INTRODUCTION TO BRONCHIECTASIS

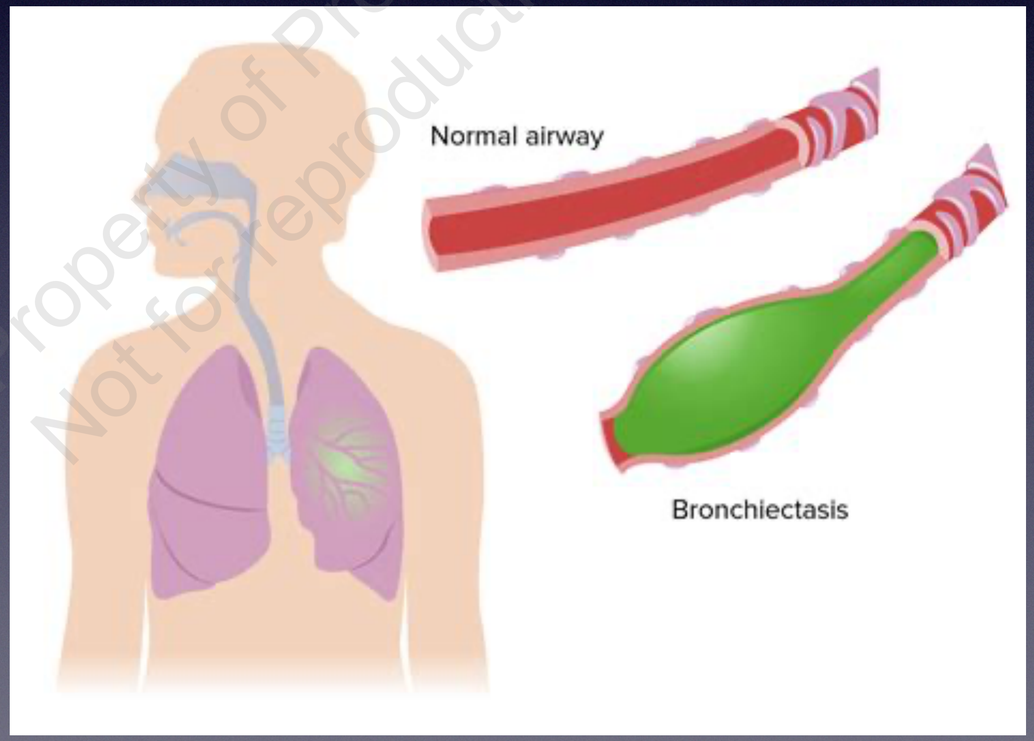
Nir Goldstein MD
Associate Professor of Medicine
Pulmonary and Critical Care
National Jewish Health, Denver

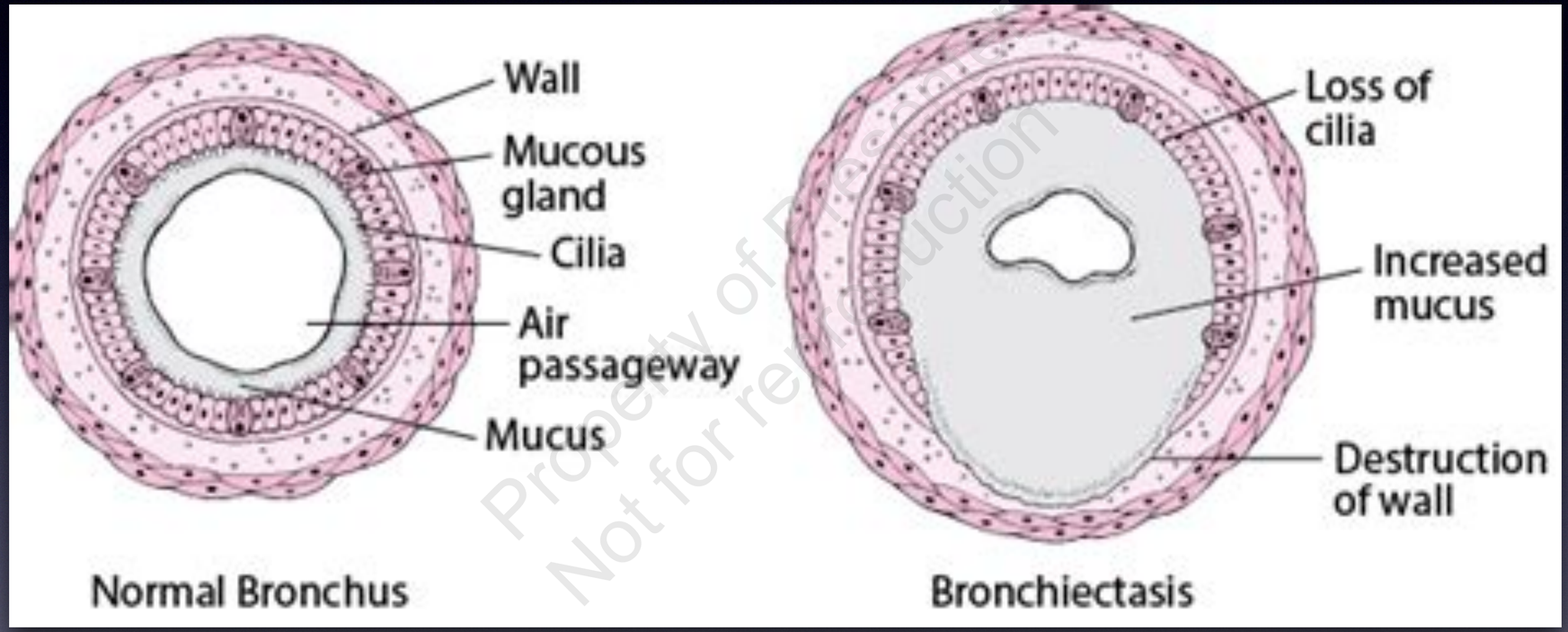
BRONCHIECTASIS

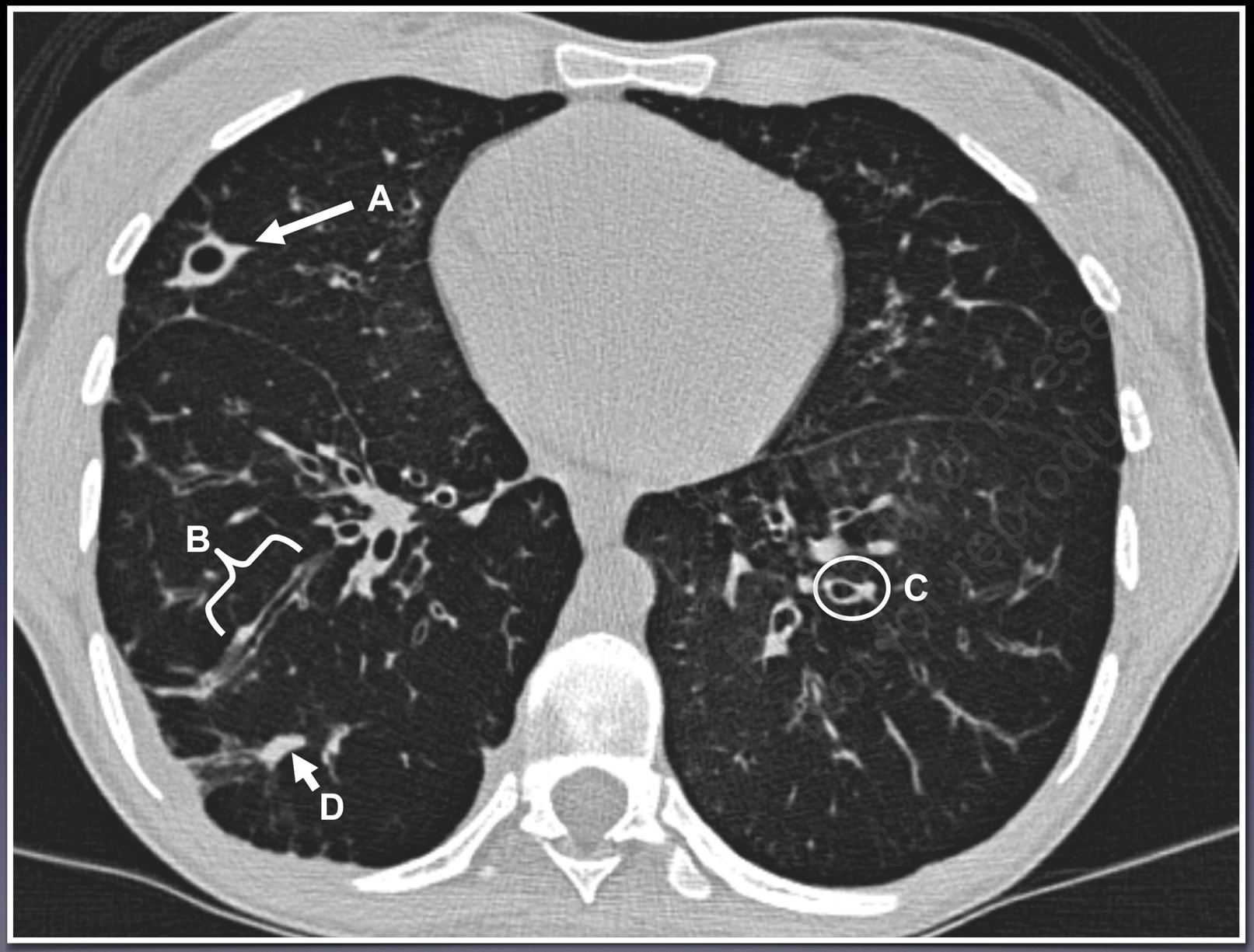
1. Definition
2. Causes
3. Evaluation
4. Treatment

