	1.23 (1.13–1.42)†
Presence of HAM	12 (34.3,20.8–50.8)	17 (14.2,9.0–21.5)	3.61 (1.23–10.61)‡
Patients with ABPA-S (normal HRCT, n = 37) excluded	n = 31	n = 87	
Duration of asthma, yr	8.9 (5.1–12.7)	8.9 (7.4–10.5)	0.98 (0.92–1.04)
Lung function abnormality on spirometry	28 (90.3,75.1–96.7)	70 (80.5,70.9–87.4)	2.23 (0.46–10.81)
Absolute eosinophil count at presentation, /μL	1,476.7 (793–2,160.3)	1,210.9 (1,009.7–1,412)	1.0 (1.0–1.0)
IgE levels (total) at presentation, IU/mL	7,267.5 (5,472.3–9,062.7)	6,522.5 (5,192.3–7,852.7)	1.0 (1.0–1.0)
IgE levels (*A fumigatus*) at presentation, kU/L	7.9 (4.9–11)	9.6 (6.7–12.4)	1 (0.95–1.05)
Extent of bronchiectasis based on number of segments involved	9.8 (8.3–11.3)	6.4 (5.9–6.9)	1.41 (1.21–1.67)‡
Presence of HAM	12 (38.7,23.7–56.2)	17 (19.5,12.6–29.1)	5.05 (1.49–17.04)†

*Data are presented as mean (95% CI) or No. (%,95% CI).

†$p < 0.05$.

‡$p < 0.001$.

Table 4—*Factors Predicting Failure To Achieve Complete Remission in Patients With ABPA: Multivariate Analysis**

Variables	Patients Who Fail To Achieve Complete Remission	Patients Who Achieve Complete Remission	Adjusted OR (95% CI)
Patients with ABPA-S (normal HRCT, n = 37) included	n = 25	n = 130	
Duration of asthma	10.3 (5.7–14.9)	8.6 (7.4–9.8)	1 (0.94–1.07)
Lung function abnormality on spirometry	23 (92,75.0–97.8)	103 (79.2,71.5–85.3)	3.13 (0.42–23.37)
Absolute eosinophil count at presentation, /μL	1,215.6 (592.9–1,838.3)	1,273.3 (1,001.4–1,545.3)	1.0 (1.0–1.0)
IgE levels (total) at presentation, IU/mL	7,020.7 (5,368.5–8,673)	6,213.9 (5,196.5–7,231.4)	1.0 (1.0–1.0)
IgE levels (*A fumigatus*) at presentation, kU/L	8.5 (4.8–12.3)	8.4 (6.3–10.5)	1.02 (0.97–1.06)
Extent of bronchiectasis based on number of segments involved	10.6 (8.9–12.3)	4.6 (4.0–5.2)	1.55 (1.29–1.85)†
Presence of HAM	8 (32.0,17.2–51.6)	21 (16.2,10.8–23.4)	3.41 (0.89–13.10)
Patients with ABPA-serologic (normal HRCT, n = 37) excluded	n = 25	n = 93	
Duration of asthma, yr	10.3 (5.7–14.9)	8.6 (7.1–10.1)	1.0 (0.94–1.07)
Lung function abnormality on spirometry	23 (92,75.0–97.8)	75 (80.6,71.5–87.4)	3.05 (0.42–22.32)
Absolute eosinophil count at presentation, /μL	1,215.6 (592.9–1,838.3)	1,298.2 (1,055.6–1,540.8)	1.0 (1.0–1.0)
IgE levels (total) at presentation, IU/mL	7,579.8 (5,525.2–9,634.5)	6,486.6 (5,223–7,750.2)	1.0 (1.0–1.0)
IgE levels (*A fumigatus*) at presentation, kU/L	8.5 (4.8–12.3)	9.3 (6.6–12.0)	1.02 (0.97–1.06)
Extent of bronchiectasis based on number of segments involved	10.6 (8.9–12.3)	6.4 (5.9–6.9)	1.52 (1.26–1.83)†
Presence of HAM	8 (32.0,17.2–51.6)	21 (22.6,15.3–32.1)	3.25 (0.85–12.46)

*Data are presented as mean (95% CI) or No. (%, 95% CI).

