

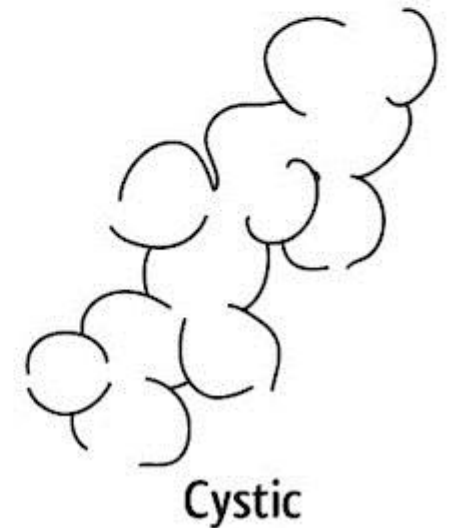
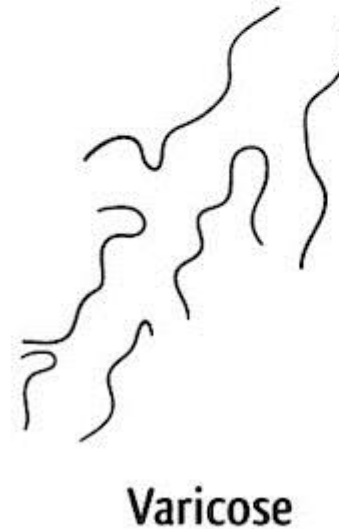
BRONCHIECTASIS

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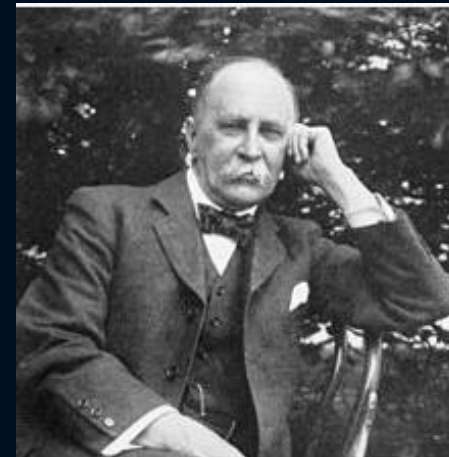
AGENDA

- OVERVIEW
- OVERLAP OF ASTHMA AND BRONCHIECTASIS
- ABPA (Allergic Bronchopulmonary Aspergillosis)
 - Diagnosis
 - Management
- Q&A
- REFERENCES



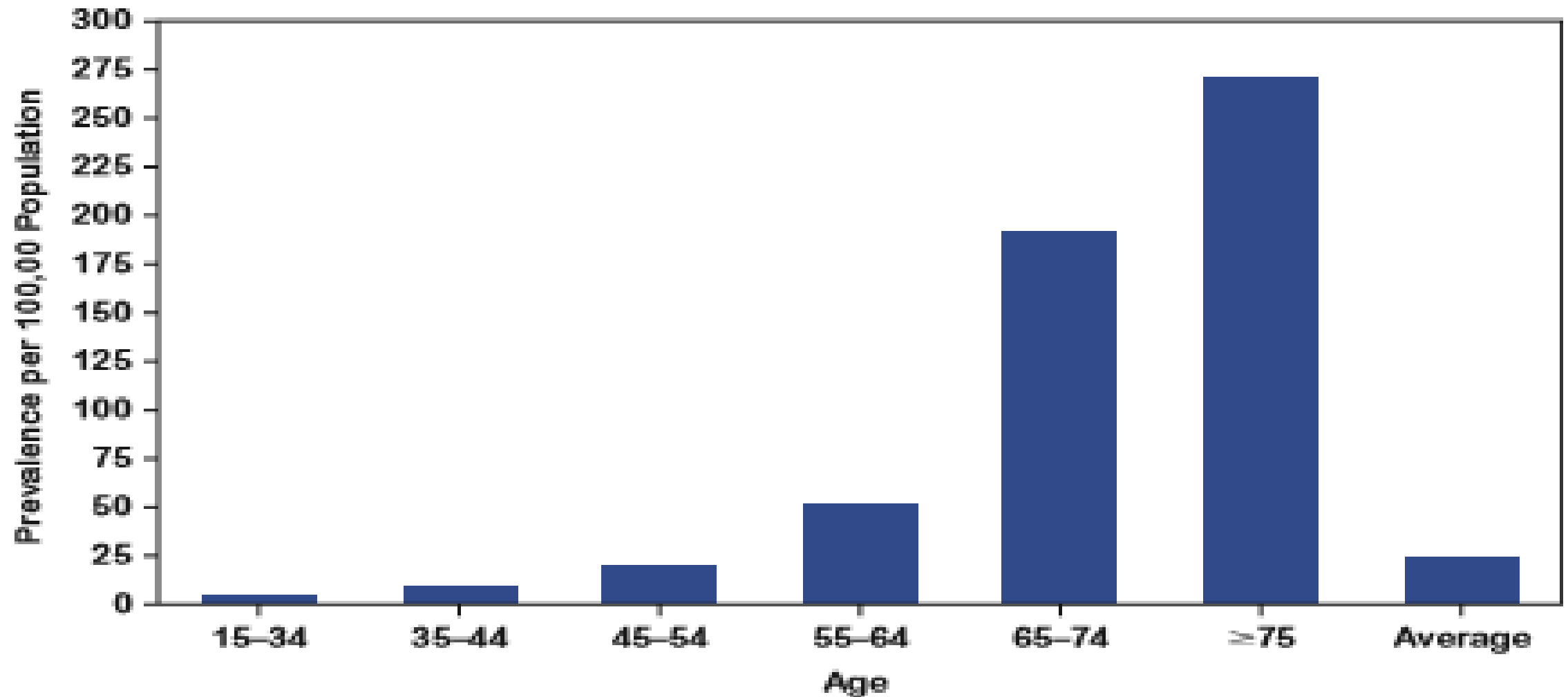
HISTORY

- First described by Rene Laennec, the man who invented stethoscope, in 1819
- Later detailed by Sir William Osler in the late 1800s



- Further defined by Reid in the 1950s, bronchiectasis has undergone significant changes in regard to its prevalence, etiology, presentation, and treatment.