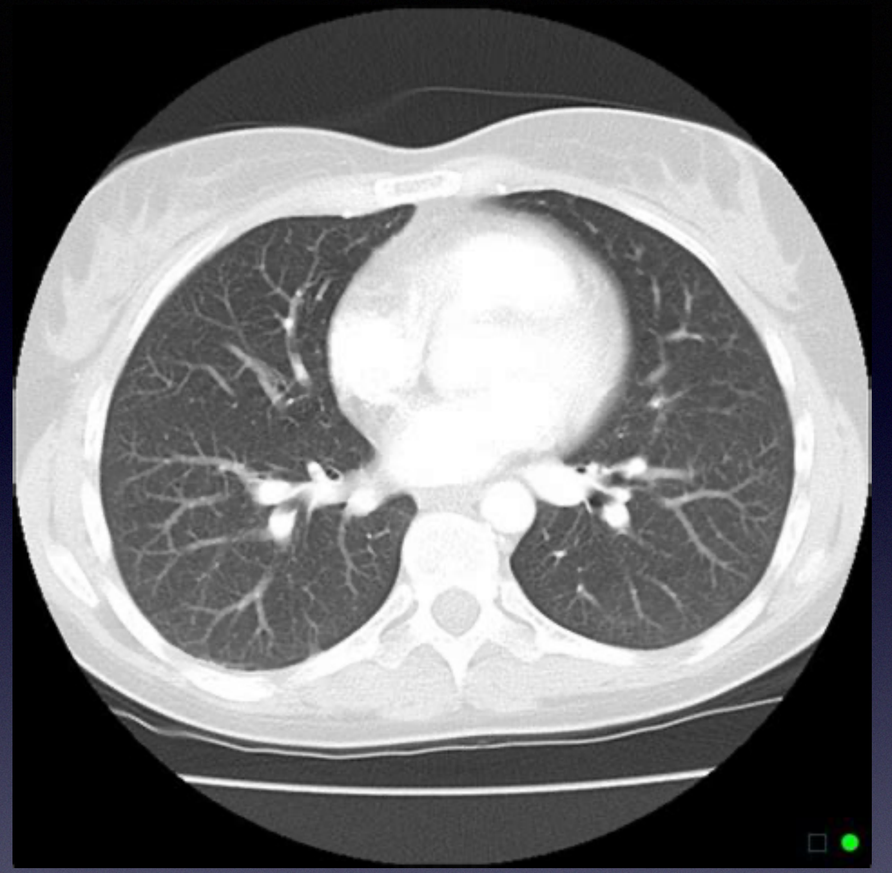
René-Théophile-Hyacinthe Laennec
(1781-1826)

Progressive respiratory disease characterized by permanent dilatation of the bronchi and associated with a clinical syndrome of cough, sputum production and recurrent respiratory infections



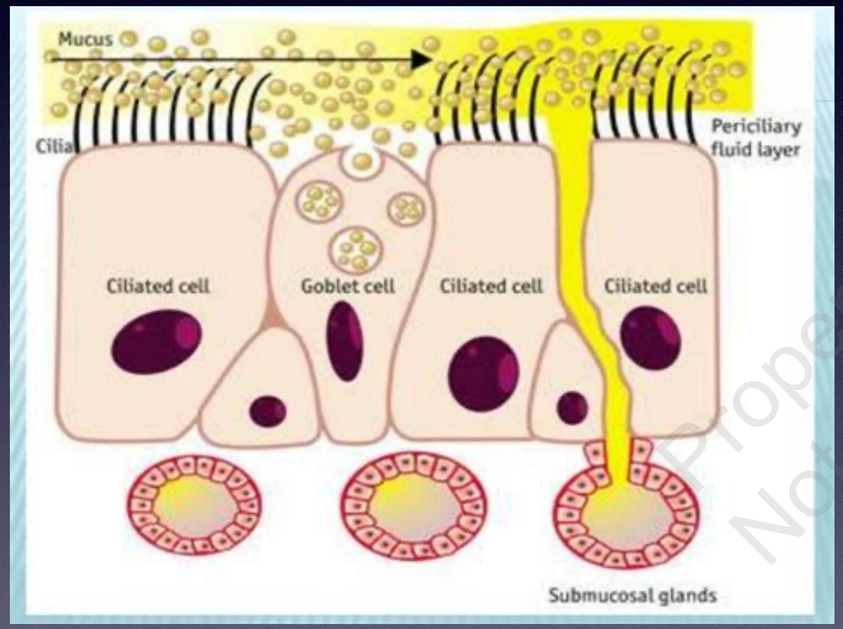

Wall
Mucous gland
Cilia
Air passageway
Mucus
Normal Bronchus
Loss of cilia
Increased mucus
Destruction of wall
Bronchiectasis

