Updated definition of allergic bronchopulmonary aspergillosis (ABPA) and assessment of therapeutic response

Ritesh Agarwal MD, DM
Professor of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research
Chandigarh, India

Disclosures

- Received grant support from Cipla Pharmaceuticals, India for conducting research in ABPA

ISHAM-ABPA working group

- **Ritesh Agarwal**
- **Inderpaul Singh Sehgal**
- **Valliappan Muthu**
- **David W Denning**
- **Arunaloke Chakrabarti**
- Kathirvel Soundappan
- Mandeep Garg
- Shivaprakash M Rudramurthy
- Sahajal Dhooria
- Darius Armstrong-James
- Koichiro Asano
- Jean-Pierre Gangneux
- Sanjay H Chotirmall
- Helmut J.F. Salzer
- James D Chalmers
- Cendrine Godet
- Marcus Joest
- Iain Page
- Parameswaran Nair
- P Arjun
- Raja Dhar
- Kana Ram Jat
- Geethu Joe
- Uma Maheswari Krishnaswamy
- Joseph L Mathew
- Venkata Nagarjuna Maturu
- Anant Mohan
- Alok Nath
- Dharmesh Patel
- Jayanthi Savio
- Puneet Saxena
- Rajeev Soman
- Balamugesh Thangakunam
- Caroline G Baxter
- Felix Bongomin
- William J Calhoun
- Oliver A Cornely
- Jo A Douglass
- Chris Kosmidis
- Jacques F Meis
- Richard Moss
- Alessandro C. Pasqualotto
- Danila Seidel
- Rosanne Sprute
- Kuruswamy Thurai Prasad
- Ashutosh N Aggarwal

Agenda

- Updated definition of ABPA
- Development of various criteria used for diagnosing ABPA
- New criteria per the revised ISHAM-ABPA working group guidelines
- Current understanding in assessing treatment response

UPDATED ABPA DEFINITION

ABPA definition

- ABPA: an allergic disorder caused by immunological reactions mounted against *A. fumigatus* colonizing the airways of patients with asthma (or cystic fibrosis)

- Allergic bronchopulmonary mycosis (ABPM): an ABPA-like syndrome caused by fungi other than *A. fumigatus.*

Agarwal R. Chest 2009; 135(3): 805-826
Chowdhary A, et al. Crit Rev Microbiol 2014; 40(1): 30-48

ABPA definition

- ABPA: an allergic disorder caused by immunological reactions mounted against *A. fumigatus* colonizing the airways of patients with asthma (or cystic fibrosis)
- Updated definition: immunological reactions mounted against any *Aspergillus spp.*, most commonly *A. fumigatus.*

- Allergic bronchopulmonary mycosis (ABPM): an ABPA-like syndrome caused by fungi other than *A. fumigatus.*
- Updated definition: an ABPA-like syndrome caused by fungi other than *Aspergillus spp.*

Agarwal R. Chest 2009; 135(3): 805-826
Chowdhary A, et al. Crit Rev Microbiol 2014; 40(1): 30-48

Why so much interest in ABPA?

- The fact that the condition responds remarkably to treatment with glucocorticoids or antifungal triazoles.
- Early detection (and treatment) can prevent the progression of bronchiectasis.
- Estimated 4.8 million cases worldwide, with 1.51 million cases in India alone.

Denning D, et al. Med Mycol 2013; 51(4): 361-70
Agarwal R, et al. PLoS One 2014; 9(12): e114745

EVOLUTION OF VARIOUS DIAGNOSTIC CRITERIA

ABPA DIAGNOSIS - A TIMELINE

2023
DELPHI CONSENSUS GUIDELINES
Collaborative effort from the ISHAM-ABPA working group
Includes ABPA and ABPM in asthma, cystic fibrosis and other airway disease