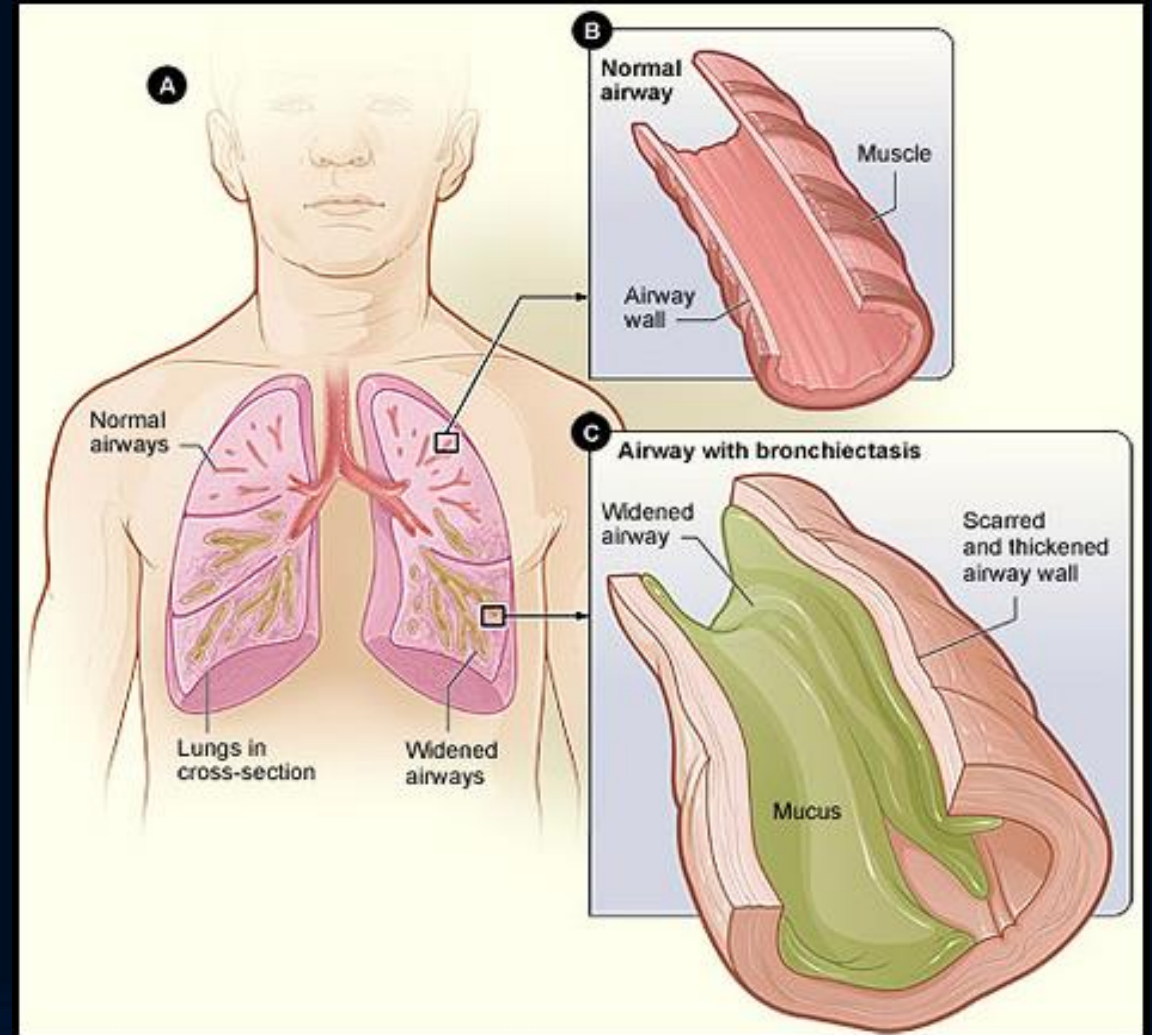
Prevalence of Bronchiectasis



Bronchiectasis increases with age. It is likely to be much more common than reported here because it is not usually detected, reported, or treated (2).

Bronchiectasis

- Derived from the Greek word “bronkhia” meaning branches of the lung’s main bronchi plus the Greek word “ektasis” meaning dilation.
- Women > Men, especially when it is of unknown cause.
- In 2001, estimated annual medical cost in the United States with bronchiectasis was \$13,244



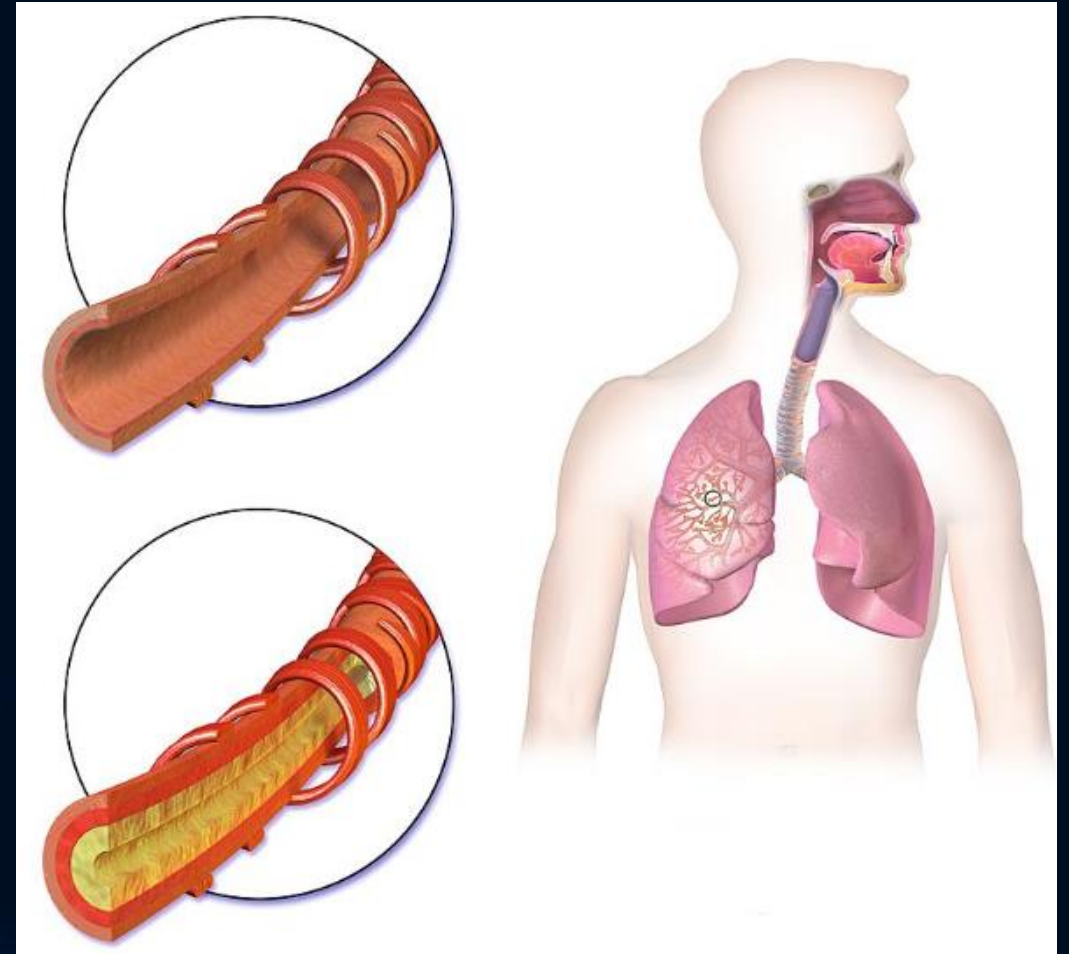
MORTALITY

	Statistics
Deaths	970
Death rate extrapolations for USA	969 per year 80 per month 18 per week 2 per day 0 per hour 0 per minute 0 per second
Hospitalizations	6,000
Physician office visits	45,000

- Calculation uses the deaths statistic: 970 deaths (NHLBI 1999)

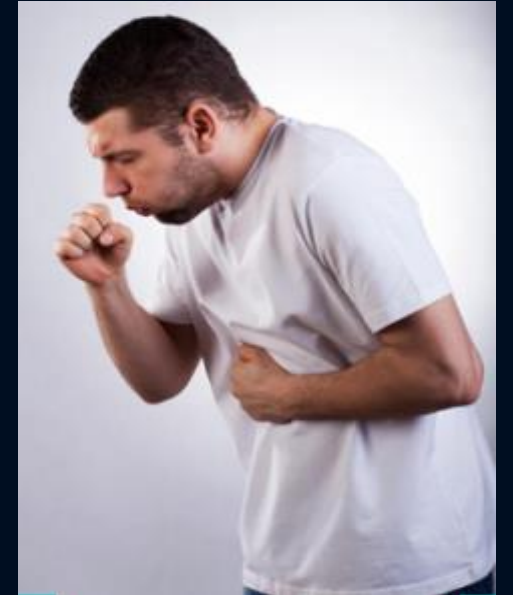
SIGNS AND SYMPTOMS

1. Chronic cough with mucus production
2. Shortness of breath
3. Coughing up blood



SIGNS AND SYMPTOMS

4. Dyspnea
5. Pleuritic chest pain
6. Wheezing
7. Fever
8. Weakness
9. Fatigue
10. Weight loss



Vignette:

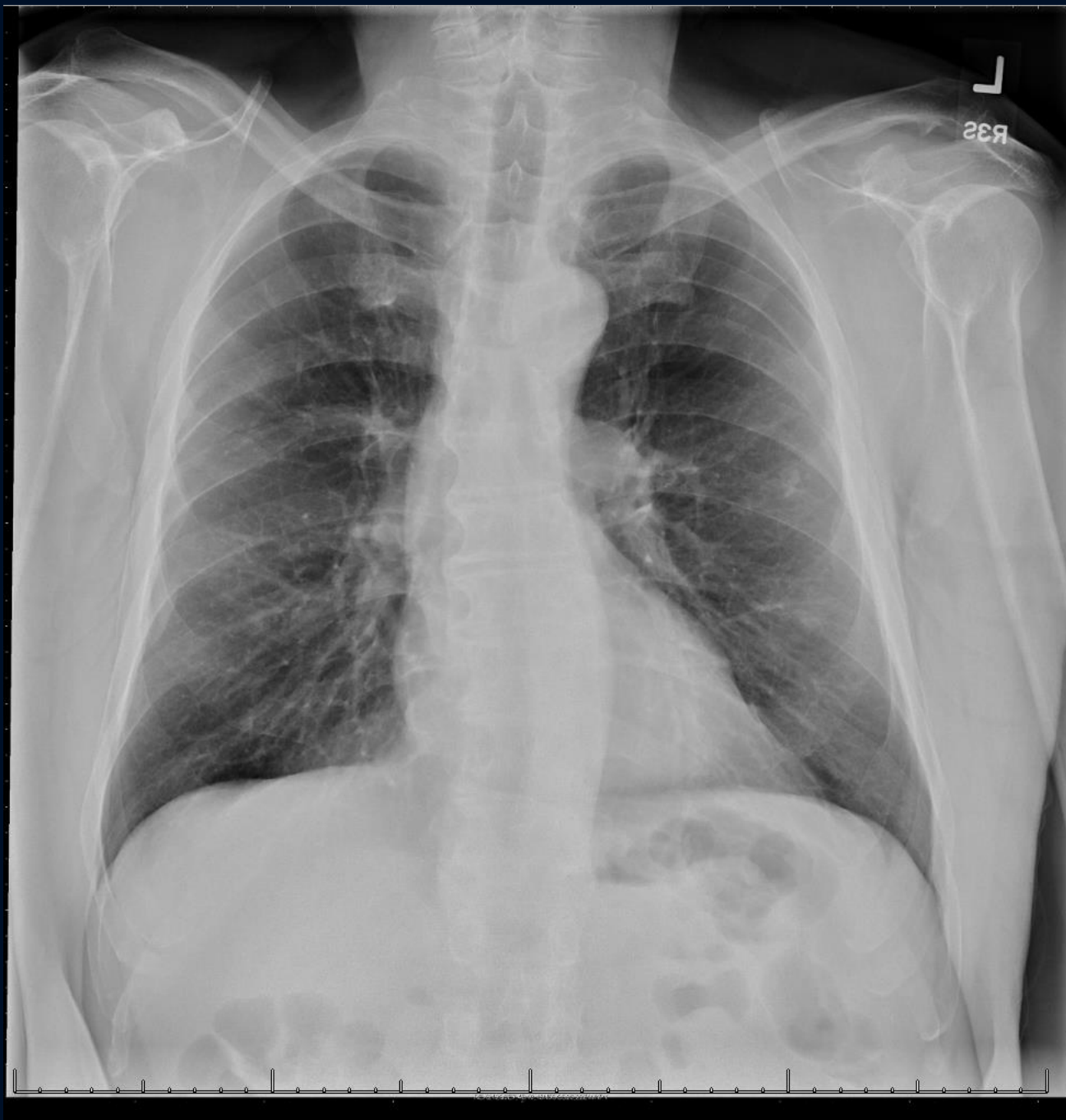
- 69 YO male with a PMHx of GERD, Allergic Rhinitis, CVA is here for evaluation.
- Reports cough for 6-8 months, worse in the morning (dry), and then after breakfast (productive). Cough then improves and seems to recur again after dinner.
- Is a home fire alarm inspector, out in the field mostly in the peninsula.
- Overall cough has not worsened however dyspnea has.

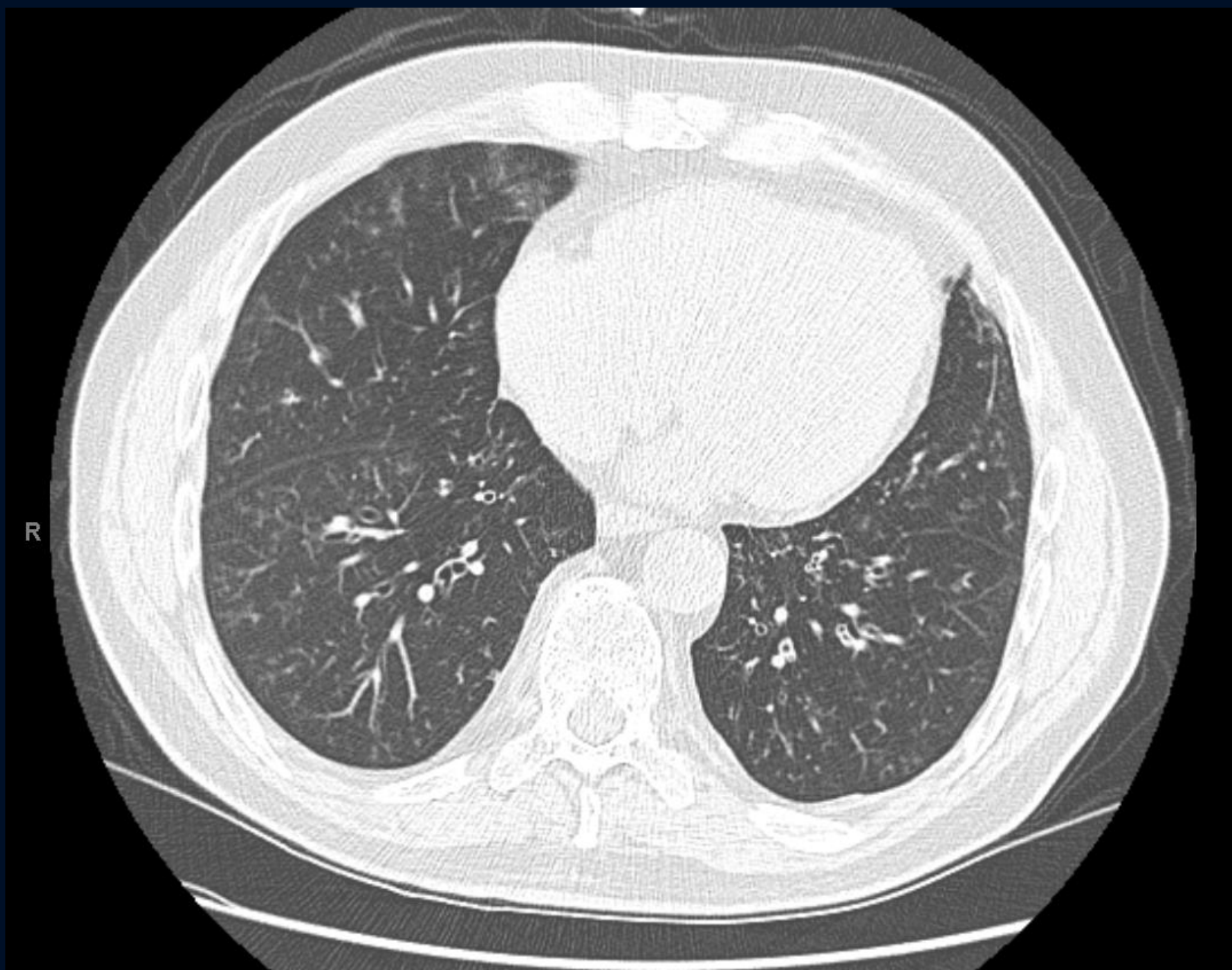
PFT

PFT FLOWSHEET (NCAL)	10/25/2016	1/4/2017
FVC (pre)	2.99	3.23
FVC (%pred)(pre)	65	70
FEV1 (pre)	1.69	1.96
FEV1 (%pred)(pre)	49	57
FEV1/FVC (pre)	57	0.61
FEF25-75 (pre)	0.82	1.01
FEF25-75 (%pred)(pre)	31	39
FVC (post)	3.04	3.31
FVC (%pred)(post)	66	72
FVC (%change)(post)	2	3
FEV1 (post)	1.78	2.05
FEV1 (%pred)(post)	51	59
FEV1 (%change)(post)	5	5
FEV1/FVC (post)	58	62
FEF25-75(post)	0.86	1.13
FEF25-75(%pred) (post)	33	43
FEF25-75(%change)(post)	5	11

Follow up:

- Coughing w/ copious mucous that is thick and tan, never blood.
- No wheezing. Dyspnea on exertion walking up the hill near his home, now has to stop half way up the hill whereas 3 months back he had no dyspnea.
- Denies choking, food regurgitation, aspiration events, dysphagia/odynophagia.
- Does have GERD and its reasonably well controlled now on BID PPI.
- Denies pleurisy, f/c/ns. +weight loss, about 10 lbs. Noticed this a few months back and it has been stable @ 163 on his home scale for the past 2-3 months.





