# Recent Advances In The Pathogenesis, Diagnosis And Management Of Allergic Bronchopulmonary Aspergillosis

**Review Article**

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# About the journal

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- **Type of study- Review Article**

# Need for the review

- Allergic bronchopulmonary aspergillosis (ABPA) is an inflammatory disease caused by immunologic reactions initiated against ***Aspergillus fumigatus*** colonizing the airways of patients with **asthma and cystic fibrosis**.
- The common manifestations include **treatment-resistant asthma, transient and fleeting pulmonary opacities and bronchiectasis**. It is believed that globally there are about five million cases of
- ABPA, with India alone accounting for about 1.4 million cases.
- The occurrence of ABPA among asthmatic patients in special clinics may be as high as 13 per cent.
- **Thus, a high degree of suspicion for ABPA should be entertained while treating a patient with bronchial asthma, particularly in specialized clinics**.
- **Early diagnosis and appropriate treatment** can delay (or even prevent) the onset of bronchiectasis, which suggests that all patients of bronchial asthma should be screened for ABPA, especially in chest clinics.

# Respiratory disorders caused by fungi

- 3 types- **Invasive, saprophytic , allergic**
- Allergic respiratory mycosis represents the most severe expression of fungal allergy
- It presents as difficult-to-treat asthma, recurrent pulmonary opacities and bronchiectasis
- **The most common fungus causing allergic pulmonary mycosis is *Aspergillus fumigatus*.**

# Naming

Allergic pulmonary mycoses is conventionally divided as

1. Allergic bronchopulmonary aspergillosis (ABPA) when the causative agent is *A. fumigatus* and
2. Allergic bronchopulmonary mycosis (ABPM) when it is caused by fungi other than *A. fumigatus*

- ABPA commonly complicates the course of patients with asthma and cystic fibrosis (CF).
- ABPA complicating asthma remains **under-recognized,** and a large number of cases (about 30%) are initially misdiagnosed as pulmonary tuberculosis, especially in developing countries
- The **diagnostic delay can be as long as 10 yr from the occurrence** of first symptoms

# Recommendations & Diagnosis Criteria

- The **International Society for Human and Animal Mycology (ISHAM**) has proposed recommendations for the diagnosis and classification of ABPA complicating asthma

- The CF Foundation  has provided guidance  for the diagnosis of ABPA complicating CF

# Facts and pathology

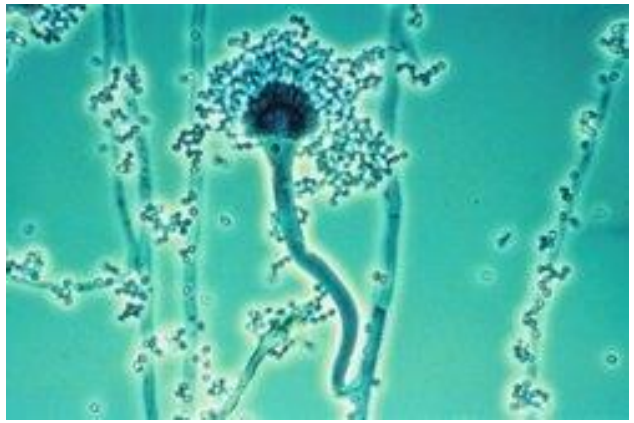
- *Aspergillus* sensitization (AS) is defined by the **presence of a type 1 reaction (immediate cutaneous hyper-reactivity) to *A. fumigatus* antigen injected intracutaneously or a raised immunoglobulin (Ig) E against *A. fumigatus***
- ***Antigen used- Recombinant antigen( better results) or Crude antigen***
- **Patients with AS can or cannot have ABPA**
- **AS with ABPA have poor lung function**
- **AS without ABPA can also have decreased Lung function if there is associated Asthma**
- ***The prevalence of ABPA in Aspergillus-sensitized asthma can be as high as 40 %, highlighting the importance of recognizing AS***
- **In a systematic review, the pooled prevalence of AS and ABPA complicating asthma in chest clinics was about 28 and 13 % respectively**
- The prevalence of ABPA is higher in patients with severe acute asthma

**Table I.** Recent studies describing the prevalence of *Aspergillus* sensitization (AS) and allergic bronchopulmonary aspergillosis (ABPA) in bronchial asthma

| Author (yr) | Type of study | Country | Prevalence of AS, n (%) | Prevalence of ABPA, n (%) |
|---|---|---|---|---|
| Prasad *et al* (2008)[21] | Prospective | India | 74/244 (30.3) | 18/244 (7.4) |
| Agarwal *et al* (2010)[22] | Prospective | India | 87/242 (35.9) | 54/242 (22.3) |
| Ghosh *et al* (2010)[23] | Prospective | India | 54/215 (25.1) | 15/215 (6.9) |
| Sarkar *et al* (2010)[24] | Prospective | India | 40/126 (31.7) | 10/126 (7.9)* |
| Ma *et al* (2011)[25] | Prospective | China | 11/200 (5.5) | 5/200 (2.5) |
| Agin and Namavary (2012)[26] | Prospective | Tehran | 42/201 (20.9) | - |
| Mathur and Mathur (2016)[27] | Prospective | India | 27/300 (9) | 8/296 (2.7) |
| Kozlova *et al* (2017)[28] | Prospective | Russia | 50/140 (36) | 5/140 (3.6) |
| Nath *et al* (2017)[29] | Prospective | India | 135/350 (35.1) | 76/350 (21.7) |
| Kalaiyarasan *et al* (2018)[30] | Prospective | India | 13/70 (18.6) | 9/70 (12.9) |
| Bhankhur *et al* (2019)[31] | Prospective | India | - | 35/50 (70) |
| Savio *et al* (2019)[32] | Prospective | India | 122/205 (59.6) | - |

*Includes fungi other than *Aspergillus fumigatus*

# Pathogenesis of ABPA

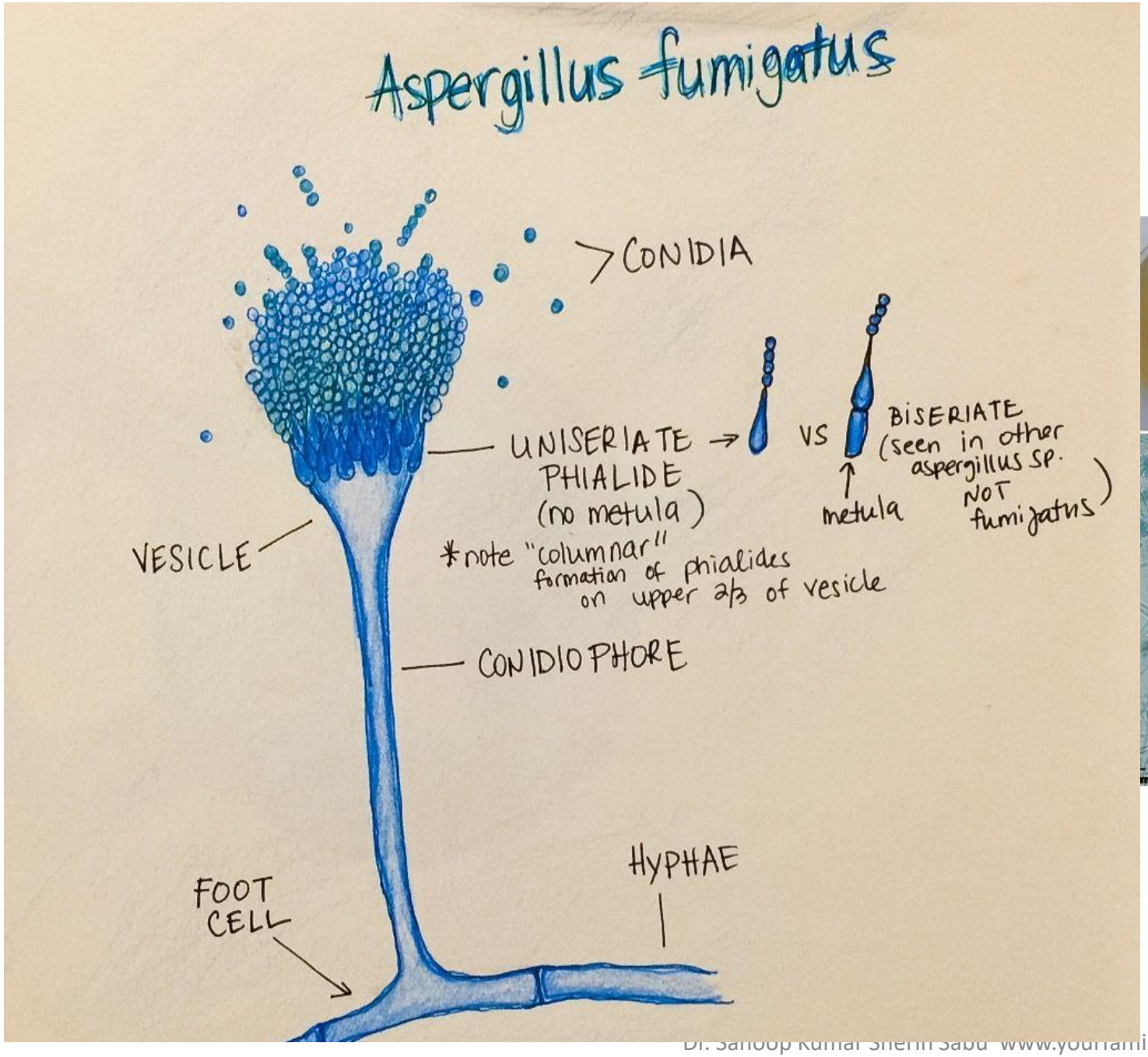


- *Aspergillus* is a ubiquitous mould
- Its conidia (2-3.5 μm), being in the respirable range, can easily enter the airways.
- While exposure to large numbers of conidia of *A. fumigatus* may cause ABPA ,
- Not all asthmatics develop the disorder despite dwelling in the same environment
- The **pathogenesis of ABPA remains unclear**. But 2 important factors are