2021
ASANO et al.
Japanese ABPM working group criteria
Emphasis on fungal cultures and mucus plugs

2021
SAXENA et al.
Refined and modified ISHAM-ABPA working group criteria
tested using a latent class analysis

2013
ISHAM-ABPA working group criteria
First global attempt to formulate an objective
and evidence-based criteria

2003
CF foundation consensus conference criteria
Stevens et al. proposed a consensus criteria for
diagnosing ABPA in CF

1979
NELSON et al.
First diagnostic criteria for ABPA in CF

1977
ROSENBERG et al.
First formal criteria

HINSON et al. 1952
First description of ABPA in medical literature

Clinical and Immunologic Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis

MICHAEL ROSENBERG, M.D.; ROY PATTERSON, M.D.; RICHARD MINTZER, M.D.;
BARRY J. COOPER, M.D.; MARY ROBERTS; and KATHLEEN E. HARRIS; Chicago, Illinois

Rosenberg M, et al. Ann Intern Med 1977; 86(4): 405-414

Rosenberg-Patterson criteria

Major criteria

- Asthma
- Radiological opacities
- Type 1 *Aspergillus* skin test positive
- Specific *Aspergillus*-IgE elevated
- Precipitins (*Af*) in serum
- IgE levels elevated in serum
- Central bronchiectasis
- Eosinophilia

Minor criteria

- Presence of *Aspergillus* in sputum
- Expectoration of brownish-black mucus plugs
- Delayed type 3 skin test reaction to *Aspergillus* antigen

Rosenberg M, et al. Ann Intern Med 1977; 86(4): 405-414

Limitations with the Patterson criteria

- No agreement on the number of components to make the diagnosis.
- Laid equal weightage on all the components.
- Lack of consensus on the cut-off values for immunological tests.

Patterson criteria	Sensitivity (%)	Specificity (%)
At least 5	100	87
At least 6	100	100
At least 7	39.3	100
All 8 major	12.5	100

Agarwal R. Int J Respir Care 2010; 6(2): 53-54, 56-63
Agarwal R, et al. Plos One 2013; 8(4): e61105

Other criteria

Aspergillosis and Atopy in Cystic Fibrosis[1-3]

LOIS A. NELSON, MARY LOU CALLERAME, and ROBERT H. SCHWARTZ

Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis—State of the Art: Cystic Fibrosis Foundation Consensus Conference

David A. Stevens,[1] Richard B. Moss,[2] Viswanath P. Kurup,[3] Alan P. Knutsen,[4] Paul Greenberger,[5] Marc A. Judson,[6] David W. Denning,[7] Reto Crameri,[8] Alan S. Brody,[9] Michael Light,[10] Marianne Skov,[12] William Maish,[11] Gianni Mastella,[13,a] and participants in the Cystic Fibrosis Foundation Consensus Conference[b]

Nelson LA, et al. Am Rev Respir Dis 1979; 120(4): 863-873
Stevens DA, et al. Clin Infect Dis 2003; 37 Suppl 3: S225-64

Diagnostic criteria

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*

[1]Department of Pulmonary Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [2]Division of Medical Mycology, Department of Medical Microbiology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [3]Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, New Delhi, India, [4]Department of Pulmonary Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [5]Department of Medical Microbiology and Infectious Diseases, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands, [6]Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [7]Department of Internal Medicine, All India Institute of Medical Sciences, New Delhi, India, [8]Department of Pediatrics, Stanford University, Palo Alto, CA, USA and [9]Manchester Academic Health Science Centre, The National Aspergillosis Centre, University of Manchester, University Hospital of South Manchester, Manchester, UK

Agarwal R, et al. Clin Exp Allergy 2013; 43(8): 850-873

Diagnostic criteria for ABPA

Predisposing conditions

- Bronchial asthma, cystic fibrosis

Obligatory criteria (both should be present)

- Type I *Aspergillus fumigatus* (*Af*) skin test positive or *Af*-IgE >0.35 kUA/L
- Serum 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
- Eosinophil count >500 cells/μL (may be historical)