†$p < 0.001$.

Clinical significance of decline in serum IgE levels in allergic bronchopulmonary aspergillosis

Ritesh Agarwal [a,*], Dheeraj Gupta [a], Ashutosh N. Aggarwal [a], Akshay K. Saxena [d], Biman Saikia [b], Arunaloke Chakrabarti [c], Surinder K. Jindal [a]

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Table 2 Decline in IgE levels at six weeks.

Percentage decline		
Baseline IgE ≤2500 IU/mL ($n = 11$)		26.1% (19.9–32.3)
Baseline IgE >2500 IU/mL ($n = 43$)		44% (38.9–49.1)*
All patients ($n = 54$)		38.8% (32.4–45.1)
35% decline in IgE levels		
	IgE ≤2500 IU/mL ($n = 11$)	IgE >2500 IU/mL ($n = 43$)
IgE decline < 35%	9 (81.8; 52.3–94.5)	13 (30.2; 18.6–45.1)
IgE decline ≥ 35%	2 (18.2; 51.4–47.7)	30 (69.8; 54.9–81.4)*
Decline in ABPA-s vs. ABPA-CB		
	ABPA-s ($n = 10$)	ABPA-CB ($n = 44$)
Absolute decline	2652 (399–4905)	4136 (2526–5745)
Percentage decline	35.8 (26.6–45.1)	41.4 (36.1–46.7)

All the results are expressed as mean (95% confidence intervals) and number (percentage with 95% confidence intervals) unless otherwise stated.

*p-value less than 0.05.

Table 4 Factors predicting relapse and complete remission in patients with allergic bronchopulmonary aspergillosis - multivariate analysis. All the results are expressed as mean (95% confidence intervals) and number (percentage, 95% confidence intervals) unless otherwise stated.

Variables	Relapse ($n = 24$)	No relapse ($n = 30$)	Adjusted OR (95% CI)
Duration of asthma (in years)	10 (6.5–13.4)	12.2 (6.8–17.6)	1.06 (0.99–1.13)
Lung function abnormality on spirometry	17 (70.8, 50.8–85.1)	23 (76.7, 59.1–88.2)	2.48 (0.37–16.83)
Absolute eosinophil count at presentation, cells/μL	1095.9 (773.1–1418.7)	1185.6 (804.3–1567)	0.99 (0.99–1)
Total IgE levels at presentation, IU/mL	8204.6 (5573.5–10835.7)	7529.3 (4808.6–10252)	1 (1–1)
Percentage decline in IgE levels at six weeks	42.8 (35.8–49.8)	38.4 (32.1–44.7)	1.02 (0.95–1.1)
A. fumigatus specific IgE levels at presentation, kUA/L	16.2 (8.7–23.7)	14.1 (5.6–22.5)	1.0 (0.96–1.04)
Lung segments involved by bronchiectasis on HRCT	9.0 (7.1–10.8)	5.0 (3.2–6.9)	**1.22 (1.03–1.45)***
Presence of high-attenuation mucus	12 (50, 31.4–68.6)	2 (6.7, 1.8–21.3)	**38.07 (1.96–740.24)***
Variables	Complete remission ($n = 39$)	No complete remission ($n = 15$)	Adjusted OR (95% CI)
Duration of asthma (in years)	9.6 (6.9–12.4)	14.3 (5.9–22.8)	1.06 (0.99–1.13)
Lung function abnormality on spirometry	29 (74.4, 58.9–85.4)	11 (73.3, 48.1–89.1)	1.64 (0.26–10.25)
Absolute eosinophil count at presentation, cells/μL	1158.1 (853.4–1462.8)	1113.7 (640.9–1586.6)	1 (0.99–1.0)
Total IgE levels at presentation, IU/mL	7242.3 (4990.3–9494.4)	9355.9 (5858.6–12853.2)	1 (1–1)
Percentage decline in IgE levels at six weeks	38.6 (33.1–43.9)	45.1 (35.9–54.2)	1.07 (0.99–1.15)
A. fumigatus specific IgE levels at presentation, kUA/L	16.2 (8.9–23.4)	12 (3.8–20.2)	0.96 (0.91–1.01)
Lung segments involved by bronchiectasis on HRCT	5.8 (4.2–7.3)	9.4 (6.6–12.2)	**1.29 (1.06–1.57)***
Presence of high-attenuation mucus	6 (15.4, 7.2–29.7)	6 (40.0, 19.8-64.3)	2.79 (0.38-20.66)