CAUSES

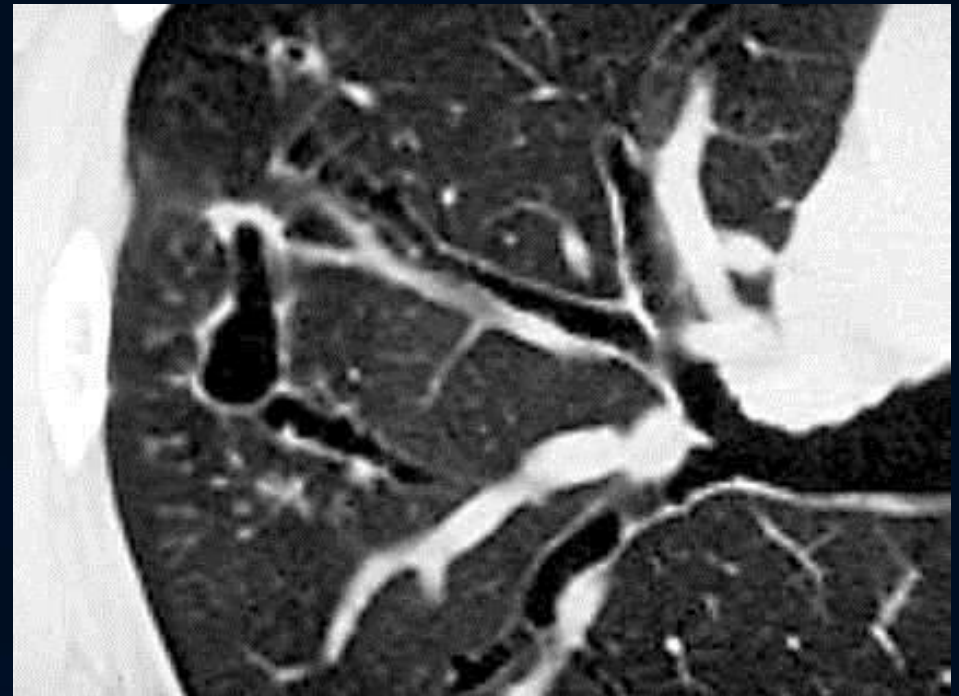
1. Lung infections that can lead to bronchiectasis:
 - Severe pneumonia
 - Whooping cough or measles (uncommon in the United States due to vaccination)
 - Tuberculosis
 - Fungal infections
2. Conditions that damage the airways and raise the risk of lung infections:
 - Cystic fibrosis – leads to almost 50% of cases in the US
 - Immunodeficiency disorders such as common variable immunodeficiency and, less often, HIV and AIDS
 - Allergic bronchopulmonary aspergillosis

CAUSES

3. Conditions that damage the airways and raise the risk of lung infections:
 - Primary ciliary dyskinesia
 - Recurrent aspiration
 - CTD: Rheumatoid arthritis, Sjögren's syndrome, and Crohn's disease.