Agarwal R, et al. Clin Exp Allergy 2013; 43(8): 850-873

Challenges in validating a diagnostic criteria for ABPA

- No single reference standard for diagnosing ABPA.
- How does one evaluate the diagnostic performance of a criterion when there is no reference standard?
- Latent class analysis…

Diagnostic performance…

OPEN ACCESS Freely available online

PLOS ONE

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]

1 Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India, **2** Department of Immunopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, **3** Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Chandigarh, India, **4** Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Original Article

Which Are the Optimal Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis? A Latent Class Analysis

Puneet Saxena, MD, DM[a], Hansraj Choudhary, MSc[a,b], Valliappan Muthu, MD, DM[a], Inderpaul Singh Sehgal, MD, DM[a], Sahajal Dhooria, MD, DM[a], Kuruswamy Thurai Prasad, MD, DM[a], Mandeep Garg, MD[a,c], Biman Saikia, MD[a,d], Ashutosh Nath Aggarwal, MD, DM[a], Arunaloke Chakrabarti, MD[a,b], and Ritesh Agarwal, MD, DM[a] *Chandigarh, India*

Agarwal R, et al. Plos One 2013; 8(4): e61105
Saxena P, et al. J Allergy Clin Immunol Pract 2021; 9(1): 328-335 e1

Diagnostic performance…

	Sensitivity (%)	Specificity (%)
A.fumigatus skin test positivity	82.9	81.4
A.fumigatus-specific IgE >0.35 kUA/L	98.2	72.1
A.fumigatus-specific IgG >27 mgA/L	94.6	77.2
Total eosinophil count >500 cells/μL	73.3	66.0
Serum total IgE >500 IU/mL	97.7	49.3
Bronchiectasis on chest CT	100	92.5
Mucoid impaction on chest CT	67.7	98.9
High-attenuation mucus on chest CT	36.0	100.0

Saxena P, et al. J Allergy Clin Immunol Pract 2021; 9(1): 328-335 e1

New(er) diagnostic criteria for ABPA

- Predisposing conditions
  - Bronchial asthma, cystic fibrosis
- Obligatory criteria (both should be present)
  - ~~Type I *Af* skin test positive or~~ serum *Af*-IgE >0.35 kUA/L
  - Serum total IgE levels >~~10~~500 IU/mL
- Other criteria (at least two of three)
  - Presence of *Af* ~~precipitating (or~~ IgG) antibodies in serum
  - ~~Imaging consistent with ABPA~~ Bronchiectasis on CT chest
  - Eosinophil count >500 cells/μL

Saxena P, et al. J Allergy Clin Immunol Pract 2021; 9(1): 328-335

New(er) diagnostic criteria for ABPA using LCA

Criteria	Sensitivity (%)	Specificity (%)
Patterson criteria	81.3	98.2
ISHAM criteria	88.5	99.1
Modified ISHAM criteria	100	100

Agarwal R, et al. Front Cell Infect Microbiol 2022; 12: 861866
Saxena P, et al. J Allergy Clin Immunol Pract 2021; 9(1): 328-335

Japanese group criteria

New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation

Koichiro Asano, MD,[a] Akira Hebisawa, MD, PhD,[b] Takashi Ishiguro, MD, PhD,[c] Noboru Takayanagi, MD, PhD,[c] Yasuhiko Nakamura, MD, PhD,[b] Junko Suzuki, MD,[d] Naoki Okada, MD,[a] Jun Tanaka, MD,[a] Yuma Fukutomi, MD, PhD,[e] Shigeharu Ueki, MD, PhD,[f] Koichi Fukunaga, MD, PhD,[g] Satoshi Konno, MD, PhD,[h] Hiroto Matsuse, MD,[i] Katsuhiko Kamei, MD,[j] Masami Taniguchi, MD,[e] Terufumi Shimoda, MD,[k] and Tsuyoshi Oguma, MD,[a] Japan ABPM Research Program *Kanagawa, Tokyo, Saitama, Akita, Sapporo, Chiba, and Fukuoka, Japan*