1. **Persistence of fungi in the airways (due to abnormal clearance)**
2. **Skewed hyper-immune T-helper 2 (Th2) response (possibly due to the HLA-DR2/DR5 bearing dendritic cells).**

- Several defects in innate and adaptive immunity have been identified that lead to persistence of *A. fumigatus* and a distorted immune response
- **Vitamin D deficiency** has been proposed as a pathogenetic factor in ABPA complicating CF. but role in Asthma and ABPA is unclear

# Aspergillus fumigatus



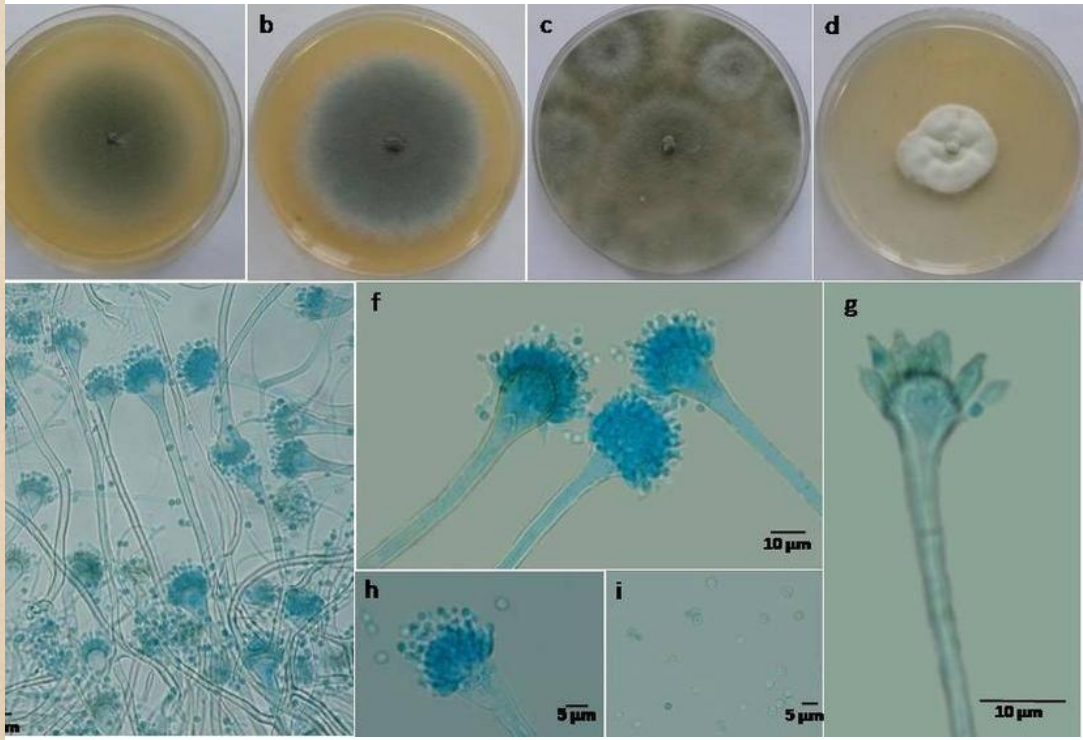



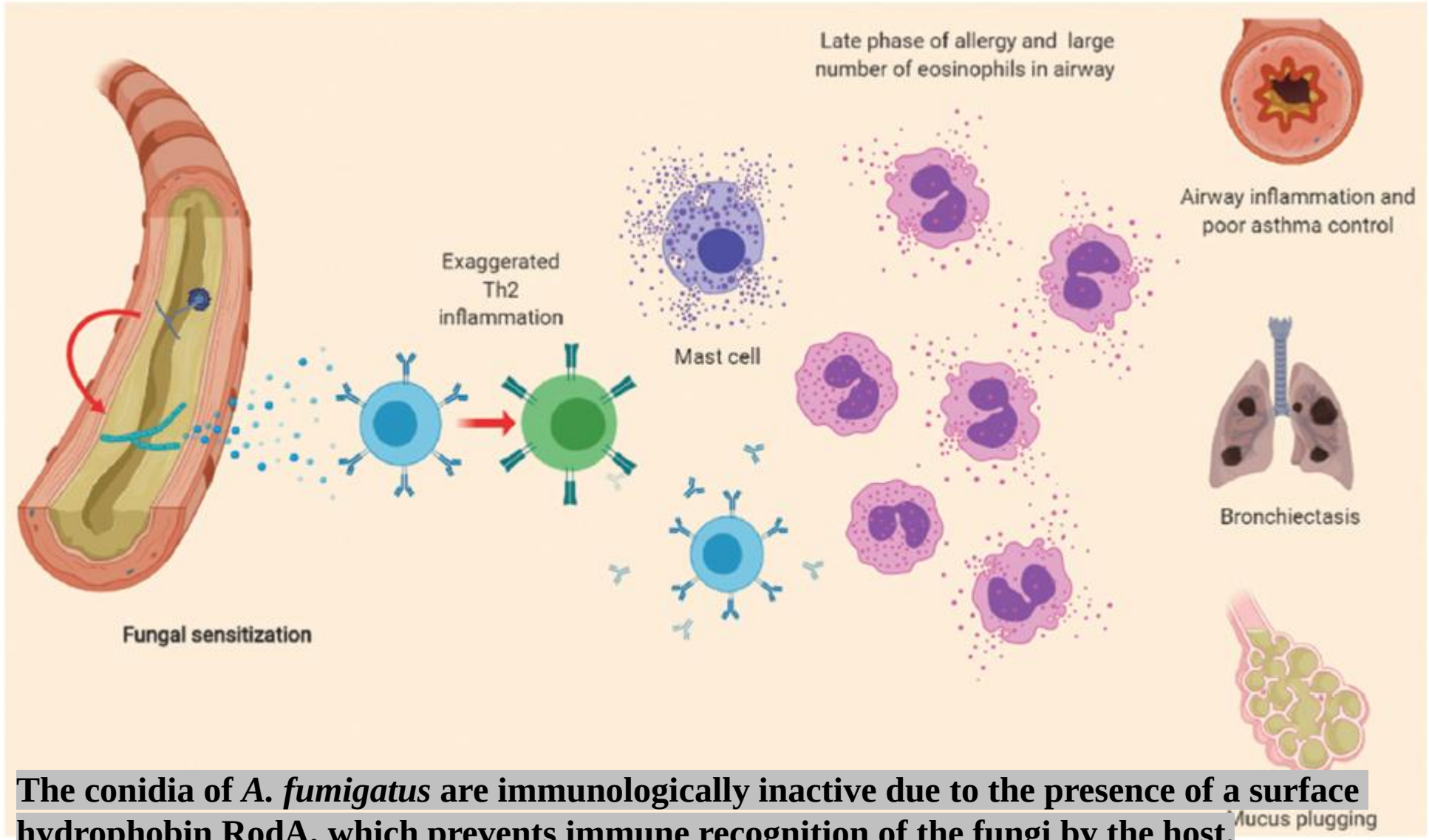
**Table II.** Genetic factors identified in the pathogenesis of allergic bronchopulmonary aspergillosis complicating asthma

| |
|---|
| Defects in innate immunity |
| Surfactant protein A2 gene polymorphisms |
| Mannose-binding lectin gene polymorphisms |
| Toll-like receptor 9 gene polymorphisms |
| Toll-like receptor 3 gene polymorphisms |
| CARD9 gene polymorphisms |
| *EEA1* mutations |
| *ZNF77* polymorphism |
| Adaptive immunity |
| HLA associations |
| Interleukin 4 receptor alpha polymorphisms |
| Interleukin 13 polymorphisms |
| Interleukin 10 promoter polymorphisms |
| Interleukin 15 polymorphisms |
| Tumour necrosis factor-α polymorphisms |
| Transforming growth factor-β polymorphisms |
| Others |
| *CFTR* gene mutation |
| *CHIT1* gene mutations |

*CHIT1*, chitotriosidase 1; *CFTR*, cystic fibrosis transmembrane conductance regulator; *EEA1*, early endosome antigen 1; *CARD9*, caspase recruitment domain-containing protein 9

*Source*: Refs 3, 35-41

- **Skewed hyper-immune T-helper 2**
- **Vitamin D deficiency ( in CF)**




**The conidia of *A. fumigatus* are immunologically inactive due to the presence of a surface hydrophobin RodA, which prevents immune recognition of the fungi by the host.**
**But asthmatic patients who are genetically predisposed to develop ABPA, defective clearance of the conidia of *A. fumigatus* allows them to germinate into hyphae.**

# Pathology of ABPA

- The diagnosis of ABPA is primarily immunological, and lung biopsy is not required in the majority55. Thus, **limited information is available on the pathology of ABPA**

**Usually biopsy findings are only related to underlying diseases like bronchiectasis or asthma**

- In some patients with ABPA, fungi can also be demonstrated in the lung parenchyma
- Airways in ABPA are infiltrated by **inflammatory cells, mainly the eosinophils but also the neutrophils**
- Rarely, the course of **ABPA may be complicated by invasive or chronic aspergillosis**

# Clinical features

- There is **no age or gender preference** for the development of ABPA
- **Poorly controlled asthma**
- Patients may be asymptomatic
- ***ABPA may also uncommonly occur in patients who do not have a history of bronchial asthma***