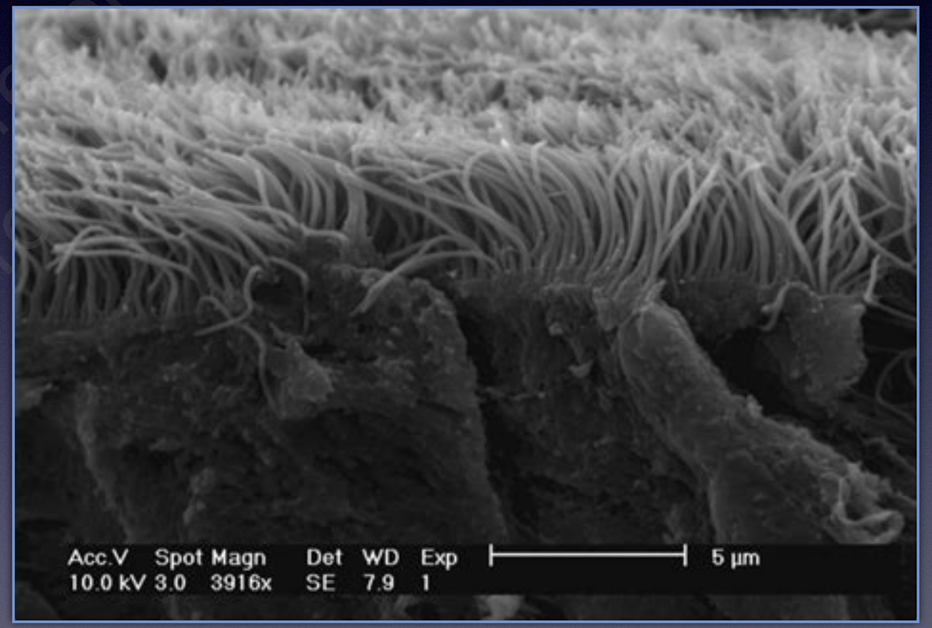

A
B
C
D



Airway Defense Mechanisms

Muco-cilliary clearance





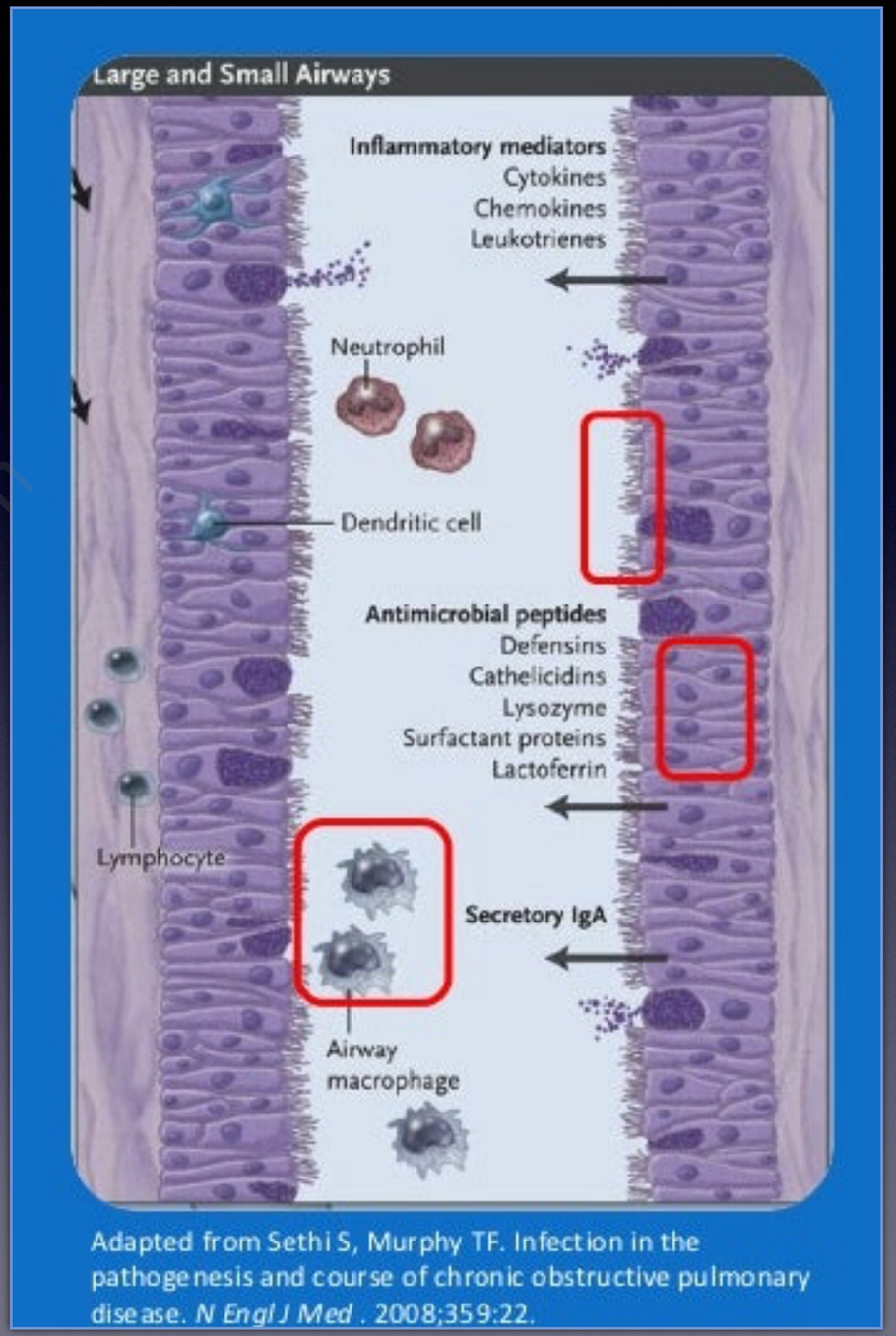
Immune Defenses

Innate Immunity

- Cellular : Neutrophils ; Macrophages ; NK cells
- Proteins: TLR, Cytokines, Antimicrobial proteins

Adaptive Immunity

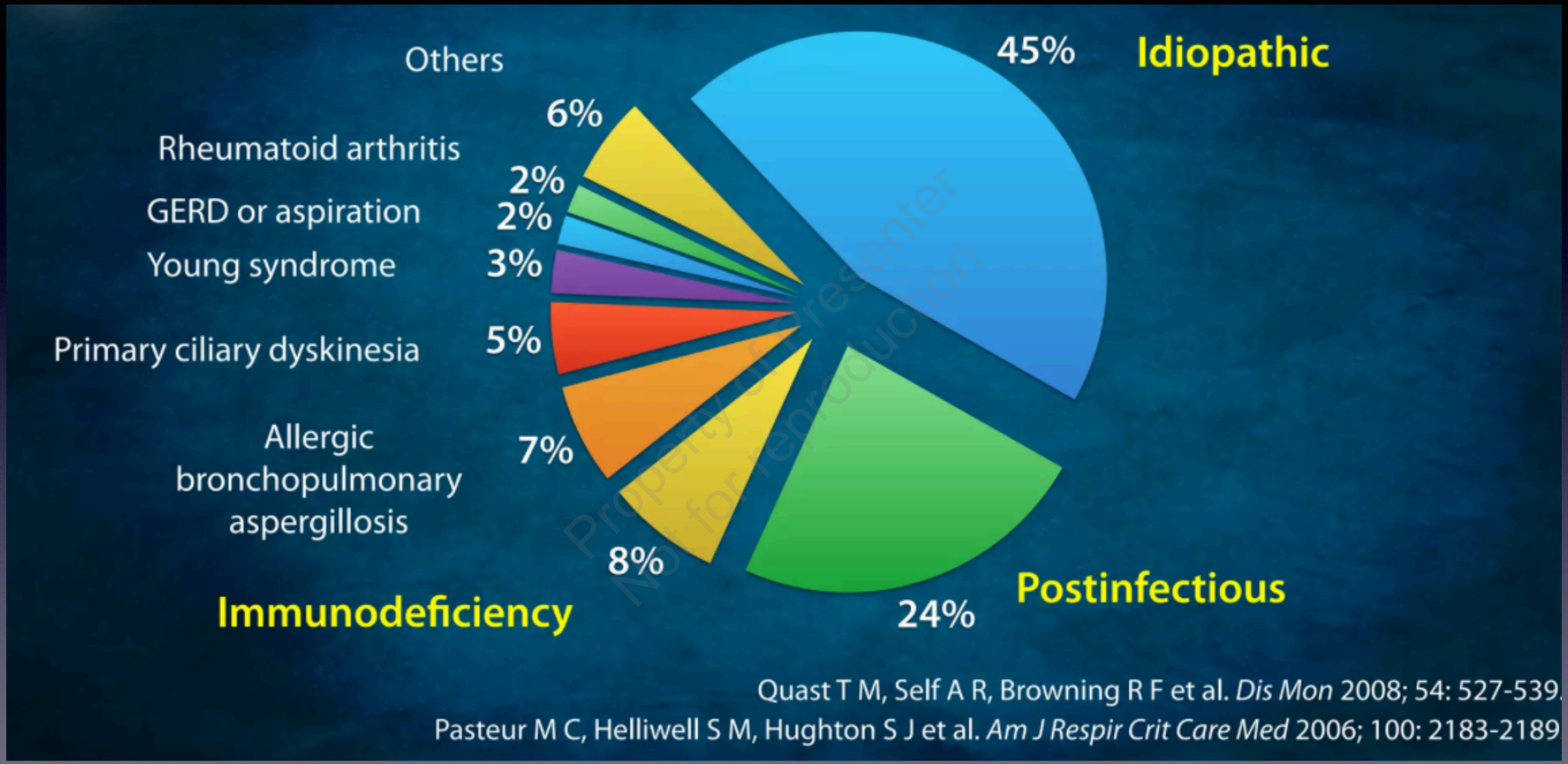
- Immunoglobulins
- T and B Lymphocytes



Adapted from Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* . 2008;359:22.