*$p < 0.05$.

Radiological staging

- Gree nberger et al. prop osed ABPA-S as the earliest stage of ABPA with less sev ere immu nological findings comp ared to ABPA -CB However in their study only A. fumigatus-specific IgG levels were higher in ABPA-CB, while the other immunological parameters (total and A. fumigatus specific IgE) were similar in the two groups

  Ann Allergy 1993; 70:333–8.

- Thereafter, Kumar et al. classified ABPA into three groups namely ABPA-S, ABPA-CB and ABPA-CB with other radiological findings (ABPA-CBORF) , and they propose ABPA CB ORF being the severe most form of the disease

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  Chest 2003; 124:890–2

Table 2—*Skin Tests and Serologic Values in ABPA-S, ABPA-CB, and ABPA-CB-ORF

Variables	Skin Tests		ABPA-S Absolute Eosinophil Counts	ABPA-CB Total IgE, ng/mL	ABPA-CB-ORF IgE-*Af*, IU/mL	IgG-*Af* (Positive)	Precipitating Antibodies (Positive)
	Type I (Positive)	Type III (Positive)					
ABPA-S	6 (100)	2 (33)	935	597 ± 330.22	9.88 ± 7.45	6 (100)	3 (50)
ABPA-CB	6 (100)	3 (50)	1,008	2,571 ± 1,492.14	43.12 ± 38.02	4 (66)	4 (66)
ABPA-CB-ORF	6 (100)	1 (16)	1,233	3,435 ± 3,948.7	47.91 ± 33.00	4 (66)	6 (100)

*Data are presented as No. (%) or mean ± SD unless otherwise indicated.

New radiological staging

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

Evidence

An Alternate Method of Classifying Allergic Bronchopulmonary Aspergillosis Based on High-Attenuation Mucus

Ritesh Agarwal[1]*, Ajmal Khan[1], Dheeraj Gupta[1], Ashutosh N. Aggarwal[1], Akshay K. Saxena[2], Arunaloke Chakrabarti[3]

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Table 2. Clinical, spirometric, serological differences and outcomes in patients with allergic bronchopulmonary aspergillosis (ABPA) based on the classification by Greenberger et al with and without the presence of high attenuation mucus (HAM) and other radiologic findings (ORF).