Other features

- Haemoptysis, low-grade fever, weight loss and malaise. ( Makes it mimic and misdiagnose as TB)
- Expectoration of brownish mucus plugs is a characteristic symptom but seen in only 31-69 per cent of the patients
- Clubbing- if underlying longstanding Bronchiectasis
- Polyphonic wheeze is the most common finding
- pulmonary hypertension and respiratory failure

# Diagnosis of ABPA

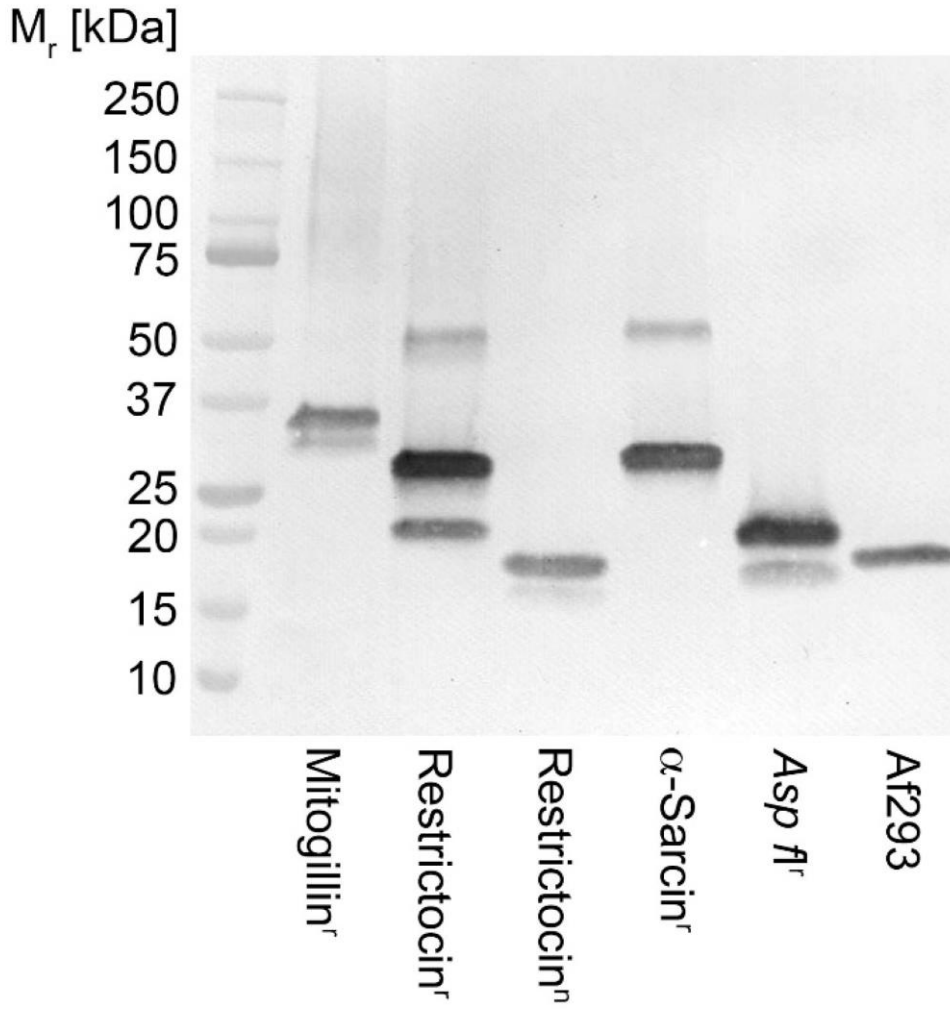
1. Immunological investigations
2. Radiological investigations
3. Others

# 1. *Immunological investigations*

1. *Aspergillus fumigatus*-specific immunoglobulin E (IgE):
2. *Aspergillus* skin test
3. Serum total IgE levels
4. *Aspergillus fumigatus*-specific IgG
5. Peripheral blood eosinophil count
6. Basophil activation test (BAT):

# *Aspergillus fumigatus*-specific immunoglobulin E (IgE)

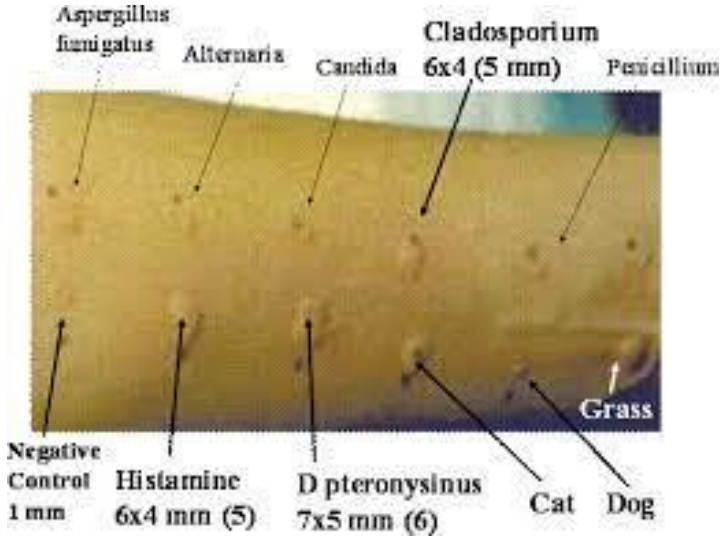
- IgE (>0.35 kUA/l) is **currently the most sensitive investigation in the diagnosis of ABPA and is also considered the preferred test for screening asthmatic patients for ABPA**.
- But this is not helpful in the follow up of patients




Allergen-specific IgE levels expressed as units of specific IgE, kUA/l (A stands for **allergen-specific**), using WHO standards for total IgE determination

# *Aspergillus* skin test

- Performed either using a skin prick or by intradermal injection
- Sensitivity of skin testing in the diagnosis of ABPA ranges from 88 to 94 % so chances of missing is there
- Skin testing is currently **not the favored** test for screening asthmatic patients for ABPA, due to lack of sensitivity, cumbersome procedures.



# Serum total IgE levels

- **Useful test in the diagnosis and follow up** of patients with ABPA.
- A normal serum total IgE nearly excludes active ABPA as the cause of patient's symptoms.
- sensitivity of serum total IgE (cut-off 500 IU/ml) in screening asthmatic patients for ABPA is good (96%)
- but the specificity is poor (24%) .
- **Hence, it is not a good test for screening for ABPA**
- An increase in serum total IgE along with clinical and radiological deterioration indicates an ABPA exacerbation

# *Aspergillus fumigatus*-specific IgG

- *A. fumigatus*-specific IgG detected **using double gel diffusion technique has a sensitivity of only 27 %** in the diagnosis of ABPA
- commercial **enzyme immunoassay** methods for measuring *A. fumigatus*-specific IgG have a sensitivity exceeding 90 %
- Thus not much useful

# Peripheral blood eosinophil count

- **Though previous cut off was >1000, The current accepted cut-off for peripheral blood eosinophil count is 500 cells/µl ( based on recent studies and metanalysis)**

# Basophil activation test (BAT):

- BAT is an *in vitro* flow cytometry-based cellular assay that **measures the activation of basophils** upon allergen stimulation
- BAT identifies activated basophils with the aid of surface markers including CD63, CD193 and CD203c
- there is a limited utility of BAT in ABPA complicating asthma both in the diagnosis of ABPA and differentiating ABPA from AS
- The test should be should be performed within a few hours of collection of the blood sample

# *2. Radiological investigations*

- Chest radiograph
- Computed tomography of the chest:
- Magnetic resonance imaging of the chest

# Chest radiograph

- 2 types -transient or fixed
- Characteristic (transient) fleeting opacities are found during ABPA exacerbations
- Fixed abnormalities are encountered in the advanced stages.
- Most common finding is that of a normal chest radiograph, which means that a CXR is not the best tool. It just helps to find disappearance of a finding
- most common + finding is- consolidation

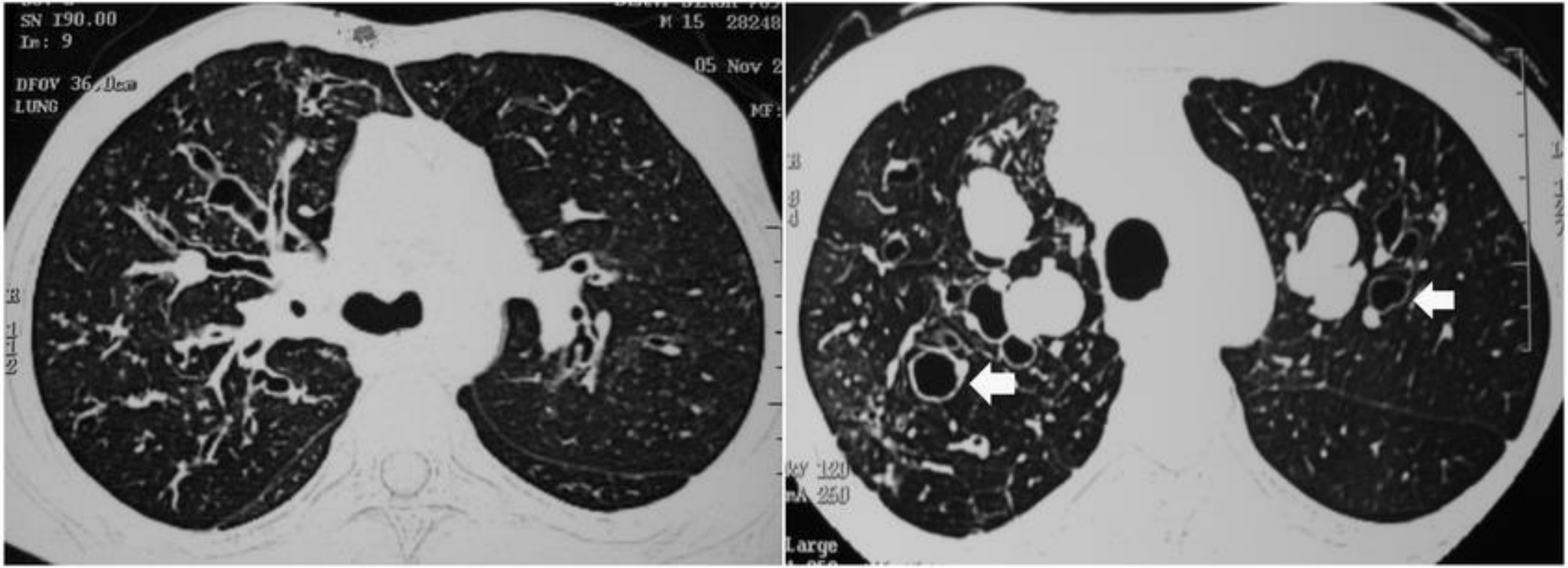
**The areas of consolidation identified on the CXR were found to represent bronchi on CT**