Possible Causes

- **Congenital:**
  - Tracheobronchomegaly
  - Cartilage deficiency
  - Pulmonary sequestration
  - Yellow nail syndrome
  - Young's syndrome
  - Alpha-1 antitrypsin Def
  - Primary ciliary dyskinesia
  - Cystic Fibrosis
- **Other:**
  - ABPA
- **Immunodeficiency:**
  - Hypogammaglobulinemia
  - CLL
  - Chemo
  - Immunosuppression
- **Post infectious:**
  - Bacteria
  - Mycobacterium
  - Aspergillus
  - Viruses
- **Rheumatologic:**
  - RA
  - SLE
  - Sjögren's syndrome
  - IBD
- **Aspiration/Inhalation:**
  - Chlorine
  - Overdoses
  - Foreign bodies



Quast T M, Self A R, Browning R F et al. *Dis Mon* 2008; 54: 527-539.
Pasteur M C, Helliwell S M, Hughton S J et al. *Am J Respir Crit Care Med* 2006; 100: 2183-2189

Two Hit Hypothesis

Mucocilliary Defects

CF

PCD

Immune Defects

Primary - CVID

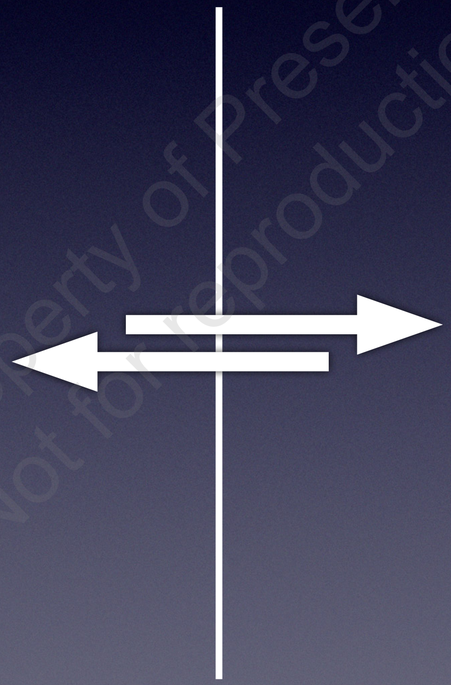
Secondary - ChemoRx

Other Conditions

RA

Sjogren's

IBD



Acute /Severe

Infection - Viral

Inhalation / Radiation

Recurrent

Aspiration

Infection

Persistent

ABPA

TBM

Bronchial Obstruction

Evaluation of Bronchiectasis : General Considerations

1. Definitive Diagnosis
2. Look for Cause
3. Underlying / Associated Conditions
4. Assess Severity of Disease
5. Microbiology
6. Non-Respiratory issues

