For Those Who Lover Sputum: Bronchiectasis

Douglas B. Hornick, MD

Pulmonologist w/ an Infectious Attitude

Division of Pulmonary/Critical Care & Occ Med

Carver UI College of Medicine

Objectives

- Increase understanding of the general characteristics of non-CF Bronchiectasis
- Develop an approach to work-up & management
- Categorize & review heterogeneous causes

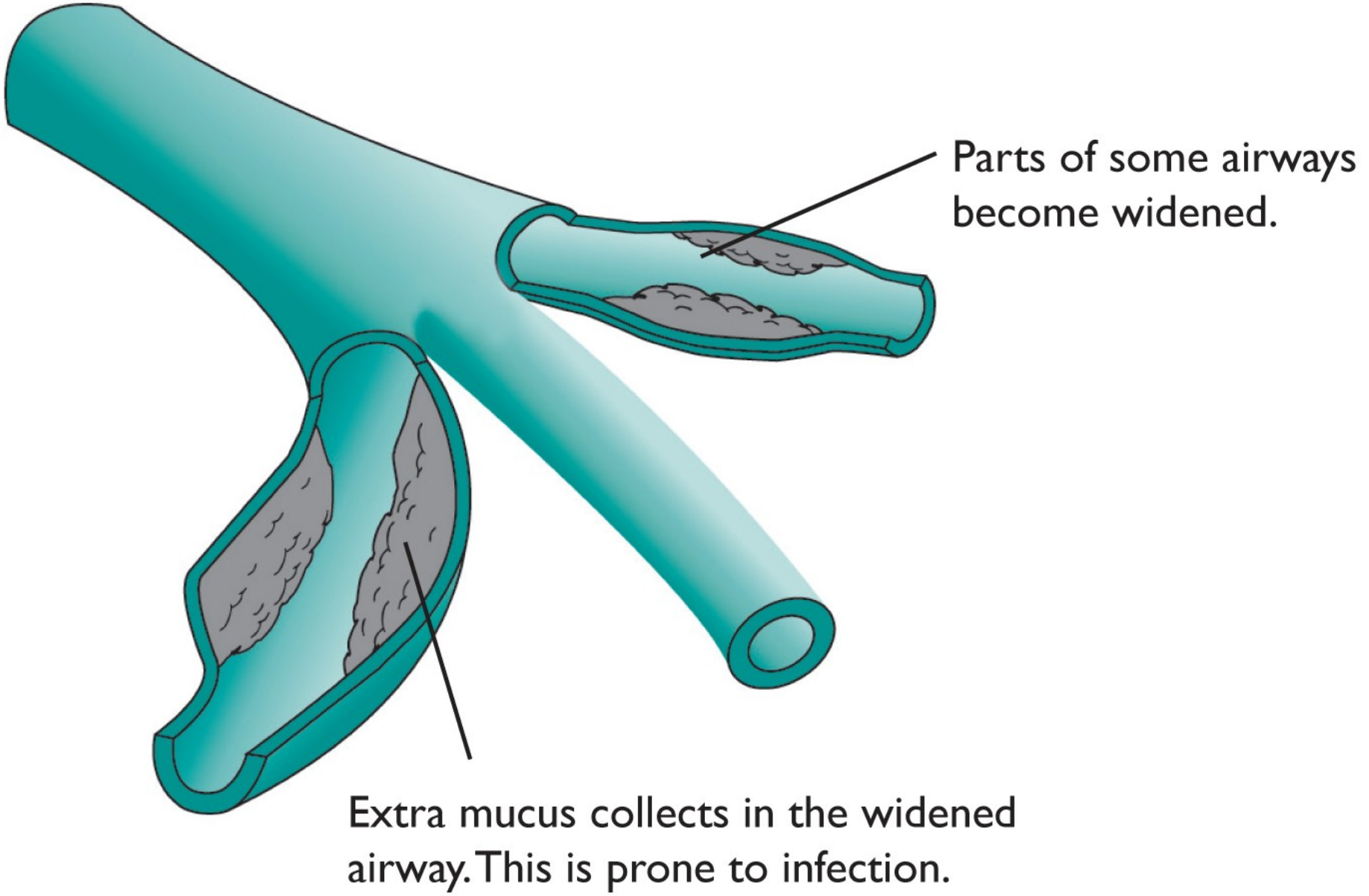
Disclosure: No Conflicts of Interest

Key References

- McShane P, et al. Non CF Bronchiectasis Review. *Am J Respir Crit Care Med* 2013;188:647-56
- Pasteur MC et al, BTS Guidelines for Non-CF Bronchiectasis *Thorax* 2010;65:i1-i58
- *Clinics in Chest Med*, May 2013
- Barker AF: *NEJM* 2003; 346:1383-1393
- Ten Hacken NHT, et al: *BMJ* 2007;335:1089-93