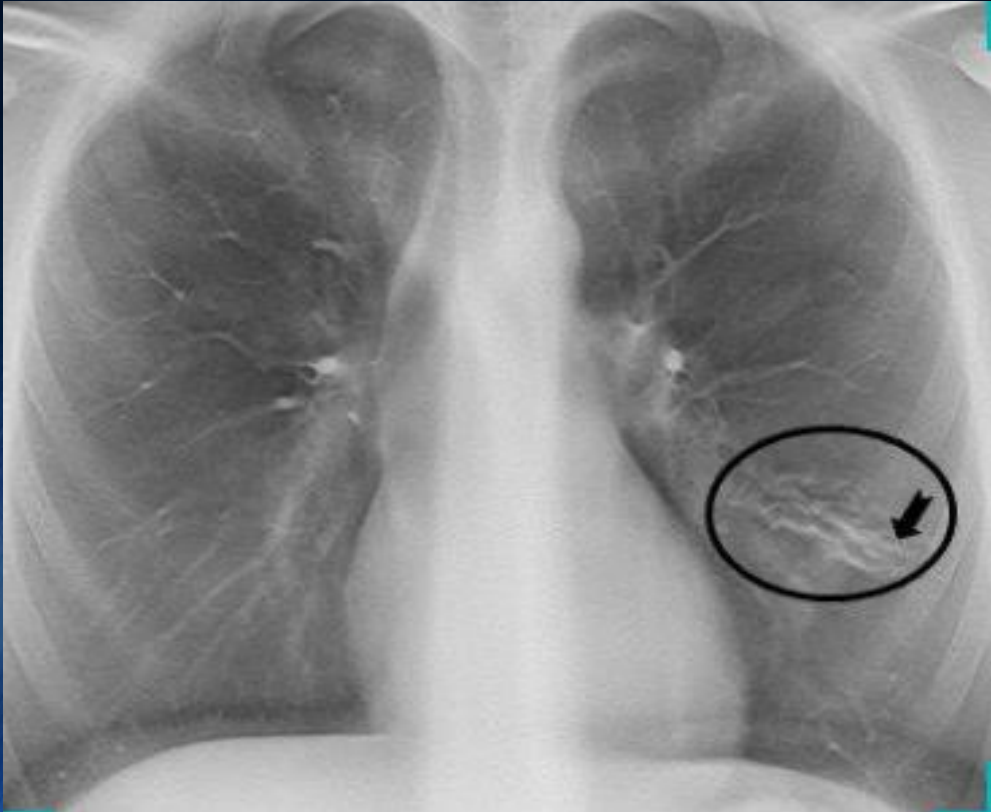
TYPES OF BRONCHIECTASIS

1. Cylindrical bronchiectasis



TYPES OF BRONCHIECTASIS

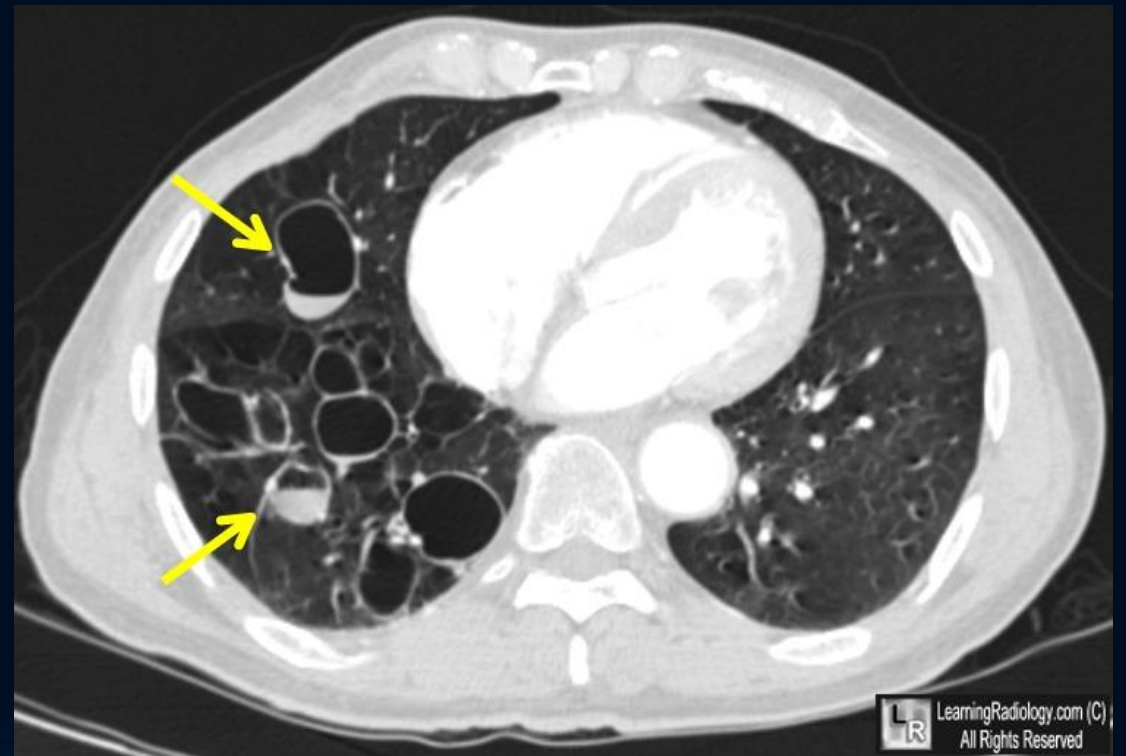
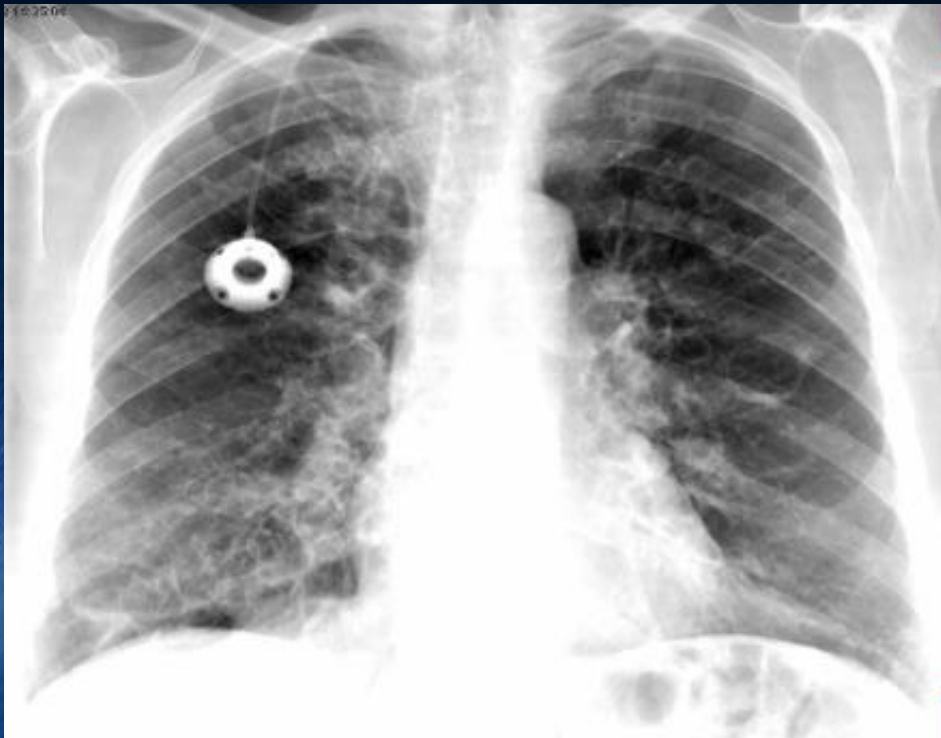
2. Saccular or varicose bronchiectasis



Source: Robert G. Wells: Diagnostic Imaging of Infants and Children
www.accesspediatrics.com
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TYPES OF BRONCHIECTASIS

3. Cystic bronchiectasis



FACED vs BRONCHIECTASIS SEVERITY INDEX (BSI)

- Both are scoring systems for assessment of the NCFB severity and prognosis.
- Both scores embrace diverse clinical, functional, radiological and microbiological aspects that are characteristics of the disease.
- FACED score incorporating the variable “exacerbations” and/or “hospitalizations” better classifies severity and risk of future exacerbations and hospitalizations in a cohort of patients.

Differences	FACED	BSI
Structure	Easy-to-use tool incorporating 5 dichotomic variables	Relatively complex, awarding different point values for each of the variables and including multiple variables
Variables	<ol style="list-style-type: none"> FEV₁ % predicted (cut-off 50%, maximum value 2 points), Age (cut-off 70 years, maximum value 2 points), Presence of chronic colonization by <i>Pseudomonas aeruginosa</i> (dichotomic, maximum value 1 point), Radiological extension (number of lobes affected, cut-off 2 lobes, maximum value 1 point) Dyspnea (cut-off grade II on the Medical Research Council [MRC] scale, maximum value 1 point). 	<ol style="list-style-type: none"> Age: less than 50 years (0 points); 50-69 years (2 points), 70-79 years (4 points), more than 80 years (6 points) Body mass index (BMI): less than 18.5 (2 points), more than 18.5 (0 points) FEV₁ % predicted: less than 80% (0 points), 50-80% (1 point), 30-49% (2 points), less than 30% (3 points) Hospital admission in previous year: no (0 points), yes (5 points) Exacerbations in previous year: 0-2 (0 points), 3 or more (2 points) MRC dyspnea score: 1-3 (0 points), 4 (2 points), 5 (3 points) <i>Pseudomonas aeruginosa</i> colonization: no (0 point), yes (3 points) Colonization with other microorganisms: no (0 point), yes (1 point) Radiological severity (more than 3 lobes involved or cystic bronchiectasis): no (0 points), yes (1 point)
Aim	prediction of the probability of all-cause mortality of the patients with NCFB in the next 5 years	identification of the patients with NCFB with higher risk for future mortality, hospitalization and exacerbations

OVERLAP OF ASTHMA AND BRONCHIECTASIS

- Chronic bronchiectasis is associated with impaired mucociliary clearance and increased bronchial secretions, leading to worse airway obstruction and airflow limitation.
- About 2% to 3% of people with Asthma also have bronchiectasis.
- People with both conditions are more likely to have severe asthma and more frequent asthma attacks than people with asthma alone.
- More steroids and have more visits to the emergency room.

Importance of fractional exhaled nitric oxide in diagnosis of bronchiectasis accompanied with bronchial asthma

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Contributions: (I) Conception and design: All authors; (II) Administrative support: FJ Chen, H Liao, CM Xie; (III) Provision of study materials or patients: FJ Chen, H Liao, CM Xie; (IV) Collection and assembly of data: FJ Chen, XY Huang; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors

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- FeNO is a predictor for differentiating Bronchiectasis accompanied with Asthma from Bronchiectasis alone.
- 22.5 ppb used as a cut off
- FeNO sensitivity and specificity: 90%/62.5%

Are Markers Of Eosinophilic Inflammation Able To Identify Subjects With "concomitant Asthma" In A Group Of Non-Cystic Fibrosis Bronchiectasis?

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¹University of Pisa, Pisa, Italy

- A study of 155 subjects with Non-Cystic Fibrosis Bronchiectasis (NCFB) was analyzed according to the presence of at least 1 out of 3 indices of eosinophilic airway inflammation:
 - blood eosinophil percentage
 - sputum eosinophil percentage
 - exhaled NO concentration
- Etiology of bronchiectasis:

Idiopathic 55%	Post-Infectious 27%
Post-TB 8%	Other causes 10%

PRESENCE OF MARKERS OF EOSINOPHILIC INFLAMMATION WITH NCFB

- **RESULTS**: 47 subjects (32%) showed 1 index positive for eosinophil inflammation with a predominance for FeNO (25%), followed by sputum eosinophilia (20%) and blood eosinophilia (13%)
- No difference was found for age, sex distribution, and severity index (BSI and FACED) when compared with subjects with negative indices.
- Functional findings (FEV₁/VC%, FEV₁% of predicted, reversibility test, RV) did not show difference between the 2 groups
- Only 32 subjects had performed a methacholine challenge test, 8 showed a positive test, and 7 out of these 8 had a positive methacholine test, being negative for eosinophilic inflammation.
- **CONCLUSION**: The positivity of eosinophilic inflammation indices, which are frequently observed in patients with NCF, do not identify clearly subjects with concomitant asthma.
- Methacholine challenge test, might be useful for selecting patients with bronchiectasis and concomitant asthma.