- Sensitivity for Patterson criteria, ISHAM criteria, and the new criteria: 25.3%, 77.2%, and 96.2%, respectively
- AUC of ROC curve for Patterson criteria, ISHAM criteria, and the new criteria: 0.85, 0.90, and 0.98, respectively

Asano K, et al. J Allergy Clin Immunol 2021; 147(4): 1261-1268 e5

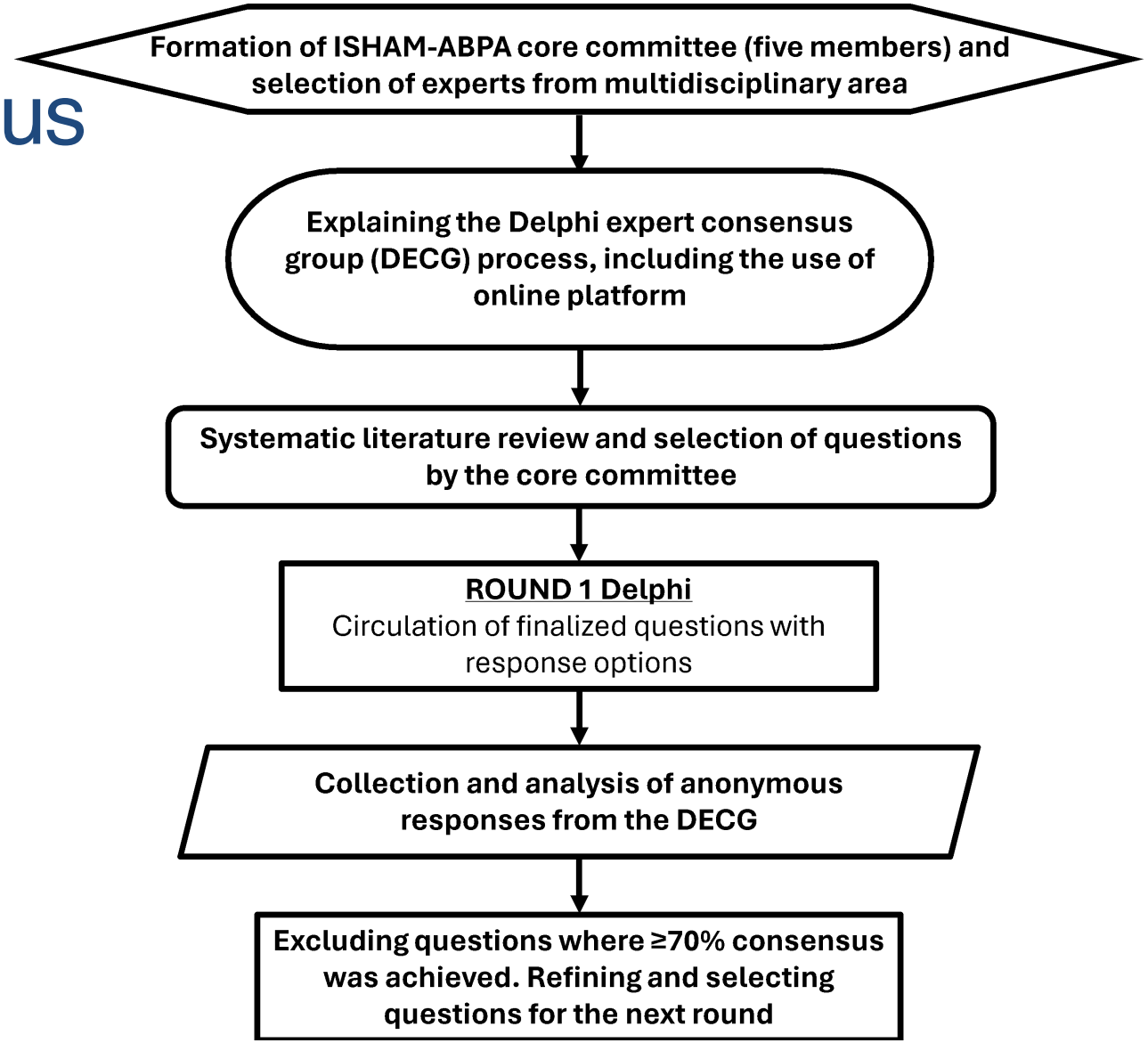
Problems with studies developing the ABPA criteria