Bronchiectasis

- Irreversible abnormal dilation of bronchial tree
- Inflamed, collapsible airways
- Bacterial Colonization (*S. aureus*, *H. influenzae*, *P. aeruginosa*)
- Chronic productive cough (wet vs. dry)
  - Collected sputum→3 layers (foam, clear, purulent)
  - cough 90%, sputum 76%, dyspnea 72%, hemoptysis 56%
- Exam: rales 70%, rhonchi 44%, wheeze 34%.
- Obstructive physiology
  - Low FEV1, FVC preserved
  - Decreased DLCO


Parts of some airways become widened.
Extra mucus collects in the widened airway. This is prone to infection.

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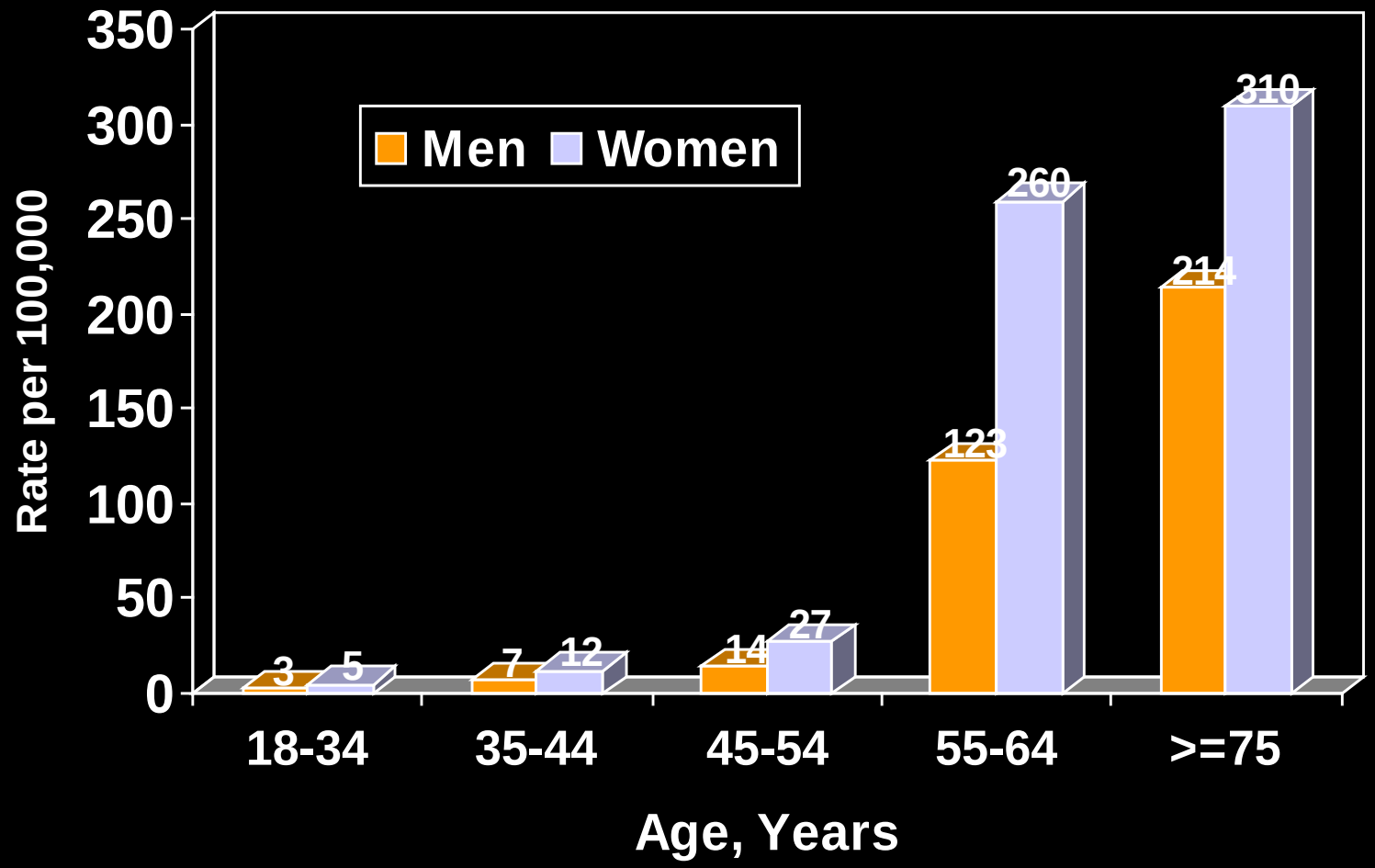
US Prevalence of Non-CF Bronchiectasis