PREVALENCE OF BRONCHIECTASIS IN PATIENTS WITH ASTHMA

- A study was conducted involving 98 patients with moderate to severe asthma
- Excluded were patients who smoke more than 10 packs/year and those previously diagnosed of BC.
- **RESULTS:**
 - Prevalence is 31.6%
 - Most common location is in the lower lobes.
 - The FACED score is 1.5 ± 1.3
 - No differences were found in the severity and asthma control, comorbidities, pulmonary function, previous admissions, or use of oral steroids or antibiotics.
 - No patient had chronic bronchial infection.
 - No differences in bacterial flora were found in patients with or without BC.

	Bronchiectasis	Non-bronchiectasis
Age, years	60.7 ± 12.6	58.9 ± 14.7
Female gender	25 (33.8%)	49 (66.2%)
BMI	28.7 ± 4.7	29.7 ± 5.8
Obesity	17 (32.1%)	36 (67.9%)
Moderate asthma	10 (28.6%)	25 (71.4%)
Severe asthma	21 (33.3%)	42 (66.7%)
Controlled asthma	4 (22.2%)	14 (77.8%)
Uncontrolled asthma	27 (33.8%)	53 (66.3%)
Disease duration, years	14.8 ± 13	18.2 ± 15.1
ACT score	15.2 ± 6	16.2 ± 4.3
Atopy	14 (29.8%)	33 (70.2%)
Post-bronchodilator therapy FEV ₁ , % predicted	79.9 ± 21.7	79.2 ± 23.1
Post-bronchodilator therapy FEV ₁ /FVC ratio	69 ± 11.2	69.9 ± 10.9
FeNO (ppb)	28 ± 27.3	23.3 ± 18.3
Emergency visits/year	2.26 ± 4.15	1.37 ± 2.8
Previous admissions/year	0.23 ± 0.5	0.18 ± 0.42
Course of Prednisone/year	1.32 ± 2.3	1.23 ± 2.4
Course of Antibiotics/year	1.13 ± 1.9	0.87 ± 1.5
Blood eosinophils (mm ³)	342 ± 356	279 ± 253
IgE (IU/ml)	136.7 ± 217	261.2 ± 655
Bronchorrhea	4 (50%)	4 (50%)
Purulent sputum	3 (100%)	0 (0%)*
Positive sputum culture	8 (61.5%)	5 (38.5%)*
Charlson score	3.7 ± 1.8	3.7 ± 2.34

Mean ± SD; n(%); *p<0,05

- **CONCLUSION:** Nearly 1/3 of patients with moderate to severe asthma have BC. However, these BC are mild according to FACED prognostic score. Patients with BC have increased purulent sputum and more positive cultures.

CHARACTERISTICS OF A SUBGROUP OF NON CYSTIC FIBROSIS BRONCHIECTASIS WITH CONCOMITANT ASTHMA

- A study of 25 asthmatics was identified in a group of 157 Bronchiectasis (1st group)
- The rest are Bronchiectasis without asthma (2nd group)

Similarities

- Age, sex, smoke habit, having mean age 58.8 (SD 16.9), 20 females, and 16 never smoking.
- Airway presence of bacteria, and for the main clinical symptoms: cough, dyspnea, recurrent exacerbations.
- Did not show significant difference for BSI, and FEV₁ baseline.

Differences

- Subjects with asthma showed higher percentage of Eosinophils in the induced sputum, mean and range 14.4% (25.9) vs 2.6% (5.5), $p < 0.0001$.
- Sputum Neutrophils were lower in asthmatics than in Bronchiectasis without asthma, 54.0% (31.3) vs 72.6% (25.1), $p = 0.005$.
- NO measures were significantly higher in bronchiectasis with asthma, 35.7 ppb (41.7) vs 20.9 ppb (17.3), $p = 0.02$.

DIAGNOSIS

- Bronchiectasis may be diagnosed clinically or on review of imaging.
- Sputum analysis, chest X-ray and high-resolution CT of the chest (lungs)

TREATMENT

- Etiology dependent
- Treatment protocols :
 - keeping immunizations up-to-date
 - eliminating aggravating factors such as cigarette smoke, alcohol and drugs
 - encouraging good nutrition
 - increasing fluid intake
 - an expectorant (to loosen the mucous) and mucous thinning medication can help decrease symptoms



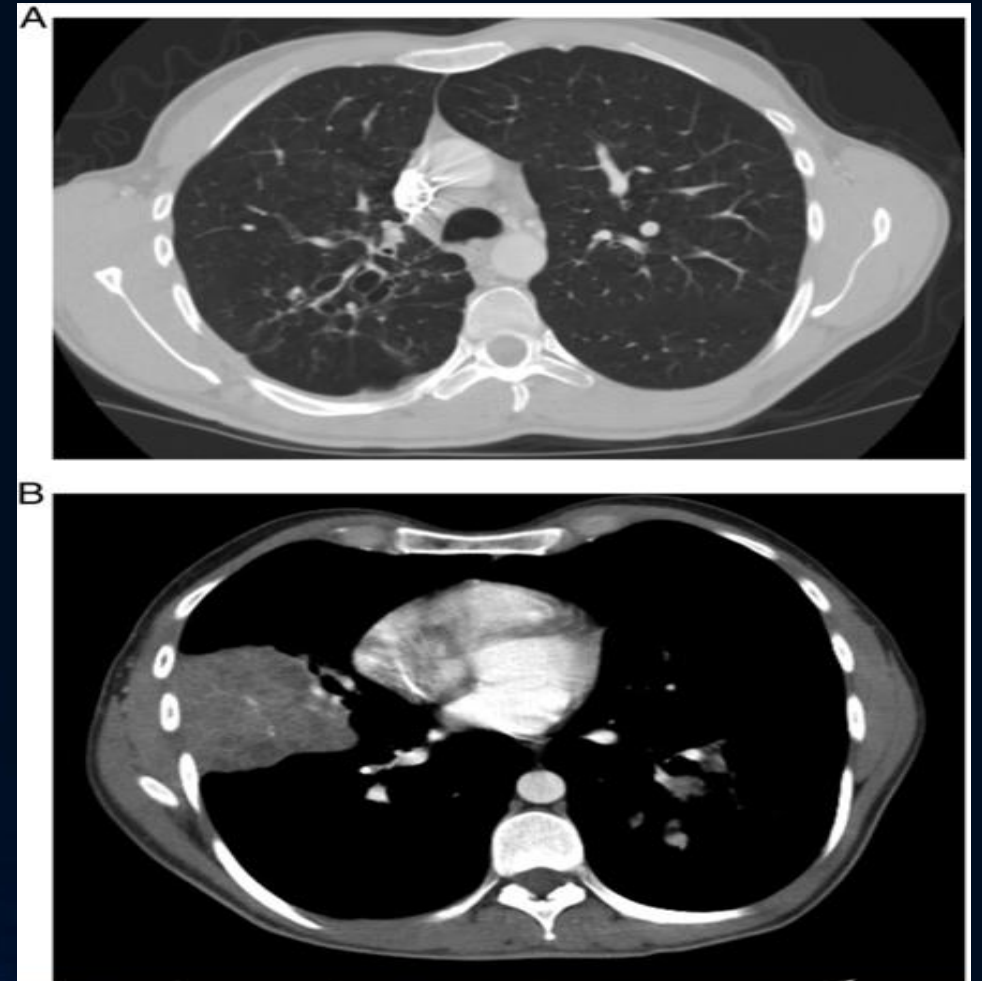
TREATMENT

- Airway clearance modalities:
 - Chest physiotherapy
 - Flutter valve
- antibiotics if patients acquire an infection
- bronchodilators, corticosteroid therapy and if needed, oxygen therapy
- hospitalization and IV medications
- surgical therapy if poorly controlled with antibiotics



Allergic Bronchopulmonary Aspergillosis (ABPA)

- The result of immune-mediated damage to, and dysfunction of, the airways triggered by *Aspergillus*
- *Aspergillus*-specific IgE levels may be more sensitive than skin testing for establishing sensitization.
- Although asthma is the most common comorbidity, patients with cystic fibrosis have a higher rate of *Aspergillus* colonization, and up to 15% of patients develop ABPA
- positive respiratory cultures are supportive but are not a formal diagnostic criterion. Even when stains or cultures are negative, *Aspergillus* DNA may be detected in respiratory samples.