- We used latent class analysis (TAGS: evaluation of tests in the absence of a gold standard) for validation, which is a probabilistic model.
- The Japanese group used a clinical reference standard for validating their criteria that already includes all the individual tests being used in the criteria.

- Hence, there was a real need for a new consensus-based diagnostic criteria.

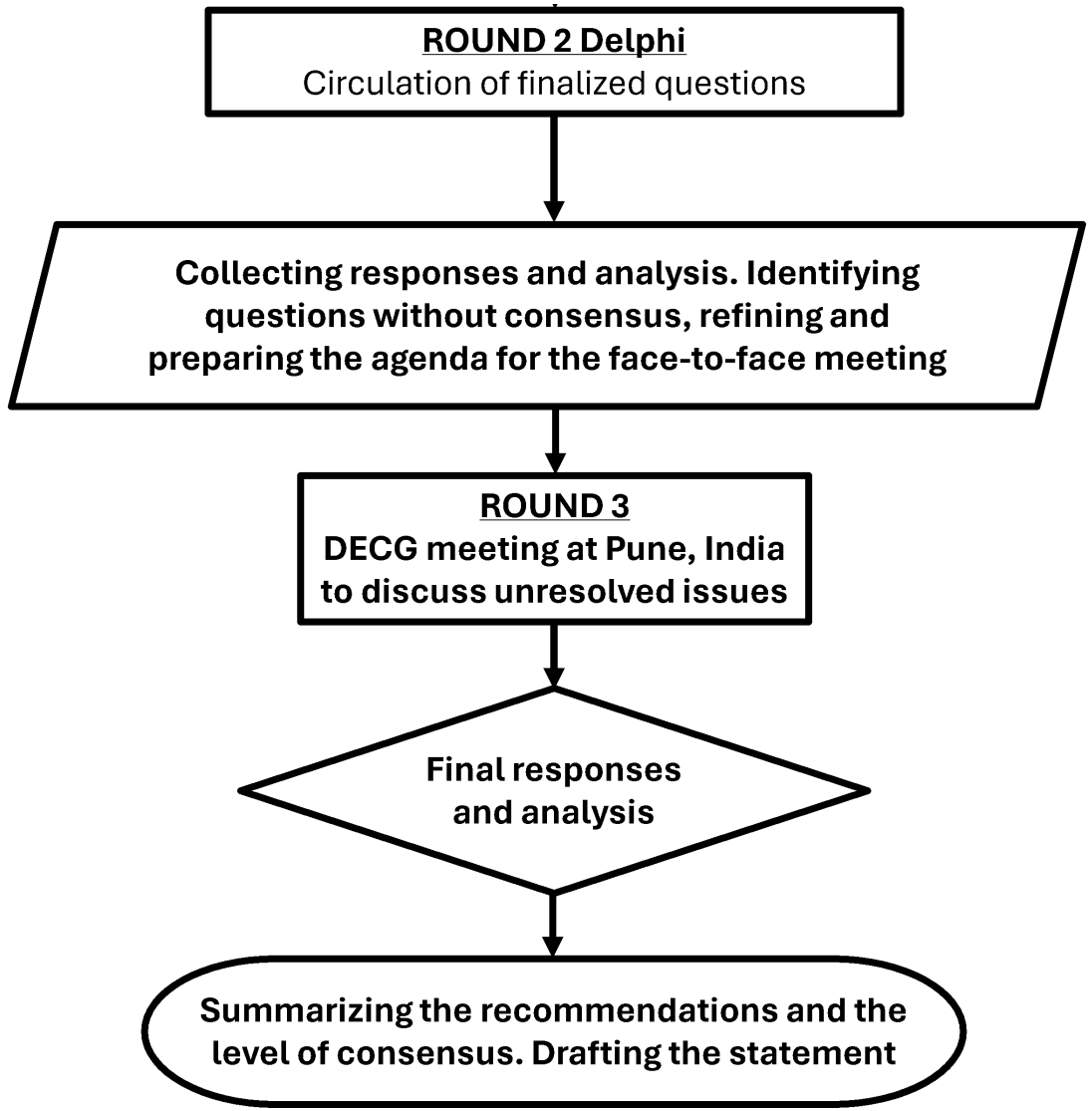
NEW DIAGNOSTIC CRITERIA

Delphi consensus



ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Delphi consensus



ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Delphi consensus on ABPA criteria

- The group suggested modifying the existing ISHAM-AWG criteria.
- Most experts felt that the criteria must be simple and allow identification and differentiation of ABPA and ABPM.
- Finally, after achieving consensus, the group recommended separate criteria for diagnosing ABPA and ABPM.

Revised ISHAM-AWG criteria for ABPA

In patients with predisposing conditions (asthma, cystic fibrosis, chronic obstructive lung disease, bronchiectasis) or compatible clinico-radiological presentation (expectoration of mucus plugs, finger-in-glove and fleeting opacities on chest radiograph, lung collapse, and others)

Essential components

- *A. fumigatus*-IgE ≥0.35 kUA/L
- Serum total IgE ≥500 IU/mL

Other components (any two)

- Positive IgG against *A. fumigatus* (FEIA or lateral flow assay)
- Peripheral blood eosinophil count ≥500 cells/μL (could be historical)
- Thin-section chest computed tomography consistent with ABPA (bronchiectasis, mucus plugging, and high-attenuation mucus) or fleeting opacities on chest radiograph consistent with ABPA

Agarwal R, et al. In peer review

Revised ISHAM-AWG criteria for ABPM

In patients with predisposing conditions (asthma, cystic fibrosis, chronic obstructive lung disease, bronchiectasis) or compatible clinico-radiological presentation