- Other transient finding in CT were - tramline shadows, finger-in-glove opacities, toothpaste shadows - all indicating mucus impaction of the bronchiectasis cavities
- Advanced stages- fibrosis and collapse- indicate the development of chronic pulmonary aspergillosis

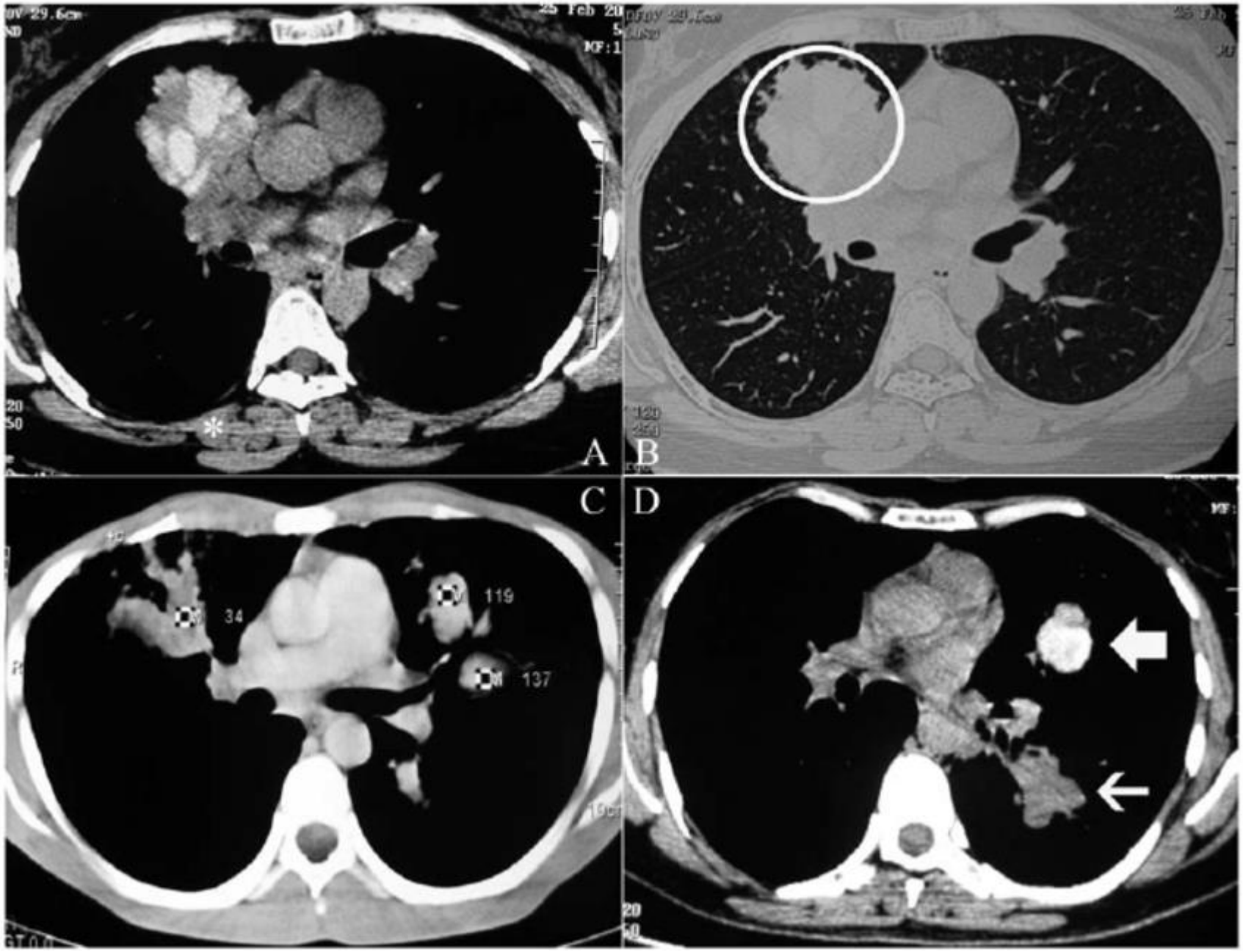
# Computed tomography of the chest

- **Thin-section (or high resolution) CT of the thorax is currently the imaging modality of choice for ABPA**

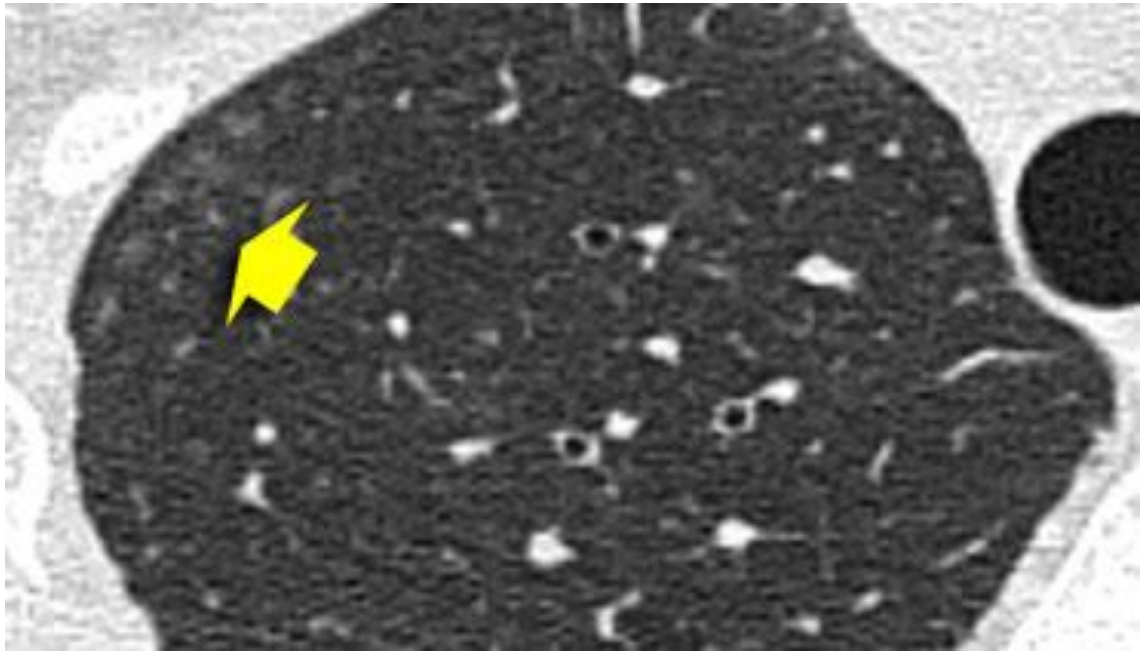
1. **Most common finding on CT chest is bronchiectasis**
    1. central bronchiectasis is believed to be characteristic for the diagnosis of ABPA
    2. But peripheral bronchiectasis can also be seen in 40 % cases
2. The **pathognomonic radiological** finding in ABPA is **high-attenuation mucus (HAM**), which is visually denser than the paraspinal skeletal muscle. The presence of HAM indicates ABPA as the aetiology of the underlying bronchiectasis
3. **Other CT findings**
    1. presence of non-hyper-attenuating mucoid impaction,
    2. centrilobular nodules
    3. tree-in-bud opacities
    4. mosaic attenuation
4. **Uncommon finding-** perihilar opacities simulating hilar lymphadenopathy , miliary nodular opacities , pleural effusions , complete lung collapse and pulmonary masses



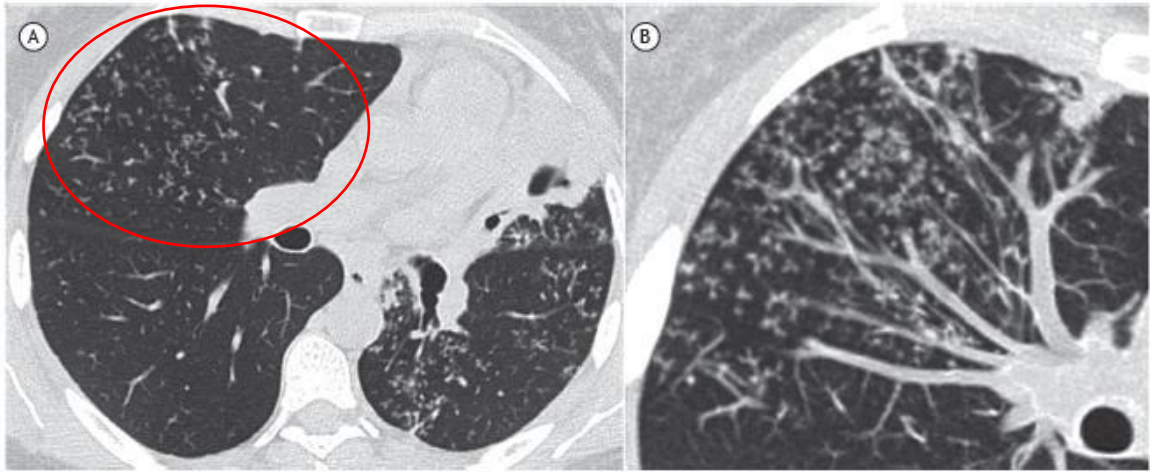

Presence of central bronchiectasis in two different patients with allergic bronchopulmonary aspergillosis. The presence of classic signet ring appearance of dilated bronchi is easily appreciable (arrows). The bronchiectasis is located predominantly in the inner half of the lung field