		All patients (n = 234)		Without HAM (n = 185)		Without ORF (n = 207)	
Characteristics	**ABPA-S (n = 55)**	**ABPA-CB (n = 179)**	**P value**	**ABPA-CB (n = 130)**	**P value**	**ABPA-CB (n = 152)**	**P value**
Clinical history							
Age, in years	35.9 (13.4)	33.6 (12.2)	0.23	33.9 (12.3)	0.37	34.1 (11.9)	0.36
Male Gender, No.(%)	25 (45.5)	98 (54.7)	0.23	73 (56.2)	0.18	83 (54.6)	0.24
Duration of asthma, in years	6 (5–12)	6 (4–14)	0.85	7 (4–15)	0.75	7 (4–15)	0.82
Spirometry, No.(%)							
Normal	15 (27.3)	40 (22.3)	0.33	21 (16.2)	0.05	36 (23.9)	0.55
Mild obstruction	14 (25.5)	45 (25.1)		34 (26.2)		39 (25.7)	
Moderate obstruction	20 (36.4)	55 (30.7)		39 (30)		48 (31.6)	
Severe obstruction	6 (10.9)	39 (21.8)		36 (27.7)		29 (19.1)	
Serological findings							
Total IgE levels, IU/mL	3850 (2650–7800)	5400 (2859–10313)	0.07	4689 (2619–7895)	0.65	5457 (2867–10314)	0.06
A fumigatus specific IgE levels, kUA/L	2.1 (0.95–9.5)	4.8 (1.7–18)	0.02	3.4 (1.4–13.8)	0.19	5.6 (1.9–17.9)	0.01
Absolute eosinophil count, cells/μL	620 (250–962)	983 (558–1770)	0.001	850 (475–1506)	0.03	1048 (650–1800)	0.0001
Type III AST, No.(%)	45 (81.8)	136 (76)	0.37	98 (75.4)	0.34	120 (79.5)	0.2
Aspergillus precipitins, No.(%)	48 (87.3)	146 (82)	0.36	103 (79.8)	0.23	117 (77)	0.46
Clinical outcome							
Number of relapses	0 (0–1)	2 (0–2)	0.0001	1 (0–2)	0.004	2 (0–2)	0.0001
Frequent (≥2) relapses, No. (%)	8 (14.5)	89 (49.7)	0.0001	49 (37.6)	0.002	75 (49.3)	0.0001

Values are expressed as mean (SD) or median (IQR) unless otherwise stated; ABPA-S - serologic ABPA; ABPA-CB - ABPA with central bronchiectasis.
The *A fumigatus* specific IgE levels and eosinophil counts were higher in ABPA-CB compared to ABPA-S. The serological severity varies once patients with HAM and ORF are excluded. On removal of HAM (column 4), only the eosinophil counts retain significance, whereas on removal of ORF (column 6), both *A fumigatus* specific IgE levels and eosinophil counts remain significant.
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Treatment regimens

Oral glucocorticoids

Regimen 1

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

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

Oral itraconazole

Dose: 200 mg twice a day, with therapeutic drug monitoring for at least 16 weeks. Response often takes longer than 16 weeks

R Agarwal et al journal of clinical and experimental allergy 2013

Choice of agent

Oral steroids

ABPA with mucoid impaction

ABPA with significant deterioration of lung function attributed to worsening asthma or ABPA (and not intercurrent infection) would require treatment with glucocorticoids

In those with mucoid impaction and proximal collapse, assessment should be made at 3 weeks and if the collapse has not resolved,therapeutic bronchoscopy should be performed

Azoles (with or without concomitant steroids)

ABPA with recurrent exacerbations (to prevent exacerbations after controlling the exacerbation with glucocorticoids)

Glucocorticoid-dependent ABPA

Inhaled steroids

Single agent ICS therapy should not be used as first-line in the management of ABPA

Can be used for the control of asthma once the oral prednisolone dose is < 10 mg/day

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Follow up and monitoring

- The patients are followed up with a history and physical examination, chest radiograph, total IgE levels and quality of life questionnaire every 8 weeks
- A ≥ 25% decline in IgE level along with clinicoradiological improvement signifies satisfactory response to therapy

- If the patient cannot be tapered off prednisolone/azole then the disease has evolved into stage 4. Management should be attempted with alternate-day prednisone/azole in the least possible dose .
- Monitor for adverse effects of treatment

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Evidences

- Steroid regimen has not been underwent RCT
- Higher dose is associated with higher remission rate and lower incidence of steroid dependent asthma [13.5% in comparison to 45% in a historical cohort where lower dose of steroid was used] – chest 2006
- A RCT (NC T009747 66) is to be published in Feb 2015 from PGIMER Chandigarh.

Azoles in ABPA

* The use of azoles in allergic bronchopulmonary aspergillosis (ABPA) seems rational, with numerous studies demonstrating short-term efficacy with the use of itraconazole.

* Further investigations are required to define the long-term treatment approach with azoles, and the individuals most likely to benefit from treatment.