1. Definitive Diagnosis : HRCT

CT imaging protocol

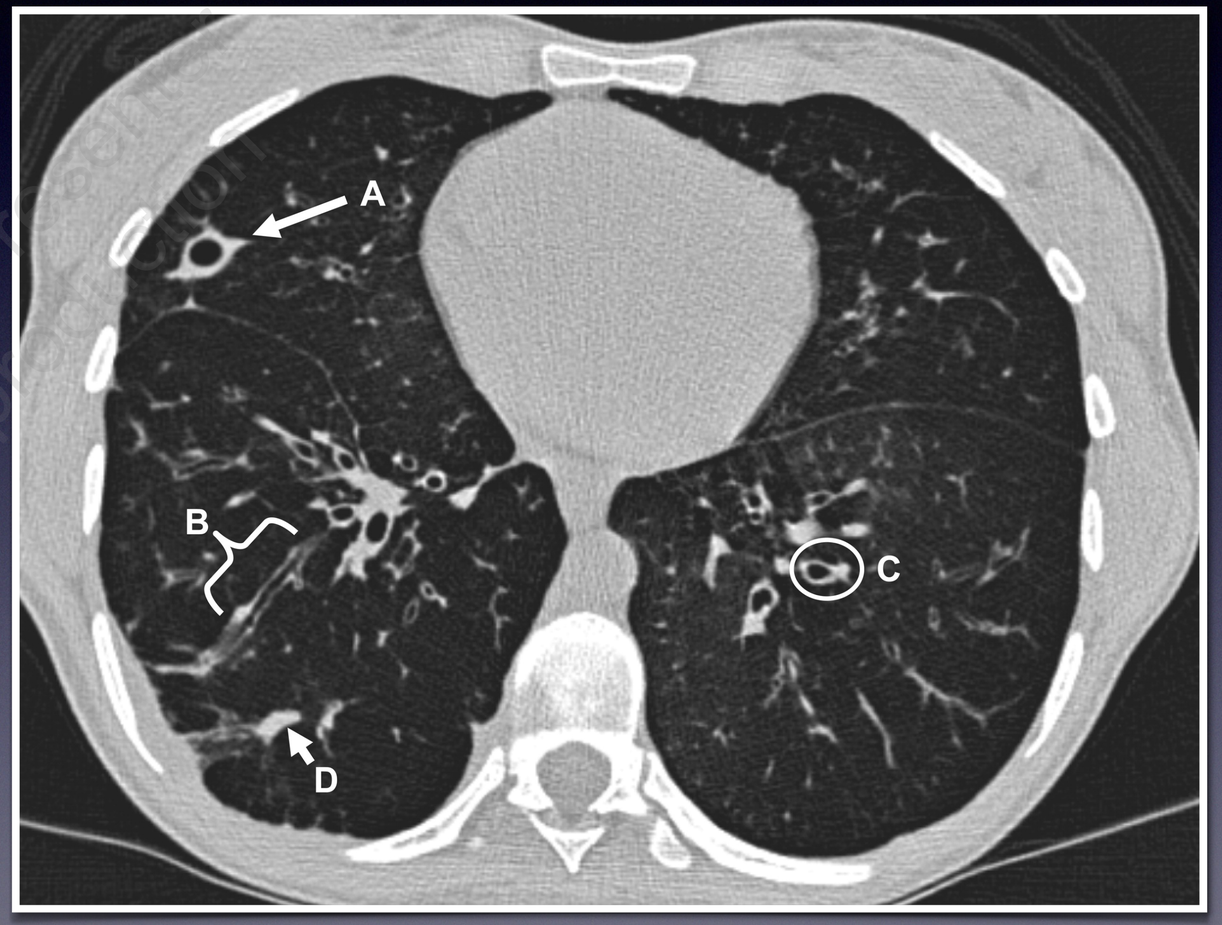
- Slice thickness: ≤1mm

CT features of bronchiectasis

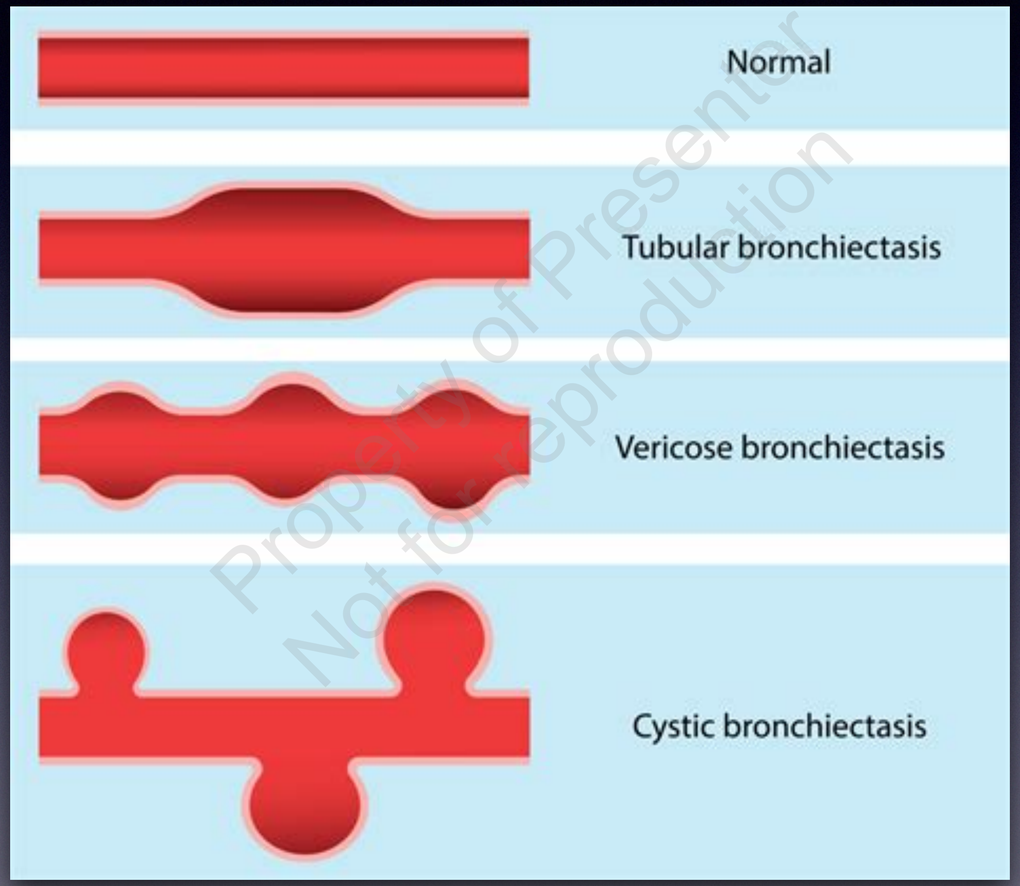
- O**ne or more** of the following:
    1. Bronchoarterial ratio >1 (internal airway lumen vs adjacent pulmonary artery)
    2. Lack of tapering
    3. Airway visibility within 1cm of costal pleural surface or touching mediastinal pleura

Other indirect signs:

- Bronchial wall thickening
- Mucus impaction
- Mosaic perfusion / air trapping on expiratory imaging



Radiographic Phenotypes



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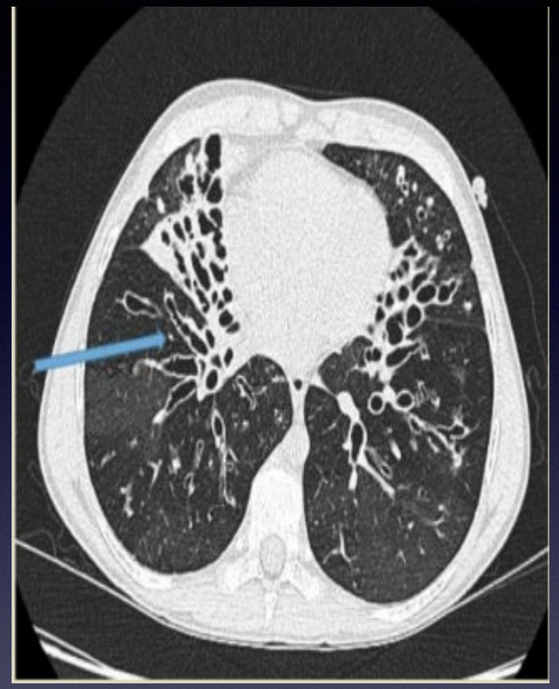
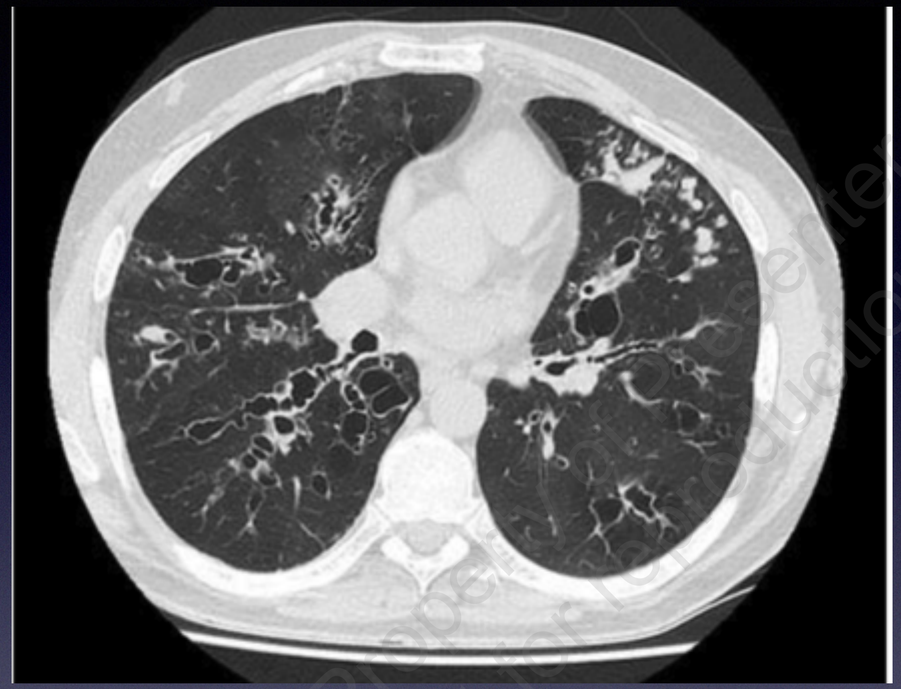
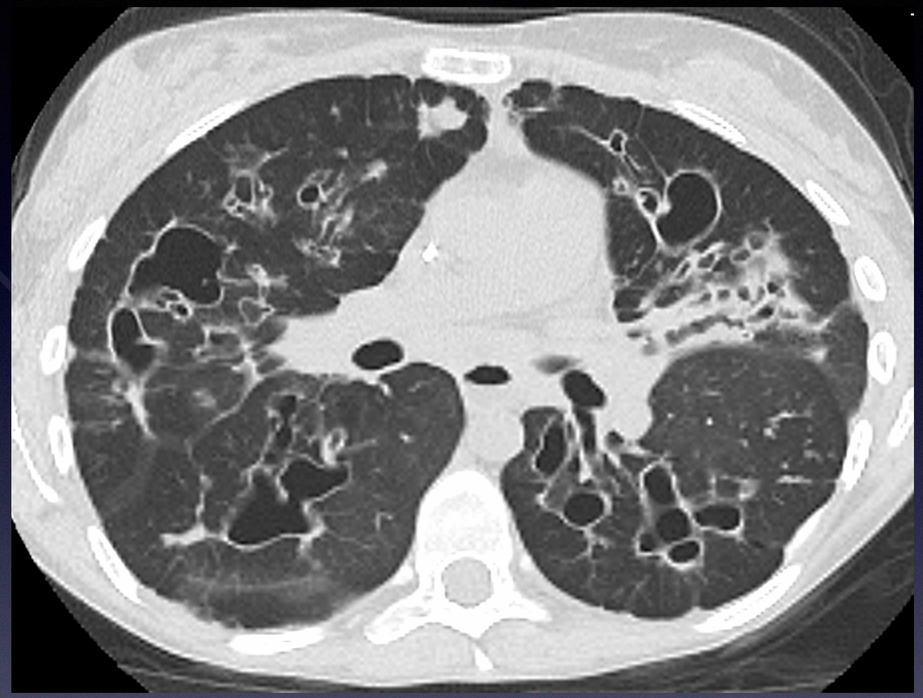


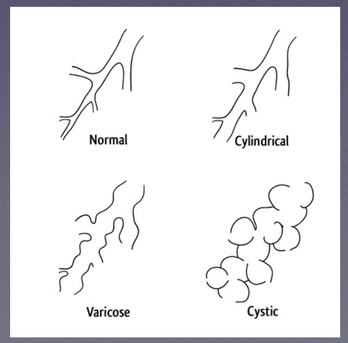
Cylindrical/tubular



Varicose



Saccular/cystic



2. Find Cause

History:

Neonatal symptoms

Infertility

Previous pneumonia or viral illness in childhood

Gastric aspiration

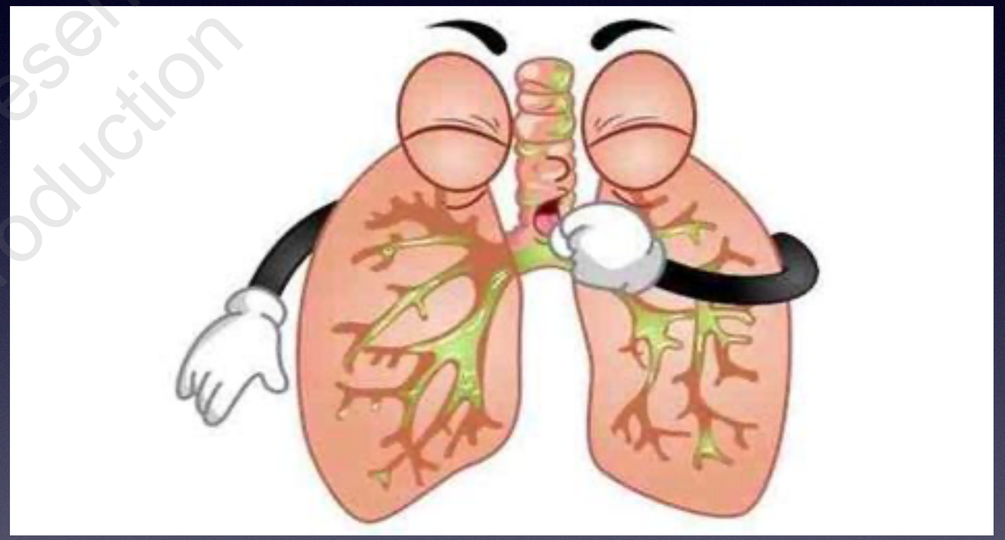
Asthma

Autoimmune symptoms

Family history

Recurrent oto-sino-pulmonary infections

Situs abnormalities



CT SCAN: Clues

Upper lobe predominant
- CF
- Sarcoidosis
- Pneumoconiosis
- Tuberculosis

Central
- ABPA
- NTM

Lower lobe predominant
- PCD
- Hereditary Immunodeficiency
- A1AT deficiency
- Chronic aspiration

Blood Tests

Diagnostic laboratory:

- Blood cell counts
- Immunoglobulin Levels
- Testing for Aspergillus
- Antibody levels against Pneumococcal Vaccine - If low, immunize with 23 valent polysaccharide pneumococcal vaccine, followed by measurement of specific antibody levels 4–8 weeks later
- Testing for Autoimmune Conditions

Conditional:

- A1AT if coexisting emphysema
- Test for CF if supporting clinical features (early onset, male infertility, malabsorption, pancreatitis)
- Test for PCD if supporting clinical features (Neonatal distress, childhood symptoms, Recurrent otitis / rhinosinusoitis, infertility)