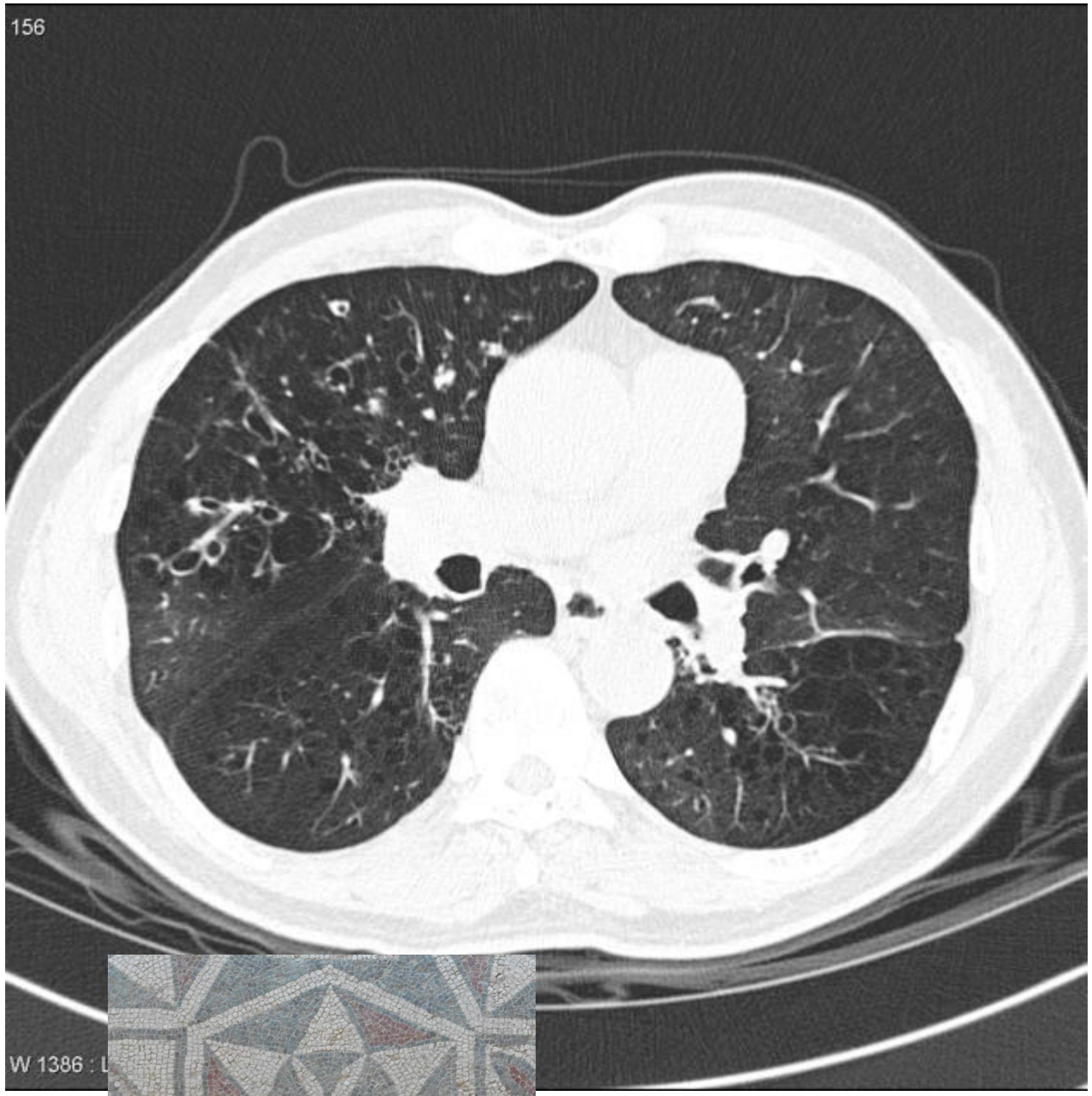

HRCT of patients with allergic bronchopulmonary aspergillosis demonstrating the presence **of high-attenuation mucus**. (A) Mediastinal window showing the presence of hyperattenuated **mucus within dilated bronchi.** The mucus is denser than the paraspinal skeletal muscle (asterisk) (B) Lung window shows that **hyperdense mucus** can occasionally be appreciated even with the parenchymal sections (circle); (C) CT Hounsfield values of **mucus in dilated bronchi**: mucus in the left lung is hyperdense with higher CT attenuation values compared to mucoid impaction in the right lung; (d) **Hyperattenuated** (bold arrow) and normal attenuation mucus (thin arrow) in the same mediastinal window. doi:10.1371/journal.pone.0015346.g002



**Tree-in-bud (TIB) opacities -** These small, clustered, branching, and nodular opacities **represent terminal airway mucous impaction with adjacent peribronchiolar inflammation**.



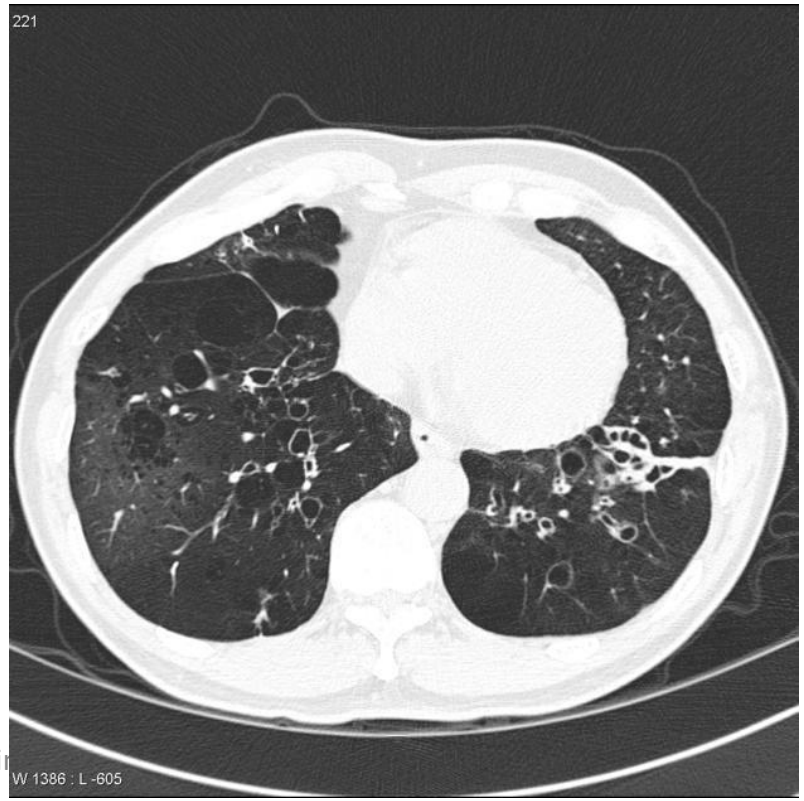

A **centrilobular** distribution is characterized by nodules that are a few millimeters away from the pleural surface and fissures but do not touch them. Hypersensitivity pneumonitis, silicosis, and bronchiolitis are examples of diseases in which this pattern may occur.






**Mosaic attenuation** is an imaging pattern on computed tomography (CT) of the chest that is defined as **variable lung attenuation that results in a heterogeneous appearance of the parenchyma**.

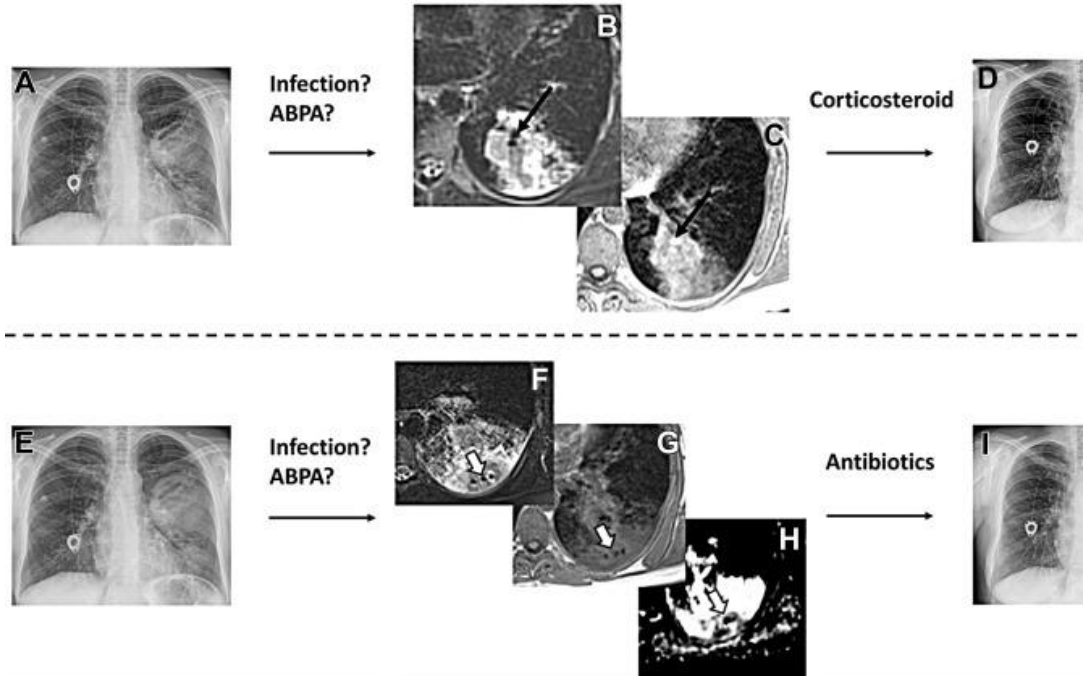
Causes- . It is a non-specific finding
Can be seen in infections, pulmonary edema, pulmonary edema, pulmonary hemorrhage, bronchiectasis