* More studies are required to determine whether azoles modify the long-term course of the disorder.

* No trial has evaluated the efficacy of azole monotherapy in acute stages of ABPA. A randomized controlled trial comparing monotherapy of itraconazole versus prednisolone in ABPA (MIPA study; ClinicalTrials.gov identifier: NCT01321827) is underway, which aims to answer this question.

* The use of newer azoles should be restricted in those patients with ABPA who are refractory to itraconazole or demonstrate significant adverse events with itraconazole therapy.

* Azoles should be judiciously used in patients with severe asthma with fungal sensitization.

Author(s): Ritesh Agarwal
Source: *Expert Review of Respiratory Medicine*, 6.4 (Aug. 2012): p363.

Reference	Study design	Patients (*n*)	Intervention	Results
ABPA				
Salez *et al.* [45]	Uncontrolled clinical trial	14	Itraconazole 200 mg/day for 12 months	Decrease of 50% in blood eosinophils
				Decrease of 50% in total IgE
				Decrease of 70% in precipitating antibodies
				Increase in FEV1
				Decrease in corticosteroid use
				Decrease in mean exacerbations 2.4 vs. 1.9 per year ($P<0.01$)
				No adverse effects
Stevens *et al.* [46]	Double-blind, placebo-controlled RCT	55	Itraconazole 200 mg b.i.d. for 16 weeks followed by itraconazole 200 mg/day for 16 weeks	Overall response rate with treatment of 46 vs. 19% with placebo ($P=0.04$)
				No significant difference in adverse events
Wark *et al.* [47]	Double-blind, placebo-controlled RCT	29	Itraconazole 400 mg/day for 16 weeks	Decrease in sputum eosinophils ($P<0.01$)
				Decrease in total IgE ($P<0.01$)
				Decrease in IgG to *Aspergillus fumigatus*
				Fewer exacerbations requiring oral corticosteroids ($P=0.03$)
				No significant difference in lung function
Chishimba *et al.* [48]	Retrospective case review	25	Voriconazole 300–600 mg/day	Improvement of symptoms in ≥70%
			Or	No change in lung function
			Posaconazole 800 mg/day	Reduction in total IgE by 27% and specific IgE by 24%
			All previously received itraconazole	Improvement in radiological infiltrates in ≥50%
				Improvement in quality of life in >55%
				Adverse events in 40% with voriconazole and 22% with posaconazole

RCT on azoles in ABPA

Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: A randomized controlled trial

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Study protocol

- At the initial screening visit, diagnosis and clinical stability were reviewed. Subjects then entered a 2-week run-in phase recording daily peak expiratory flow (PEF).
- At visit 2, clinical stability was reassessed, and stable subjects were randomized to treatment.
- Subjects then attended for 4 visits on a monthly basis. At each visit, subjects underwent clinical assessment, hypertonic saline challenge, sputum induction, quality-of-life score determination, and blood draw for immune markers.
- Subjects kept a daily diary recording PEF, medication use, and compliance
- Primary outcome : sputum eosinophil count
- Secondary outcome measure of systemic immuno activation against A fumigatus by means of blood eosinophil count and serum total IgE.

Conclusion

- In this randomized, double-blind, placebo-controlled study they have shown that in subjects with clinically stable ABPA, the addition of 400 mg of itraconazole daily reduces airway inflammation, with a reduction in sputum eosinophils and a significant decrease in sputum ECP levels. In addition, there was evidence of a reduction in systemic immune activation in those treated with itraconazole, with significant decreases in total serum IgE and IgG antibodies to *A fumigatus*, together with fewer severe exacerbations requiring treatment with prednisone.

A RANDOMIZED TRIAL OF ITRACONAZOLE IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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(N Engl J 2000;342:756-62.)