ABPA RECENT UPDATES

Pulmonary Aspergillosis Syndromes

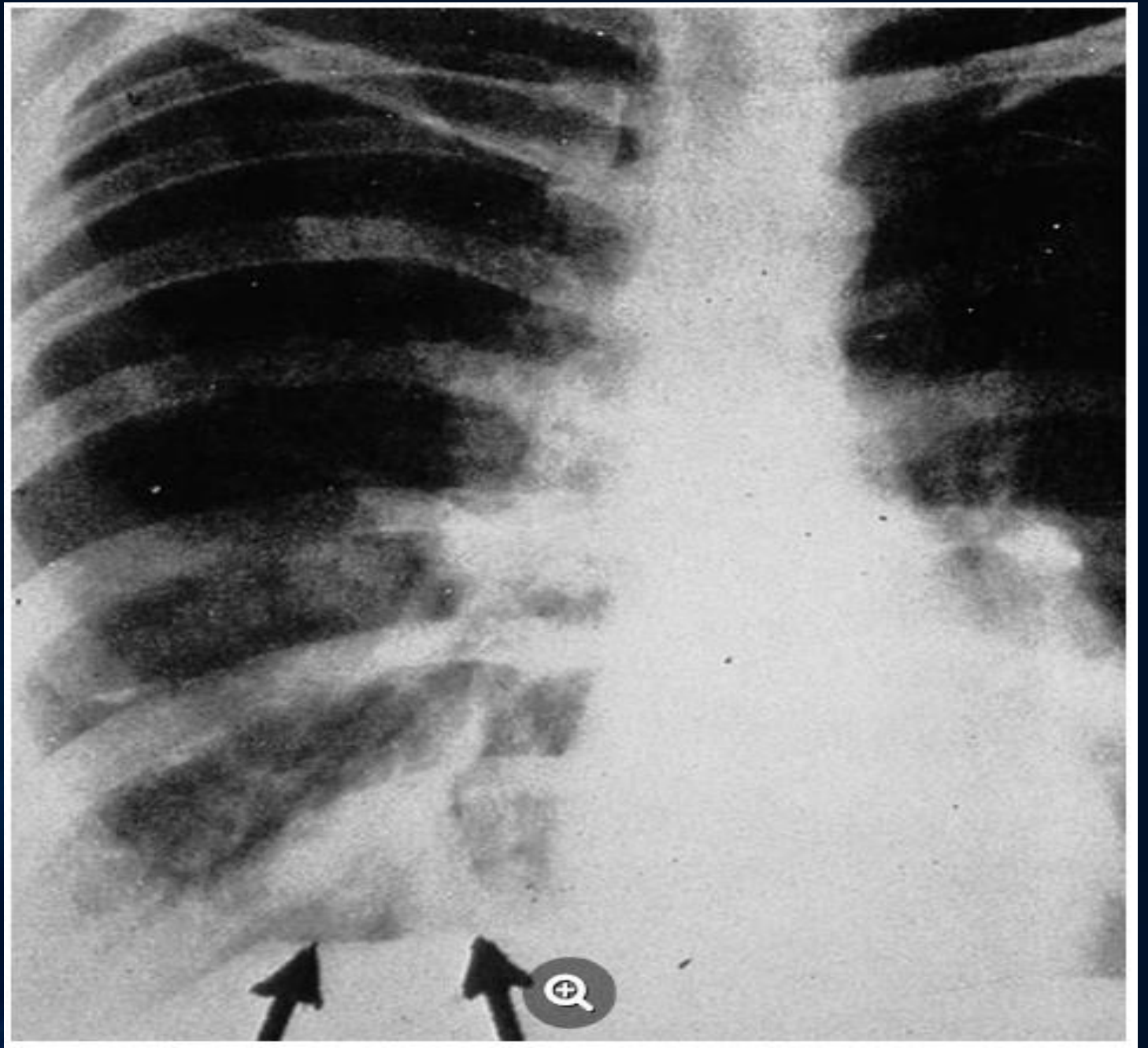
<i>Aspergillus</i> Syndrome	Syndrome	Clinical Features	Recent Updates
Allergic aspergillosis	ABPA	Worsening of underlying asthma Markedly elevated total IgE Sensitization: (+) skin testing and/or elevated <i>Aspergillus</i> -specific IgE Bronchiectasis	Cystic fibrosis is a risk factor for ABPA Bronchiectasis may be absent early in the disease course Antifungal agents benefit some patients Case reports of benefit from anti-IgE therapy

DIAGNOSING ABPA

Diagnostic Criteria	Historically Included	Recent Modifications Highlight
Predisposing condition	Asthma	Cystic fibrosis
Demonstration of fungal sensitization	Sensitization to <i>Aspergillus fumigatus</i> Positive <i>Aspergillus</i> skin test or elevated IgE levels against <i>Aspergillus fumigatus</i>	Sensitization can be to a variety of <i>Aspergillus</i> species or other fungal organisms Intradermal testing is more sensitive than skin prick The combination of serum <i>Aspergillus</i> IgE and skin testing is most sensitive
Elevated total serum IgE	Levels > 1,000 IU/mL	Levels may be lower for patients on corticosteroids or in a less active phase of disease
Positive <i>Aspergillus</i> -specific serologies	Elevated serum <i>Aspergillus</i> IgE and positive precipitins	Quantitative <i>Aspergillus</i> IgG titers often replace precipitins testing
Radiographic changes	Opacities from mucous plugging Central bronchiectasis	High attenuation mucous plugging is pathognomonic Not all patients have bronchiectasis, particularly early in disease

CHEST X-RAY

Posteroanterior chest x-ray shows "gloved finger" shadows (arrows), appearing as branched tubular densities that represent intrabronchial exudates with bronchial wall thickening



Treatment options for ABPA:



Isavuconazole

Xolair

Voriconazole

Nucala



prednisone

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TREATMENT AND MANAGEMENT OF ABPA

- Corticosteroids are the mainstay of the treatment.
- Due to asthma or cystic fibrosis, the addition of a triazole antifungal agent has been associated with improvements in lung function, serologic markers, rates of exacerbation, and corticosteroid requirements.

TREATMENT AND MANAGEMENT OF ABPA

- Omalizumab, a monoclonal antibody to IgE, may be effective in some patients.
**A patient reported improvement in dyspnea after 3 months of therapy with Omalizumab.
- Close long-term follow-up with serial assessments of total serum IgE is advised for all patients.



TREATMENT AND MANAGEMENT OF ABPA

Management of Pulmonary Aspergillosis Syndromes

Syndrome	Therapy	Dose	Comments
ABPA	Corticosteroids (prednisone)	0.5-0.75 mg/kg/d for 2-4 wk	Taper as patient responds; follow total serum IgE levels, which fall with treatment
	Itraconazole po	200 mg bid x at least 16 wk	Monitor serum levels
	Voriconazole po	150-300 mg bid x 6 mo	Dose based on serum levels; consider if itraconazole failure or intolerance
	Omalizumab sq	Based on total IgE level and weight	Case reports suggest benefit

Take Home Points:

- 1) Increased cough and copious sputum are hallmarks for Bronchiectasis
- 2) Severe persistent asthmatics should be evaluated for bronchiectasis & ABPA, if uncontrolled
- 3) There are many causes of bronchiectasis!
- 4) Let sputum culture be thy friend.
- 5) High resolution CT scan is needed in making the diagnosis.