Sputum

Expectorated or **Induced**

Bacteria

Mycobacteria

BAL

Cannot produce sputum

Suspected infection

Doing Poorly

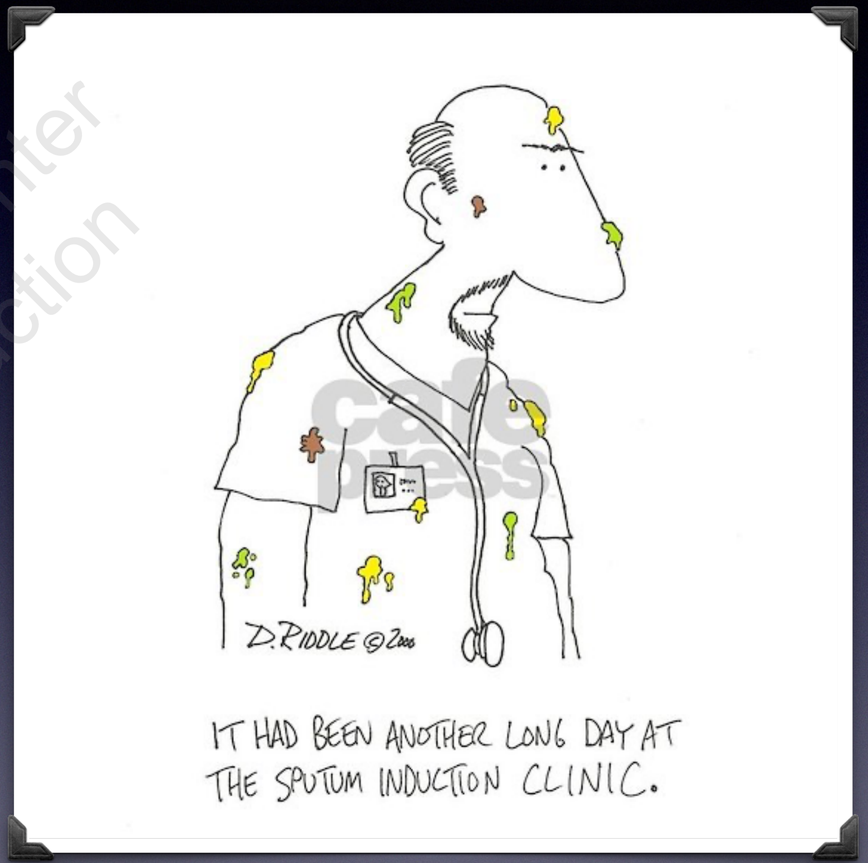
Suspected NTM by CT with negative sputa

Other

Reflux and aspiration if symptoms

Spirometry

Bronchscopy : Concern for Obstruction



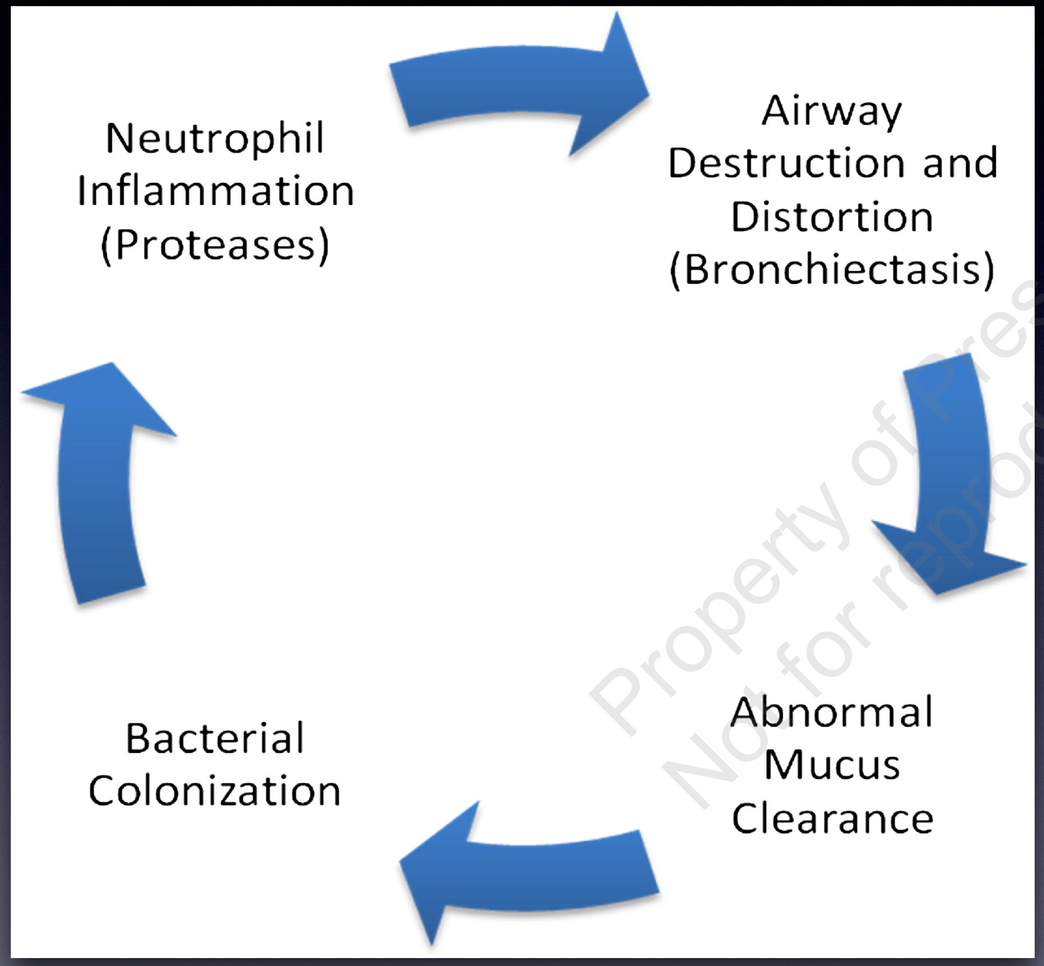
3. Assessing Severity of Bronchiectasis

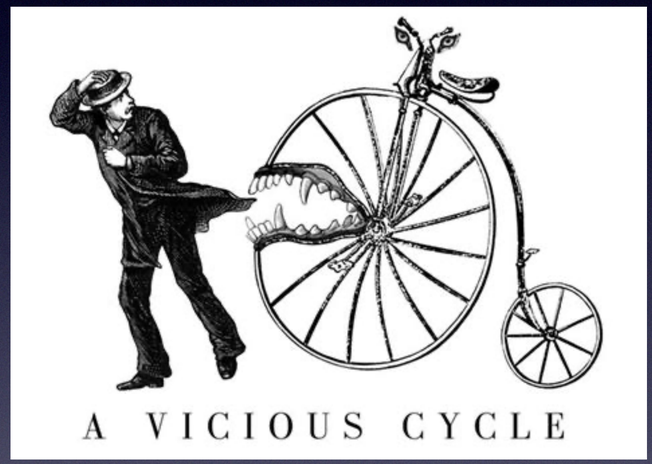
Bronchiectasis Severity Index:

1. Age
2. BMI
3. FEV1
4. Hospitalization
5. Number of exacerbations
6. Breathlessness Score
7. Pseudomonas
8. OtherOrganisms
9. Number of involved Lobes

Not only the CT

4. Therapeutic Principles





"vicious cycle hypothesis" first proposed in 1986 by Cole, remains central to our understanding

Treatment : General Considerations

1. Underlying Cause
2. Antibiotics
3. Macrolides
4. Mucoactive agents
5. Anti-inflammatory agents
6. Bronchodilators
7. Airway Clearance
8. Pulmonary Rehabilitation
9. Emerging Therapies

1. Causes of bronchiectasis that have specific treatment.

Condition or cause	Specific therapeutic measures
Allergic bronchopulmonary aspergillosis	Systemic corticosteroids, antifungal agents
Ciliary dyskinesia	Auditory monitoring, cardiac evaluation , genetic counceelling
Associated diseases (asthma, COPD, collagen diseases, inflammatory bowel disease, etc.)	Treatment of the underlying disease
Alpha-1 antitrypsin deficiency	Avoid tobacco exposure; consider replacement therapy.
Cystic fibrosis	DNase; consider CFTR modulator
Immunodeficiencies	Periodic immunoglobulin replacement
Nontuberculous mycobacterial infection	Treatment according to species and in accordance with guidelines
Bronchial obstruction	Bronchoscopic clearance or surgical treatment
Gastroesophageal reflux disease	Inhibitor of acid gastric secretion; consider surgery

2. Antibiotics

Antibiotics (oral, intravenous or nebulised) can be used in three situations:

1. To treat **exacerbations**
2. To attempt eradication of **new airway isolates**
3. As a **long term** maintenance for suppression of chronic colonization

2.1. Acute Exacerbations:

Usually 14 days of antibiotics

- Shorter Course : Mild exacerbations, exacerbations in mild patients, those associated with pathogens more sensitive to antibiotics (e.g. S. pneumoniae), or with a rapid return to baseline.

- Severe exacerbations require intravenous antibiotic therapy and/or hospitalization (tachypnea ; worsening hypoxemia, fever, hemoptysis >25ml/24hrs, Sepsis criteria)

2.2. *Eradication of new isolates.*

1. Considered for **Pseudomonas aeruginosa**

2. No evidence to support the eradication of other organisms

Possible regimens for primary *Pseudomonas aeruginosa* infection.

Treatment regimen	Frequency
Oral antibiotic + inhaled antibiotic	
Oral: Ciprofloxacin +	14-21 days
Inhaled: Gentamicin or Nebulized tobramycin or Colistimethate**	3 months
Intravenous antibiotic (antipseudomonal beta-lactam + aminoglycoside) + inhaled antibiotic	
Intravenous: Ceftazidime or Cefepime or Piperacillin + tazobactam or Meropenem +	14 days
Intravenous: Amikacin or Gentamicin or Tobramycin +	14 days
Inhaled: Gentamicin or Nebulized tobramycin or Colistimethateb	3 months

2.3. Maintenance suppression of persisting microbial colonizers

- Once established in the airway long term colonizers may be difficult to eradicate.
- A therapeutic trial of pathogen-targeted inhaled antibiotics may be considered.
- Nebulised antibiotics are associated with a 10% – 30% risk of bronchospasm. Bronchodilators may be required prior to nebulised antibiotics

Antibiotic and formulation	Dose	Frequency
Nebulized colistimethate	1,000,000 IU	1/12 h continuously
Gentamicin	80 mg	1/12 h continuously (or in alternating cycles of 28 days)
Dry powder tobramycin	112 mg	1/12 h in alternating cycles of 28 days
Nebulized tobramycin	300 mg	1/12 h in alternating cycles of 28 days

3. Macrolides for bronchiectasis.

1. Macrolide antibiotics target both inflammation and infection
2. They are efficiently delivered to sites of infection ,particularly Azithromycin.
3. Three major trials in adults and one in children have shown that azithromycin and erythromycin are effective in preventing pulmonary exacerbations (reduced by 40-60%) in patients with bronchiectasis *and* improvements in quality of life and lung function

Adverse Effects.

1. Gastrointestinal effects (mainly diarrhoea) are common but are generally mild.
2. Cardiac arrhythmias : risk is very small with oral treatment. Caution should be taken with prolonged QTc interval.
3. Resistance to macrolides is very likely to develop with prolonged macrolide treatment. However, the negative consequences of macrolide resistance for individual patients treated with macrolides are unclear.

Dose regimens vary:

Azithromycin

- 500 mg 3 times a week (Monday, Wednesday, Friday)
- 250 mg daily
- 250 mg 3 times a week (if unable to tolerate higher dose)

- Positive clinical trials have treated for 6 or 12 months.
- The maximum benefit of macrolide treatment is thought be attained after at least 3 months of treatment.

Checklist prior to starting Azithromycin:

- ☑ Frequent exacerbations (3 or more exacerbations in past year)
- ☑ Exclude non-tuberculous mycobacterial infection (sputum culture x3)
- ☑ Assess cardiac risks (QTc interval, arrhythmia) – ECG

4. Mucoactive treatment

Recommendation

- Trial long-term mucoactive treatment (≥3 months) if **difficulty in expectorating** sputum and and if **standard airway clearance techniques have failed** to control symptoms

4.1. Mucoactive agents

- The following mucoactive agents can be used to assist with airway clearance in patients with bronchiectasis:
    - Isotonic saline (0.9%)
    - hypertonic saline (3% – 7%)

- There is no evidence to support the use of N-acetylcysteine or Guaiafenesin in bronchiectasis.
- Avoid recombinant human DNase in adult patients with Non-CF bronchiectasis.