***ABPA can present without any radiological manifestations, which emphasizes the fact that the diagnosis of ABPA is primarily immunological***

# Magnetic resonance imaging of the chest

- Magnetic resonance imaging (MRI) has traditionally been avoided for the evaluation of lung due to the
  - low proton density of lung
  - high propensity for an artefact.
- The counterpart of HAM on MRI seems to be **inverted mucus impaction**, **-a hyper-intense signal on T1-weighted** images and **hypo-intense signal on T2-weighted images**
- Not used routinely



## *Other investigations*

- Sputum cultures
- Pulmonary function tests
- Galactomannan detection:
- Thymus and activation-regulated chemokine (TARC):

# Sputum cultures

- Patients with **ABPA are colonized not only** by the causative fungus but also by other fungi and bacteria.
- Growth of *A. fumigatus* in the sputum is supportive but not diagnostic of ABPA as the fungi are ubiquitous
- So **not a very useful tool in diagnosis**
- Use is
  - ***for performing drug-susceptibility testing and real-time molecular testing for resistance, of the isolates obtained, before treatment***

# Pulmonary function tests

- Used for classifying the severity of the lung disease
- PFT shows  obstructive defect with a reduction in diffusion capacity
- **Bronchoprovocation testing** with *Aspergillus* antigens used in past is not used now due to triggering bronchospasm

# **Galactomannan** detection

- Galactomannan is a polysaccharide component of the *Aspergillus* cell wall.
- **Serum** or **bronchoalveolar lavage fluid** galactomannan is widely used in the **diagnosis of invasive pulmonary** aspergillosis.
- But for ABPA its not useful - the sensitivity 25.7 % and specificity 82% of serum galactomannan index (cut-off, 0.5)

# Thymus and **activation-regulated** chemokine (TARC):

- Due to the profound **Th2 immune response**, the overexpression of the **thymus and activation-regulated chemokine (TARC, CCL17)** has been evaluated in patients with ABPA.
- **Some studies shows higher levels of thymus and activation regulated chemokines.**
- But is **currently little utility** of measuring TARC levels in patients with ABPA.

# Diagnostic criteria and algorithm

- **Rosenberg-Patterson criteria** (8 major, 3 minor) were the most widely used for the diagnosis of ABPA in asthma before 2013
- In 2013 **The International Society for Human and Animal Mycology (ISHAM)** has proposed recommendations for the diagnosis and classification of ABPA complicating asthma

| *Major criteria* |
| --- |
| • Bronchial asthma |
| • Immediate cutaneous hypersensitivity to *A fumigatus* antigen |
| • Serum total IgE levels (>1000 IU/mL) |
| • Serum *A fumigatus* specific IgG and/or IgE levels more than twice the mean plus two standard deviation values in patients with Aspergillus hypersensitive asthma |
| • Central bronchiectasis on HRCT chest |
| • Serum precipitins against *A fumigatus* |
| • Fleeting or fixed pulmonary opacities on chest radiograph |
| • Peripheral blood eosinophil count >1000 cells/μL |
| *Minor criteria* |
| • Sputum cultures demonstrating growth of *A fumigatus* |
| • Expectoration of brownish-black mucus plugs |
| • Type III skin reactions to *A fumigatus* antigen |

The presence of six out eight major criteria makes the diagnosis almost certain.
doi:10.1371/journal.pone.0015346.t006

**Rosenberg-Patterson criteria (8 major, 3 minor)**

**Table III.** International Society for Human and Animal Mycology-Allergic Bronchopulmonary Aspergillosis (ISHAM-ABPA) Working Group criteria used for the diagnosis of ABPA

| |
|---|
| Predisposing conditions |
| Asthma, cystic fibrosis |
| Obligatory criteria (both should be present) |
| Immediate cutaneous hyper-reactivity to *Aspergillus* antigens or *Aspergillus fumigatus*-IgE >0.35 kUA/l |
| Total IgE >1000 IU/ml |
| Other criteria (at least 2 out of 3) |
| Peripheral blood eosinophil count >500 cells/µl |
| Transient pulmonary infiltrates on chest radiograph |
| Presence of precipitins (IgG) against *A. fumigatus* |
| ISHAM-ABPA Working Group diagnostic criteria for ABPA (suggested modifications) |
| Predisposing conditions |
| Asthma, cystic fibrosis |
| Obligatory criteria (both should be present) |
| *A. fumigatus*-IgE >0.35 kUA/l |
| Total IgE >1000 IU/ml |
| Other criteria (at least 2 out of 3) |
| Peripheral blood eosinophil count >500 cells/µl |
| Bronchiectasis on computed tomography of the chest |
| *A. fumigatus*-IgG >27 mgA/l |

*Source*: Adapted with permission from Ref. 3

500

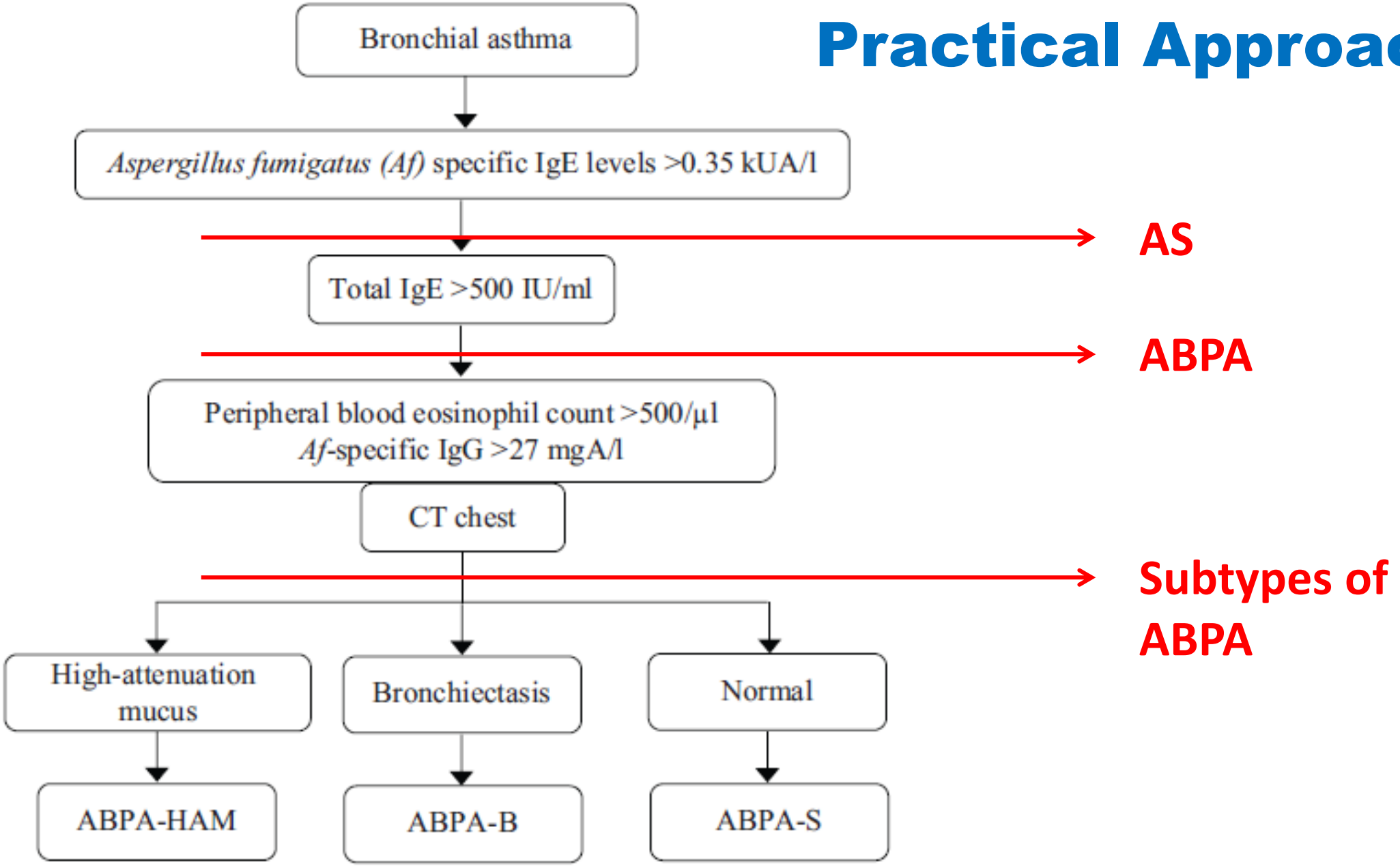
**Table IV.** International Society for Human and Animal Mycology-Allergic Bronchopulmonary Aspergillosis (ISHAM-ABPA) Working Group radiologic classification

| Classification | Features |
|---|---|
| ABPA-S | All the diagnostic features of ABPA (Table III) but no evidence of bronchiectasis on CT |
| ABPA-B | All findings of ABPA including bronchiectasis on CT of the chest |
| ABPA-HAM | All features of ABPA including HAM on CT of the chest |
| ABPA-CPF | ABPA with other radiologic features such as pulmonary fibrosis, bleb, bullae, pneumothorax, parenchymal scarring, emphysematous change, multiple cyst, fibrocavitary lesions, aspergilloma, pleural thickening |