TABLE 2. CRITERIA FOR ENTRY INTO AND EXCLUSION FROM THE STUDY.*

Entry criteria†

Asthma (defined as a ratio of forced expiratory volume in one second to forced vital capacity <0.7) within 2 weeks before entry
Aspergillus-specific IgE within 2 weeks before entry‡
Total serum IgE concentration >400 IU per milliliter within 2 weeks before entry (or >250 IU per milliliter, with evidence of fluctuation with disease activity)§
Dependence on corticosteroid therapy (need for ≥10 mg of prednisone or equivalent per day orally) within 2 weeks before entry¶
Documented history of immediate reaction to aspergillus antigen on skin testing
Documented history of pulmonary infiltrates characteristic of allergic bronchopulmonary aspergillosis‖
History of IgG antibody against aspergillus documented by any method**

Exclusion criteria

Treatment with itraconazole for ≥5 days within 2 months before entry
Use of any other antifungal agents within 14 days before entry
Treatment with any investigational drug either concurrently or within 1 month before entry
Pregnancy or lactation
Serum aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase concentrations >5 times the normal concentration or bilirubin concentration >2 mg per deciliter (34 μmol per liter)
Use of rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, astemizole, terfenadine, histamine H_2 blockers, or omeprazole or continual use of antacids
History of hypersensitivity to azole compounds
An age <13 years and weight <40 kg
Unreliability in following physicians' directives
Inability to take oral medication

STUDY DESIGN

- The study of patients with allergic bronchopulmonary aspergillosis had two phases.
- The first phase was a double-blind comparison of itraconazole at the dose most commonly prescribed for the treatment of deep mycoses, 200 mg twice daily, and an identical-appearing placebo over a 16-week period.
- The second phaseinvolved open-label treatment of all patients with a smaller dose of itraconazole (200 mg daily) for another 16 weeks, to assess the effects of this dose and of long-term treatment.
- During the initial 16-week trial, investigators were required to attempt to taper the doses of corticosteroids used by the patients, beginning after 4 weeks. For patients who were receiving at least 10 mg of prednisone or its equivalent per day at entry and during the trial, the dose was to be reduced by not more than 50 percent every four weeks; once patients began receiving less than 10 mg per day, the dose was to be reduced to zero over a period of at least four weeks.

TABLE 3. DEFINITION OF A RESPONSE IN THE DOUBLE-BLIND TRIAL.*

Reduction in the dose of corticosteroid by 50 percent or more
Decrease in the total IgE concentration by 25 percent or more
At least one of the following
Increase in exercise tolerance by at least 25 percent
Improvement by 25 percent in results of at least one of five pulmonary-function tests†
Resolution of infiltrates present at enrollment and attributable to allergic bronchopulmonary aspergillosis and no subsequent development of infiltrates, or absence of development of any infiltrates during the study if no infiltrates were present at enrollment‡

RESULT

- At the end of 16 weeks response rate was significantly higher for itraconazole group than for placebo.
- In subgroup analysis response rate was higher in patients with bronchiecstasis than in patients without it.

Anti IgE theapy for ABPA

Allergic bronchopulmonary aspergillosis treated successfully for one year with omalizumab

Jennifer Collins et al Journal of asthma and allergy 2012

Results: A total of 21 charts were screened for the diagnosis of ABPA and bronchial asthma. Four patients with ABPA were identified; two of these patients were male. The median monthly systemic corticosteroid use at 6 months and 12 months decreased from baseline usage. Total serum IgE decreased in all patients at 12 months of therapy. Pre-bronchodilator forced expiratory vital capacity at one second (FEV_1) was variable at 1 year of treatment. There was an improvement in Asthma Control Test (ACT) symptom scores for both daytime and nighttime symptoms.

Conclusions: Treatment with omalizumab creates a steroid-sparing effect, reduces systemic inflammatory markers, and results in improvement in ACT scores in patients with ABPA.

Take home message

- All patients with asthma should be screened for allergic sensitivity.
- Early initiation of therapy may prevent permanent damage to lung; new revised diagnostic criteria help in this regard, but validation studies are needed.
- Role of antifungal and its exact place in treatment algorithm is yet to be defined