Essential components

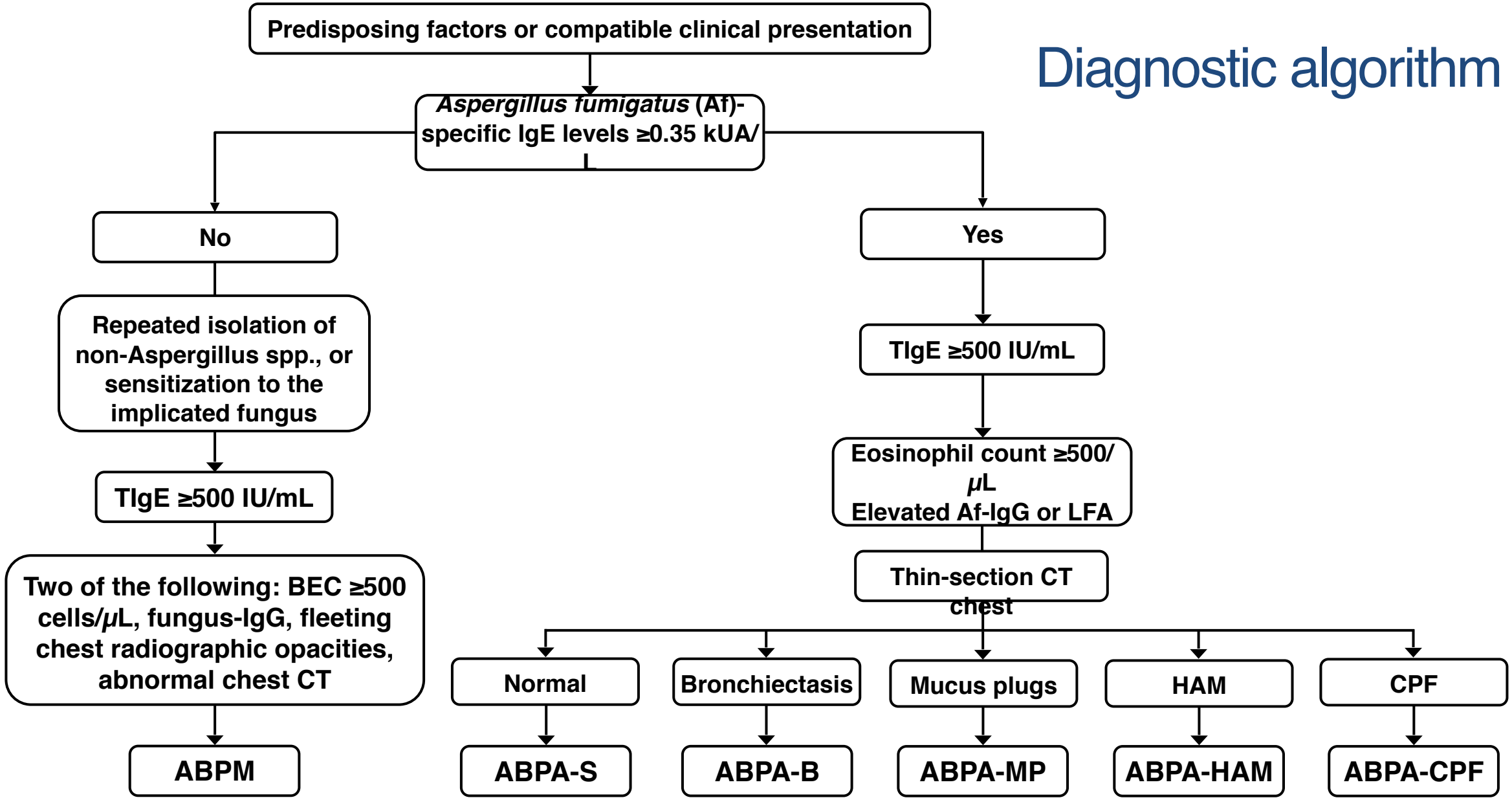
- Elevated fungus-specific IgE
- Serum total IgE ≥500 IU/mL

Other components (any two)

- Positive fungus-specific IgG
- Peripheral blood eosinophil count ≥500 cells/μL (could be historical)
- Thin-section chest computed tomography consistent with ABPA (bronchiectasis, mucus plugging, and high-attenuation mucus) or fleeting opacities on chest radiograph consistent with ABPA
- Two sputum (or one bronchoalveolar lavage fluid) fungal cultures growing the causative fungus

Agarwal R, et al. In peer review

Diagnostic algorithm



Agarwal R, et al. In peer review

ASSESSING TREATMENT RESPONSE IN ABPA

Monitoring treatment response

- Multidimensional assessment: clinical symptoms, serum total IgE, and chest radiographs.
- Symptom monitoring should be done using a semi-quantitative Likert scale, even for patient care.
- A more quantitative scale, like a visual analog scale (VAS) for clinical trials.
- Quality-of-life questionnaires are discouraged for routine patient care but suggested for clinical trials.