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OVERLAP OF COPD AND BRONCHIECTASIS

- 27 out of 54 patients with COPD was diagnosed with high-resolution computed tomography (HRCT) to evaluate the frequency and severity of bacterial exacerbations in COPD patients with Bronchiectasis (BE).
- A significantly higher mean number of exacerbations in a 12-month period in COPD patients with BE (2.9 ± 0.5) was found, as compared to their mean number in controls (2.5 ± 0.3) ($p = 0.0008$).
- Mean duration of exacerbation was significantly longer in COPD patients with BE as compared to their mean duration in controls (6.9 ± 1.8 vs. 5.7 ± 1.4 ; $p = 0.0085$).
- Mean exacerbation-free interval in days, in patients with COPD with BE, was significantly shorter than in COPD patients in whom BE were excluded (56.4 ± 17.1 vs. 67.2 ± 14.3 ; $p = 0.0149$).
- Overall, the findings indicate that coexisting BE in COPD patients may lead to more frequent exacerbations with a longer duration.

FREQUENCY OF UNTREATED HYPOGAMMAGLOBULINEMIA IN BRONCHIECTASIS

- Patients with antibody deficiency and on adequate doses of immunoglobulin replacement would not appear to have hypogammaglobulinemia.
- 1% of adults with bronchiectasis have detectable un- or undertreated hypogammaglobulinemia.
- Only 1.4% of the cohort found to have a level of hypogammaglobulinemia for which immunoglobulin replacement could be considered, which is of significance because uncorrected humoral immunodeficiency is a risk for poor outcome in many types of structural lung disease including Bronchiectasis.
- Continue recommend screening for humoral immunodeficiency in patients with Bronchiectasis, especially when the diagnosis of Bronchiectasis is first determined.

FREQUENCY OF UNTREATED HYPOGAMMAGLOBULINEMIA IN BRONCHIECTASIS

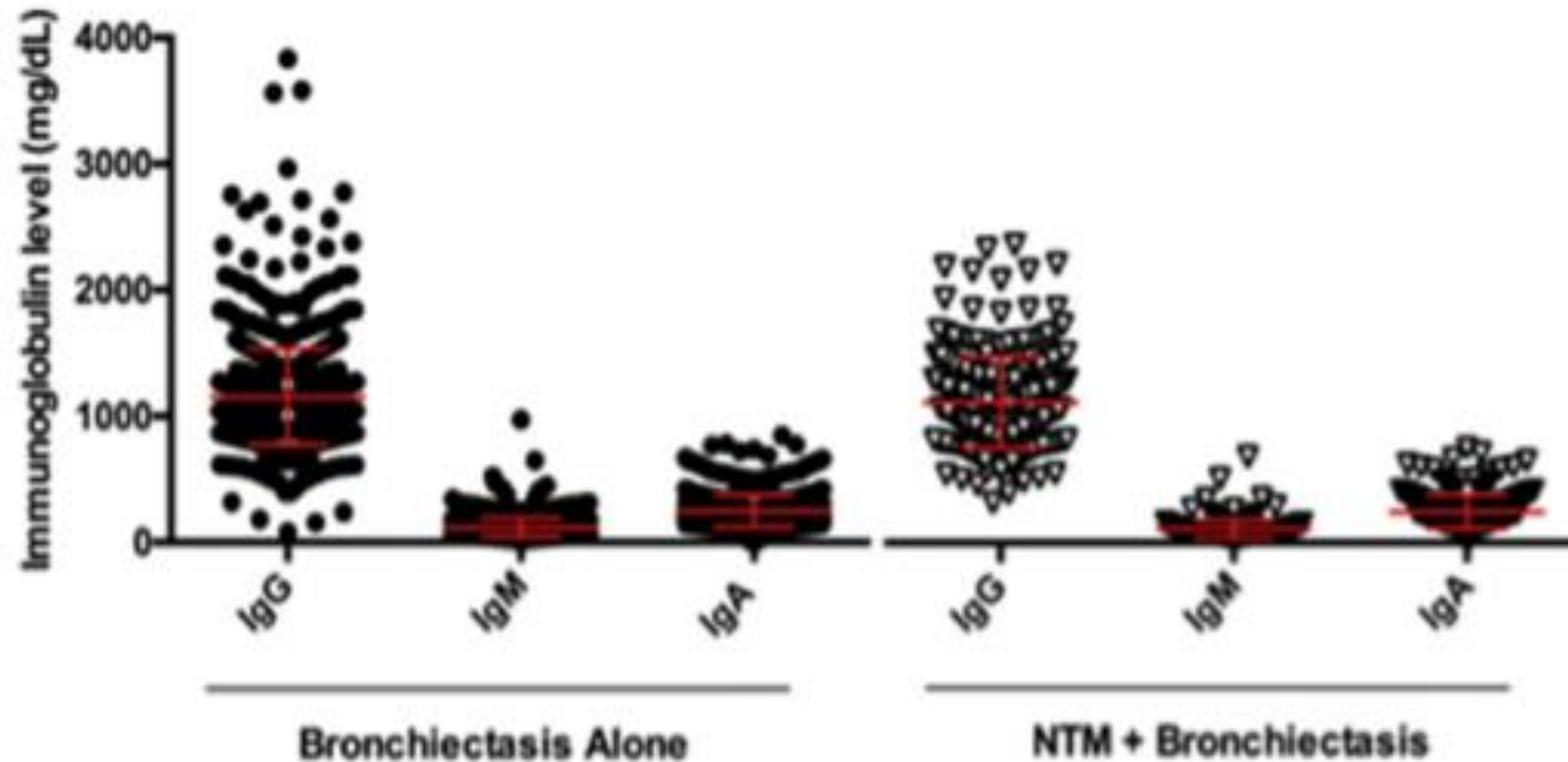


Figure 1. Immunoglobulin levels in patients with bronchiectasis and nontuberculous mycobacteria, with mean and SD (red) for the population. Reference ranges are 700 to 1,600 mg/dL for immunoglobulin G (IgG), 40 to 230 mg/dL for immunoglobulin M (IgM), and 70 to 400 mg/dL for immunoglobulin A (IgA).

ABPA AS REPETITIVE BACTERIAL PNEUMONIA

- Untreated: severe bronchiectasis and pulmonary fibrosis unless recognized promptly
- As its clinical presentation may mislead pneumonia and/or pulmonary tuberculosis, the diagnosis of ABPA is usually missed or delayed.
- 1st case reported in Vietnam:
 - The diagnosis of ABPA was obvious with lots of compatible criteria except the skin prick test. This test was negative in 0-5% of ABPA patients.
 - Bacterial pneumonia was considered to be highly likely because of productive cough, chest X ray infiltration, high white blood cells, high concentration of *Klebsiella pneumoniae* in sputum culture.
- Careful consideration of all differential diagnoses of pneumonia and a systemic approach to eosinophilic lung diseases would help to establish the diagnosis of ABPA.

EXHALED NITRIC OXIDE AND ATOPY AS MARKERS OF ABPA IN CYSTIC FIBROSIS

- In patients with ABPA, exhaled nitric oxide (eNO) was significantly elevated compared to controls.
- In both ABPA and control groups, atopy is associated with elevated eNO.
- ABPA occurs more frequently in atopic patients in this study and the higher rate of atopy than the general population is consistent with findings from adult studies.

MYCOBACTERIUM AVIUM INTRACELLULARE INFECTION COMPLICATED BY ABPA IN A NON-ASTHMATIC NONAGENARIAN

- ABPA is unlikely to present in very elderly without a history of asthma.
- Underlying MAI infection may predispose to colonization with aspergillus.
- A high index of suspicion is required to diagnose ABPA in patients with pulmonary eosinophilia but without pre-existent asthma.
- Treatment is complicated in such situations as immunosuppression with prednisone may cause dissemination of MAI infection.

ABPA IN HIV POSITIVE PATIENT

- Advanced HIV infection with lower CD₄ count may result in blunted antifungal activity thereby predisposing patients to invasive Aspergillosis.
- Developing ABPA in an HIV patient indicates the presence of an intact Th₂ system.
- Treatment of ABPA consists of an extended period of high dose steroid with or without an antifungal.
- Given the rarity of coinciding HIV and ABPA, no definitive treatment guidelines exist.