CT, computed tomography; ABPA-S, serological ABPA; ABPA-B, ABPA with bronchiectasis; ABPA-HAM, ABPA with high attenuation mucus; ABPA-CPF, ABPA with chronic pleuropulmonary fibrosis

*Source*: Reproduced with permission from Ref. 3

# Practical Approach



# Follow up plan

- BA without AS→ Follow up every 2 to 3 years with S. IgE specific to A. Fumigatus
- AS without ABPA→ follow up Total IGE levels every Year ( 40% chance of development)

# DDx

- *Aspergillus*-sensitized Bronchial Asthma
- Severe Asthma With Fungal Sensitization (Patients Do Not Meet The Criteria For ABPA, But Fungal Sensitisation Is There, And Severe Asthma Is There)
- Pulmonary Tuberculosis
- Eosinophilic Pneumonia (Acute And Chronic)
- Churg-strauss Syndrome
- Tropical Pulmonary Eosinophilia

# Natural history

- Can have **recurrent exacerbations**
- **Spontaneous improvement** of symptoms and clearing of pulmonary opacities are common
- If not recognized or treated appropriately**, the inflammation can result in irreversible pulmonary damage**

# *Staging of ABPA*

**Table V.** Staging of allergic bronchopulmonary aspergillosis (ABPA) in patients with asthma

| Stage | Definition | Features |
|---|---|---|
| 0 | Asymptomatic | No previous diagnosis of ABPA |
| | | Controlled asthma (according to Indian guidelines) |
| | | Fulfilling the diagnostic criteria of ABPA (Table IV) |
| 1 | Acute | No previous diagnosis of ABPA |
| | | Symptoms consistent with ABPA |
| | | Satisfying the diagnostic criteria of ABPA |
| 1a | With mucoid impaction | Mucoid impaction observed on thoracic imaging |
| 1b | Without mucoid impaction | Absence of mucoid impaction on thoracic imaging |
| 2 | Response | Clinical and/or radiological improvement and decline in serum total IgE by ≥25% of baseline at 8 wk |
| 3 | Exacerbation | Clinical and/or radiological worsening and increase in serum total IgE by at least 50% from the new baseline established during response/remission |
| 4 | Remission | Sustained clinical and radiological improvement and serum total IgE levels persisting at or below baseline (or increase by <50%) for ≥6 months off treatment |
| 5a | Treatment-dependent ABPA | Two or more exacerbations within six months of stopping therapy or clinical and/or radiological worsening, along with increase in serum total 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 serum total IgE and thoracic imaging) |
| 6 | Advanced ABPA | Extensive bronchiectasis due to ABPA on chest imaging along with either cor pulmonale and/or chronic Type II respiratory failure |

***Importantly, a patient does not necessarily advance from one stage to the other sequentially.***

# Treatment of ABPA

- The goals of treatment include the following:

(*i*) reduction of pulmonary inflammation,

(*ii*) control of asthma,

(*iii*) treatment of acute symptoms of ABPA,

(*iv*) prevention of ABPA exacerbations,

(*v*) halt the onset or progression to bronchiectasis.

(vi) It is important that any environmental source responsible for continuous exposure to *A. fumigatus* is eliminated.

# **Treatment** comprises two arms

(*i*) Glucocorticoids ( anti-inflammatory agents) to suppress the immune hyper-reactivity, +

(*ii*) Anti-fungal agents to reduce the fungal burden in the airways

# Glucocorticoids

- **Oral glucocorticoids** are currently the preferred treatment
  - **dose and duration of treatment were unclear.**
  - Metanalysis suggest- a slightly higher glucocorticoid dose that low dose (**prednisolone: 0.5 mg/kg for 4 wk, 0.25 mg/kg for 4 wk, 0.125 mg/kg for 4 wk, taper by 5 mg every week; total duration: 4 months**
- **Inhaled glucocorticoids (ICSs):** was also found effective in ABPA and BA, if given along with Oral GC. ICS alone is useful only for the control of asthma in patients of ABPA
- **Intravenous pulse doses of glucocorticoids** – IV 15 mg/kg of methylprednisolone for 3 consecutive days) have been used in
  - children with ABPA as an alternative to daily glucocorticoid therapy
  - Also useful in refractory ABPA exacerbation
  - steroid-resistance state in people on long term steroids in whom lead to downregulation of glucocorticoid receptors

# Antifungal agents

- Metanalysis of different studies shows that **Itraconazole is an effective agent.**
- It can be used even as a stand alone drug even in acute causes and for long term use, without Glucocorticoids.
- Newer azoles- posaconazole, isavuconazole, Voriconazole- limited studies are available. And cost is higher. Reserved only for Itraconazle resistant cases.
- Nebulized amphotericin B- clear guideline not available. Conventional preparation of amphotericin B causes bronchospasm. So its avoided.

# NEWER DRUGS

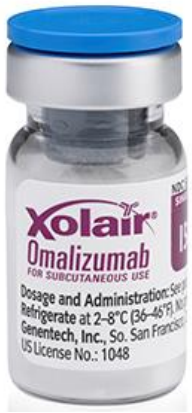
- Anti-IgE therapy :- **Omalizumab** remains a treatment option in patients with ABPA who do not tolerate first-line treatments or are refractory to other therapies. Limited studies only available

- Anti-Th2 therapies: **mepolizumab**, a monoclonal antibody against IL-5 (100 mg subcutaneous every 4 wk) and benralizumab, a monoclonal antibody against IL-5Rα). But studies not promising.

# Omalizumab

- Omalizumab is a recombinant humanized IgG1 monoclonal antibody targeting human immunoglobulin E (IgE) and thereby preventing its interaction with the high-affinity **receptor Fc-epsilon-RI typically found on eosinophils, mast cells, and basophils, and is critical in the allergic cascade.**
- Omalizumab has a vital role in managing moderate to severe Ig-E medicated asthma and, more recently, a role in chronic urticaria.
- It received initial approval for use in 2003 for the treatment of **moderate to severe** asthma for adults and pediatric patients six years of age and older who have a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms are not adequately controlled with inhaled corticosteroids.
- It is not approved for the relief of acute bronchospasm or status asthmatics
- It is FDA-approved for treating adolescents 12 years of age and older and adults with **chronic spontaneous urticaria** who has symptoms despite H1 antihistamine treatment. It is not approved for other types of urticaria.
- add-on maintenance therapy of **nasal polyps** for adults 18 years of age and above with inadequate response to nasal corticosteroids.
- **ABPA** not responding to steroids

- Available as Omalizumab 75 mg or 150mg / 0.5 mL injection solution in a single-dose prefilled syringe. Or also Omalizumab 150 mg lyophilized powder for reconstitution in a single-dose vial.




**Asthma**

- The recommended dose for treatment of asthma is 75 mg - 375 mg by subcutaneous injection every two or four weeks.
- The basis for dose and frequency is calculated considering patient weight and pretreatment total IgE serum levels.
- There is no dosing adjustment based on total IgE levels taken during treatment.
- No dose adjustment is necessary for any significant weight changes

**Chronic Urticaria**

- Administer omalizumab 150 mg or 300 mg every four weeks based on initial serum total IgE level or patient weight.
- A retrospective chart review of 43 chronic urticaria patients treated with omalizumab between 2006 to 2015 found that overall, 90.2% (37/41) responded within three months duration.[8]

**Nasal Polyps**

- Administer 75 mg to 600 mg omalizumab by subcutaneous injection every two or four weeks based on initial serum total IgE level and patient weight.

**ABPA**- aim of therapy with omalizumab is to decrease the serum total IgE to <21 IU/ml, and the dose required to achieve this is 0.016 mg/kg/IU (IgE/ml). A maximum dose of omalizumab 1200 mg monthly have been.