Mechanism of action of HS

Not fully understood, mechanisms include:

- Increases the osmotic gradient of water to the bronchial surface, rehydrating and increasing the volume of the epithelial lining fluid
- Decreases mucus viscosity
- Stimulates cough
- Accelerates mucociliary clearance via electrostatic interactions with mucins
- Inhibits epithelial sodium channels
- Possible anti-inflammatory effects
- Activation of antimicrobial peptides
- Inhibition of Pseudomonas aeruginosa growth due to an antimicrobial effect

Saline for Nebulization

- Effect appears to be dose-dependent - higher concentrations increase the amount of expectorated sputum but adverse events also increase.
- Most commonly used concentrations are 6% or 7%.
- The volume of HS that is usually used ranges from 4 ml to 5 ml.
- In most studies, HS is used twice a day
- Nebulization system most commonly used system is the jet type

- **Clinically significant benefits with both HS and IS:**
  - Reduce exacerbations
  - Ease clearing secretions
  - Reduce Chronic colinization, in particular Pseudomonas aeruginosa
  - Reduce sputum burden

5. Anti-Inflammatories

5.1. Inhaled corticosteroids.

- Not be prescribed routinely unless there is an established diagnosis of coexisting asthma.
- Trials of ICS in bronchiectasis identified no beneficial effects
- Patients with bronchiectasis had a nearly 200-fold increased risk of acquiring NTM infection compared with the general population but that independently, use of ICS increased risk by 29-fold, increasing to an almost 50-fold increase in risk when taking higher-dose ICS (> 800 µg/d)

5.2. No benefit to Statins

6. Bronchodilators

- No evidence to support the routine use of bronchodilators in patients without dyspnea
- No evidence to support the routine use of anticholinergics.
- Recommend Long-acting bronchodilators in symptomatic patients with airflow obstruction
- Can use short-acting bronchodilators prior to respiratory therapy and prior to the use of inhaled hypertonic solutions and/or inhaled antibiotics.

7. Airway Clearance

- Mobilize secretions and interrupt the vicious cycle of inflammation and infection.
- Oscillatory Positive Expiratory Pressure (PEP) devices
- High-frequency chest wall oscillation (HFCWO)
- Oscillation & Lung Expansion (OLE)
- Autogenic drainage, active cycle breathing with huff coughs, manual chest percussion.

Benefits of Airway Clearance

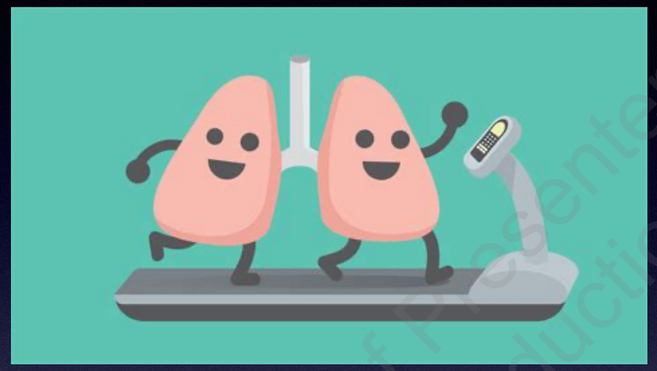
- Improvements in quality of life scores and exercise capacity with use of PEP device twice daily for 3 months.
- HFCWO :
  - Improvements in the Breathlessness, Cough, and Sputum
  - Improved FEV1 and FVC
- Adding postural drainage to CPT : Augment the amount of sputum produced during airway clearance.
- Any of the airway clearance modalities can be tailored to fit the specific preferences ,but in all cases, **education is a paramount factor in the success of therapy.**

Order of medications

A general guide is:

1. Bronchodilator inhalers (e.g. Albuterol)
2. Nebulised saline
3. Other inhaled medications (preventors)
4. *Nebulised antibiotics (Tobramycin, Colistin)
5. *The airway clearance routine should be done before inhaled antibiotics

8. Physical Exercise / Pulmonary Rehabilitation



- The frequency of exacerbations over 12 months reduced with exercise training.

- If there are exertional limitation (mMRC scale score > 1) : Encouraged to exercise regularly and participate in pulmonary rehabilitation programs.

FOLLOW-UP AND MONITORING

S**pirometry** every **6 months**, **lung volume** assessment annually, and the **six-minute walk test**

Sputum samples at regular intervals of **3-4 months** and during pulmonary exacerbations. If the patient is being treated with chronic macrolide therapy, culture for mycobacteria should be performed every 6 months

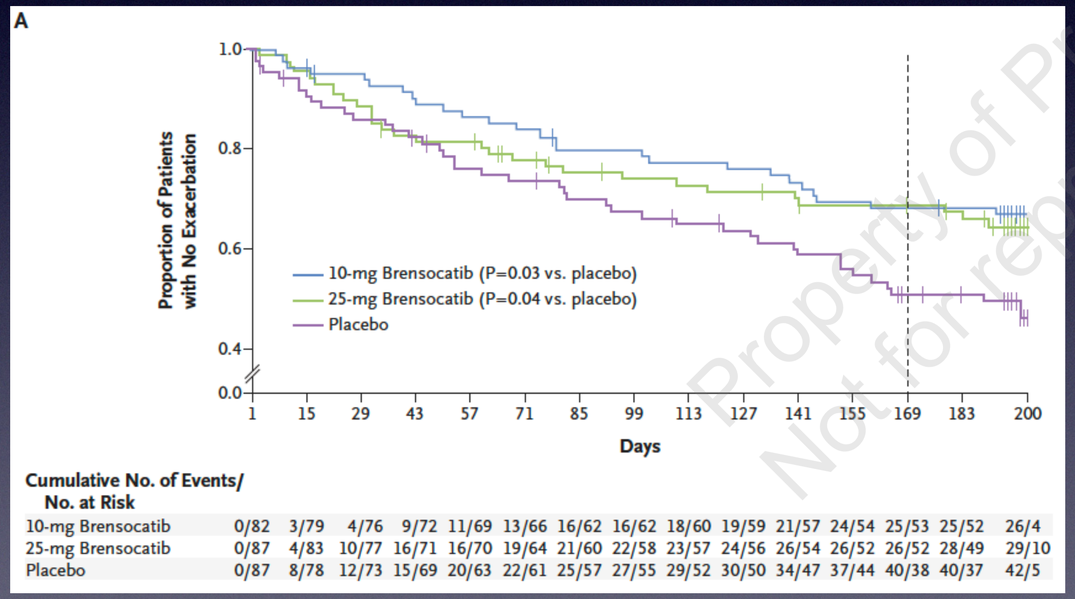
A **severity score** is calculated at the time of diagnosis with bronchiectasis. With Periodic calculation of the score (annually, for example).

WILLOW Study – Primary and Secondary Outcomes

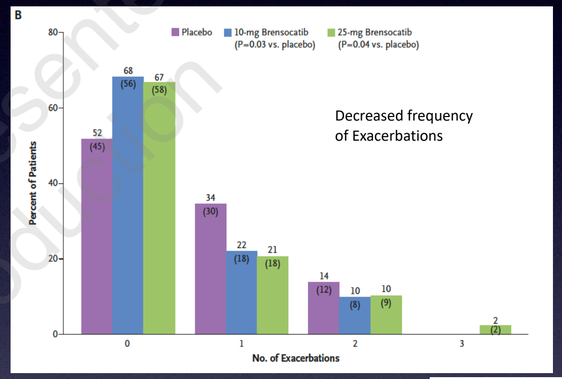
- ASPEN Trial is currently closed

BRENSOCATIB : Inhibitor of dipeptidyl peptidase 1 (DPP-1) required for activation of Neutrophil Serine Proteases

Prolonged time to first exacerbation c/w placebo:

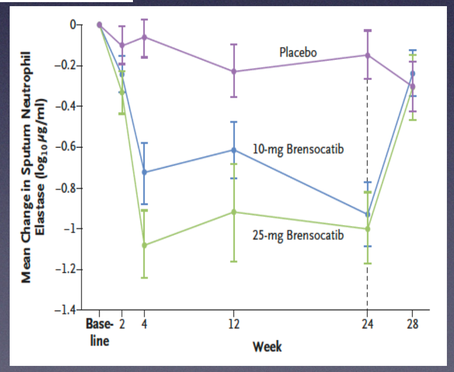


Cumulative No. of Events/ No. at Risk															
10-mg Brensocatib	0/82	3/79	4/76	9/72	11/69	13/66	16/62	16/62	18/60	19/59	21/57	24/54	25/53	25/52	26/4
25-mg Brensocatib	0/87	4/83	10/77	16/71	16/70	19/64	21/60	22/58	23/57	24/56	26/54	26/52	26/52	28/49	29/10
Placebo	0/87	8/78	12/73	15/69	20/63	22/61	25/57	27/55	29/52	30/50	34/47	37/44	40/38	40/37	42/5



Decreased frequency of Exacerbations

Decreased Sputum Neutrophil Elastase



Chalmers JD, et al. N Engl J Med 220;383:2127-37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