Agarwal R, et al. In peer review

Treatment response

Response

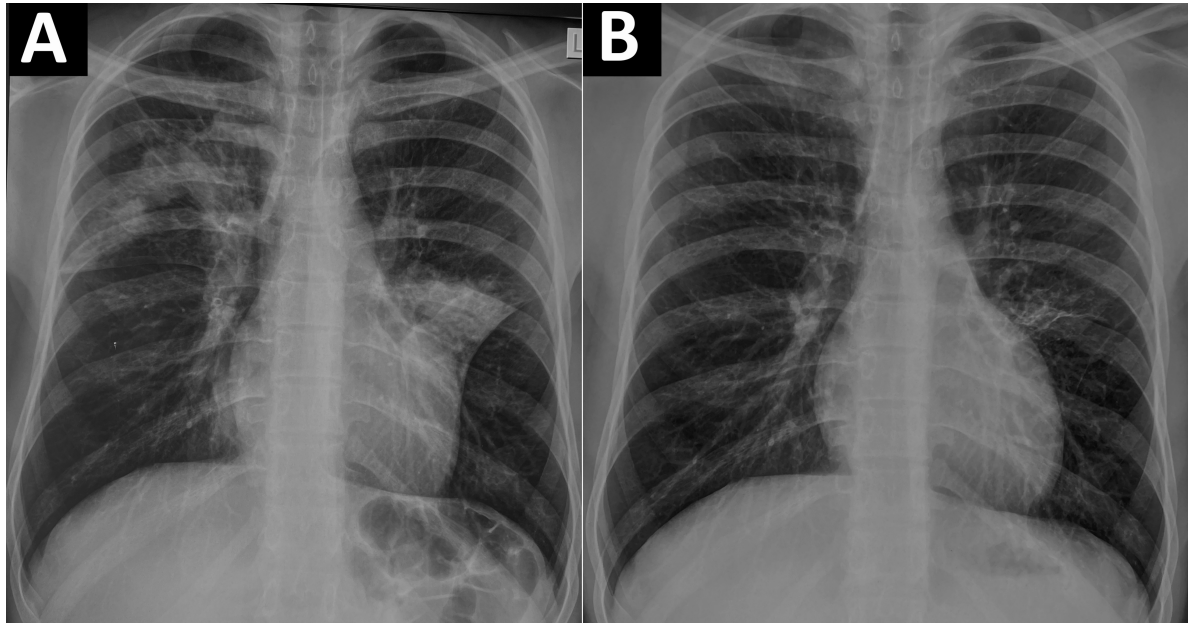
- Symptomatic improvement by at least 50% after eight weeks; and,
- Major radiological improvement (>50% reduction in radiologic opacities) or decline in serum total IgE by at least 20% after eight weeks of treatment.

Agarwal R, et al. In peer review

Treatment response

Response

- Symptomatic improvement by at least 50% after eight weeks; and,
- Major radiological improvement (>50% reduction in radiologic opacities) or decline in serum total IgE by at least 20% after eight weeks of treatment.



Agarwal R, et al. In peer review

Treatment response

Exacerbation

- Sustained (>14 days) clinical worsening, or
- Radiological worsening, and
- Increase in serum total IgE by ≥50% from the last recorded IgE value during clinical stability, along with exclusion of other causes of worsening.

Asthma exacerbation: worsening respiratory symptoms for at least 48 hours, without immunological or radiological deterioration of ABPA/M.

Infective/bronchiectasis exacerbation: clinical deterioration for at least 48 hours, without immunological or radiological deterioration of ABPA/M.

Agarwal R, et al. In peer review

Treatment response

Treatment-dependent ABPA

- Two or more consecutive ABPA/M exacerbations, each within three months of stopping glucocorticoids.
- Worsening respiratory symptoms AND worse imaging or rise in serum total IgE by 50% within four weeks on tapering oral steroids on two separate occasions.

Agarwal R, et al. In peer review

Treatment response

Remission

- Sustained (≥6 months) clinico-radiological improvement, off glucocorticoids; and,
- Lack of rise in serum total IgE by ≥50% from the last recorded IgE during clinical stability.

Patients on biologics or long-term antifungal agents may also be considered in remission if they meet the above criteria.

Agarwal R, et al. In peer review

Summary

- The ISHAM-AWG has proposed revised guidelines for diagnosing, classifying, and treating ABPA/M.

- These guidelines will help bring uniformity in diagnosis and simplify the management of ABPA/M patients in both clinical care and research.

7 online participants