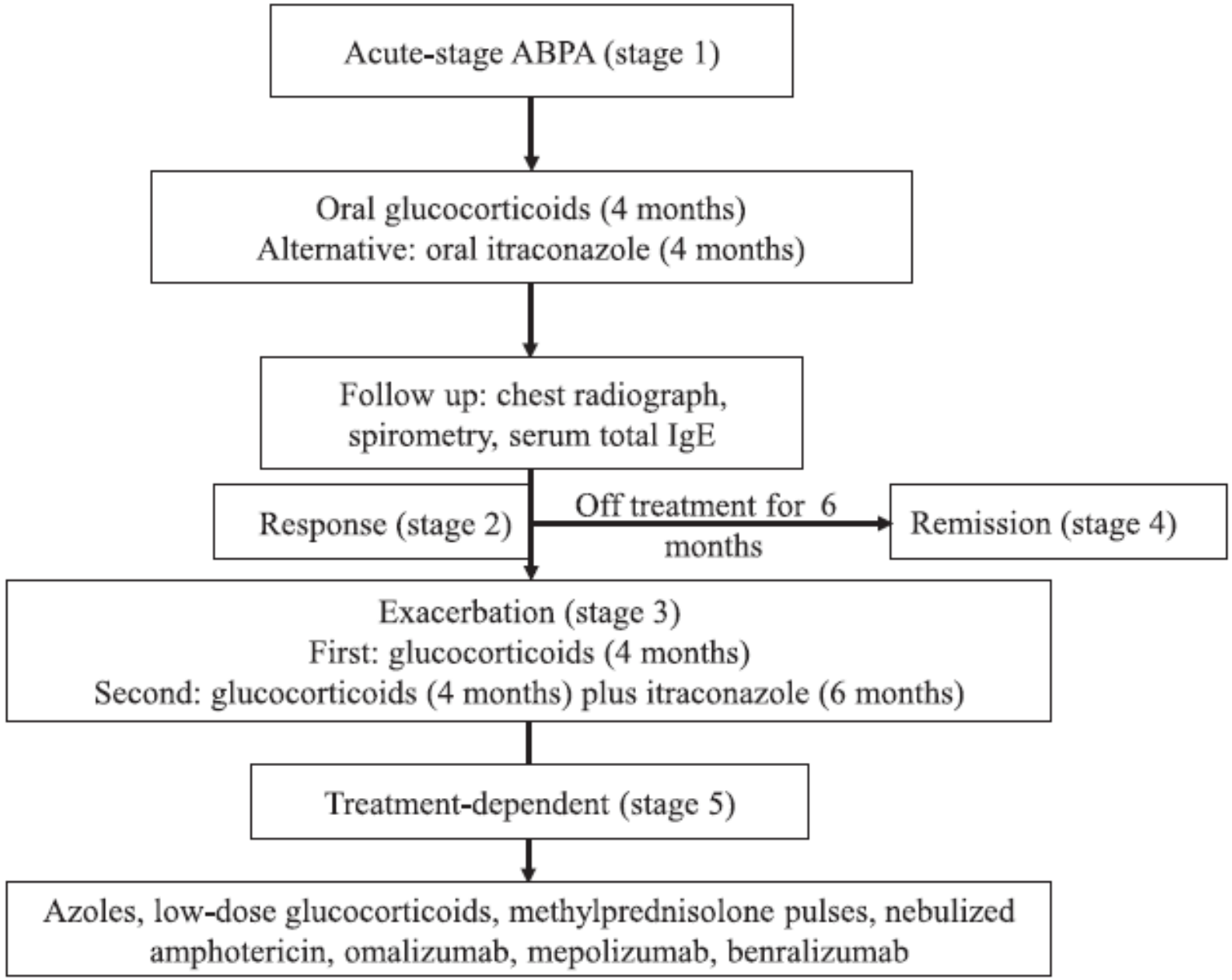



**Fig. 5.** Suggested treatment approach for allergic bronchopulmonary aspergillosis (ABPA).

**Table VI.** Treatment protocols for the management of allergic bronchopulmonary aspergillosis (ABPA)

| |
|---|
| Oral glucocorticoids |
| Prednisolone: 0.5 mg/kg for 4 wk, 0.25 mg/kg for 4 wk, 0.125 mg/kg for 4 wk, then tapered by 5 mg every wk to continue for a total duration of at least 4 months |
| Indication: First-line treatment of ABPA, both in acute-stage and during exacerbation |
| Oral azoles |
| Itraconazole: 200 mg twice a day for 24 wk<br>Indication: Second exacerbation of ABPA; glucocorticoid-dependent ABPA; alternative to glucocorticoids as first-line treatment of ABPA, especially in those with increased propensity for glucocorticoid-related side effects |
| Follow up and monitoring |
| Patients are followed up with history and physical examination, chest radiograph, spirometry and measurement of total IgE levels every 8 wk (to determine the new baseline IgE) |
| Important points |
| A 25% decline in serum total IgE along with clinical and/or radiological improvement, indicates a satisfactory response to therapy |
| A clinical or radiological worsening along with a ≥50% increase in the new baseline IgE points to an ABPA exacerbation |
| Worsening of symptoms in the absence of radiological or immunological worsening (serum total IgE) suggests an asthma exacerbation |
| Monitor for adverse effects *e.g.*, hypertension, hyperglycaemia, in case of glucocorticoids; nausea, vomiting, diarrhoea, elevated liver enzymes, in case of azoles |
| Monitor for drug-drug interactions |
| Prophylaxis for osteoporosis (with glucocorticoid therapy): oral calcium and bisphosphonates |

*Source*: Adapted with permission from Ref. 3

# ABPA in special situations and related conditions

# In children

- Diagnosis and treatment protocol in children are similar to adults
- Use slightly lower doses of steroids to reduce complications
- Omalizumab is safe

# *During pregnancy*

- The treatment of choice in pregnancy is glucocorticoids.
- The rates of miscarriage are higher in the itraconazole-exposed group
- Omalizumab is safe

# *ABPA complicating cystic fibrosis*

- ABPA is a dreaded complication of CF
- Is associated **with rapid loss of lung function, higher rates of microbial colonization and poorer nutritional status**
- There are challenges in diagnosis as the radiological and clinical worsening in CF can be due to ABPA or due to underlying CF/ bronchetasis
- Several patients demonstrate fluctuating immunological responses to *A. fumigatus*
- In this regard, **BAT** in response to stimulation by *Aspergillus* allergens is **useful in differentiating CF-ABPA from AS and *Aspergillus* colonization in CF**
- **Treatment is challenging due to malabsorption in CF, diabetes due to steroids and due to cf, worsening of underlying lung function**

# *ABPA sans bronchial asthma*

- Though ABPA most commonly occurs in those with bronchial asthma, it can occasionally develop without underlying asthma
- Majority (97%) of patients with ABPA **without asthma** have underlying bronchiectasis
- Because of absence of asthma, **patients with ABPA without asthma** are initially **misdiagnosed a**s bronchogenic carcinoma, pulmonary tuberculosis  and others.

# Conclusions

- A high-index of suspicion for ABPA should be maintained in all patients with bronchial asthma
- ABPA can occur even without BA
- ABPA worsens CF
- Suspect ABPA in any patient with worsening BA or difficult to treat bronchial asthma, or unspecified opacites in chest Xray
- ABPA is a immunological diagnosis ,not a radiological diagnosis
- Presently the criteria used is **The International Society for Human and Animal Mycology (ISHAM)**
- The most sensitive and screening test is *Aspergillus fumigatus (Af)* specific IgE levels >0.35 kUA/l
- Followup can be assesed using S. Ig E levels
- Treatment of choice is steroids.
- Oral antifungal-itraconazole can be used as a first line drug or a add on drug
- Other agesnts useful are- Pulse dose steroids, Omalizumab (Anti IgE), mepolizumab (IL-5 blocker)
- In children and pregancy treamtment and dignosis is similar
- ABPA San Bronchial asthma should not be missdiagnosed as maligancy

BUT AS FOR ME, I KNOW THAT

*my Redeemer lives,*

AND HE WILL STAND UPON THE EARTH AT LAST.

JOB 19:25

# Thankyou

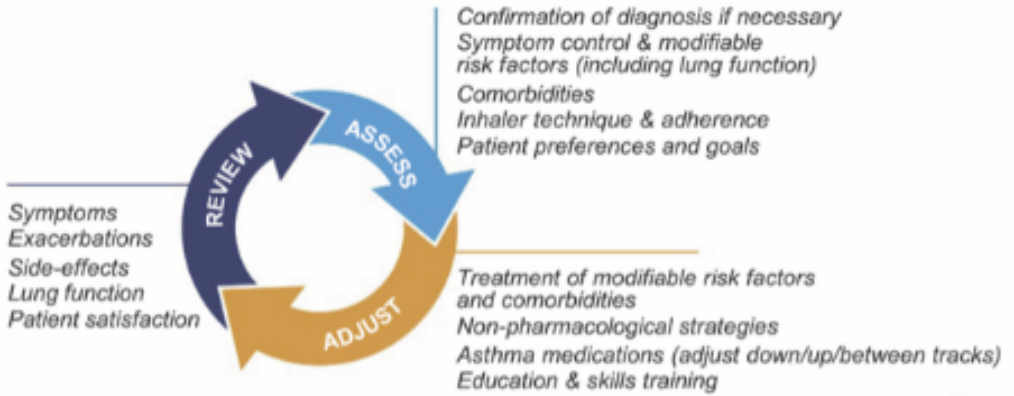
MEDITATIONS BY April

*Dr. Sanoop Kumar Sherin Sabu*

- ***Severe asthma*** *is asthma that is uncontrolled despite high dose inhaled corticosteroids (ICS)-long-acting beta$_2$-agonist (LABA), or that requires high dose ICS-LABA to remain controlled.'*

## Adults & adolescents 12+ years

**Personalized asthma management**
Assess, Adjust, Review
for individual patient needs




**CONTROLLER and PREFERRED RELIEVER**
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

| STEPS 1 – 2 | STEP 3 | STEP 4 | STEP 5 |
|---|---|---|---|
| As-needed low dose ICS-formoterol | Low dose maintenance ICS-formoterol | Medium dose maintenance ICS-formoterol | Add-on LAMA<br>Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R<br>Consider high dose ICS-formoterol |
| RELIEVER: As-needed low-dose ICS-formoterol | | | |

**CONTROLLER and ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

| STEP 1 | STEP 2 | STEP 3 | STEP 4 | STEP 5 |
|---|---|---|---|---|
| Take ICS whenever SABA taken | Low dose maintenance ICS | Low dose maintenance ICS-LABA | Medium/high dose maintenance ICS-LABA | Add-on LAMA<br>Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R<br>Consider high dose ICS-LABA |
| RELIEVER: As-needed short-acting β2-agonist | | | | |

| Other controller options for either track | *Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT* | *Medium dose ICS, or add LTRA, or add HDM SLIT* | *Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS* | *Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects* |
|---|---|---|---|---|

*GINA 2021, Box 3-5A*





GINA asthma strategy: what's new for 2021? | Implementing guidelines | Guidelines in Practice