Total Prevalence: ~52/100,000

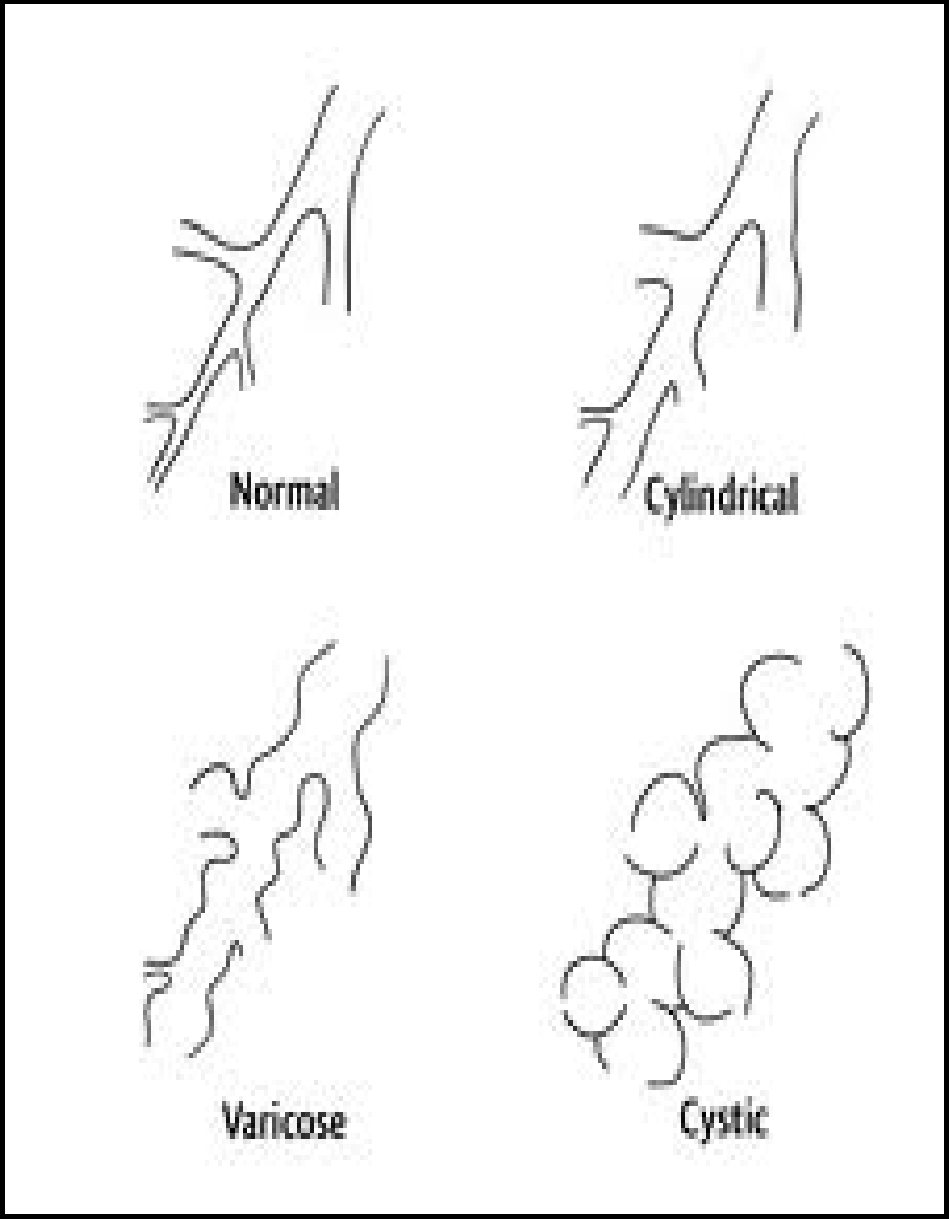


Prevalence may be increasing

Sl F>M predominance

Weycker D et al: *Clin Pulm Med* 2005

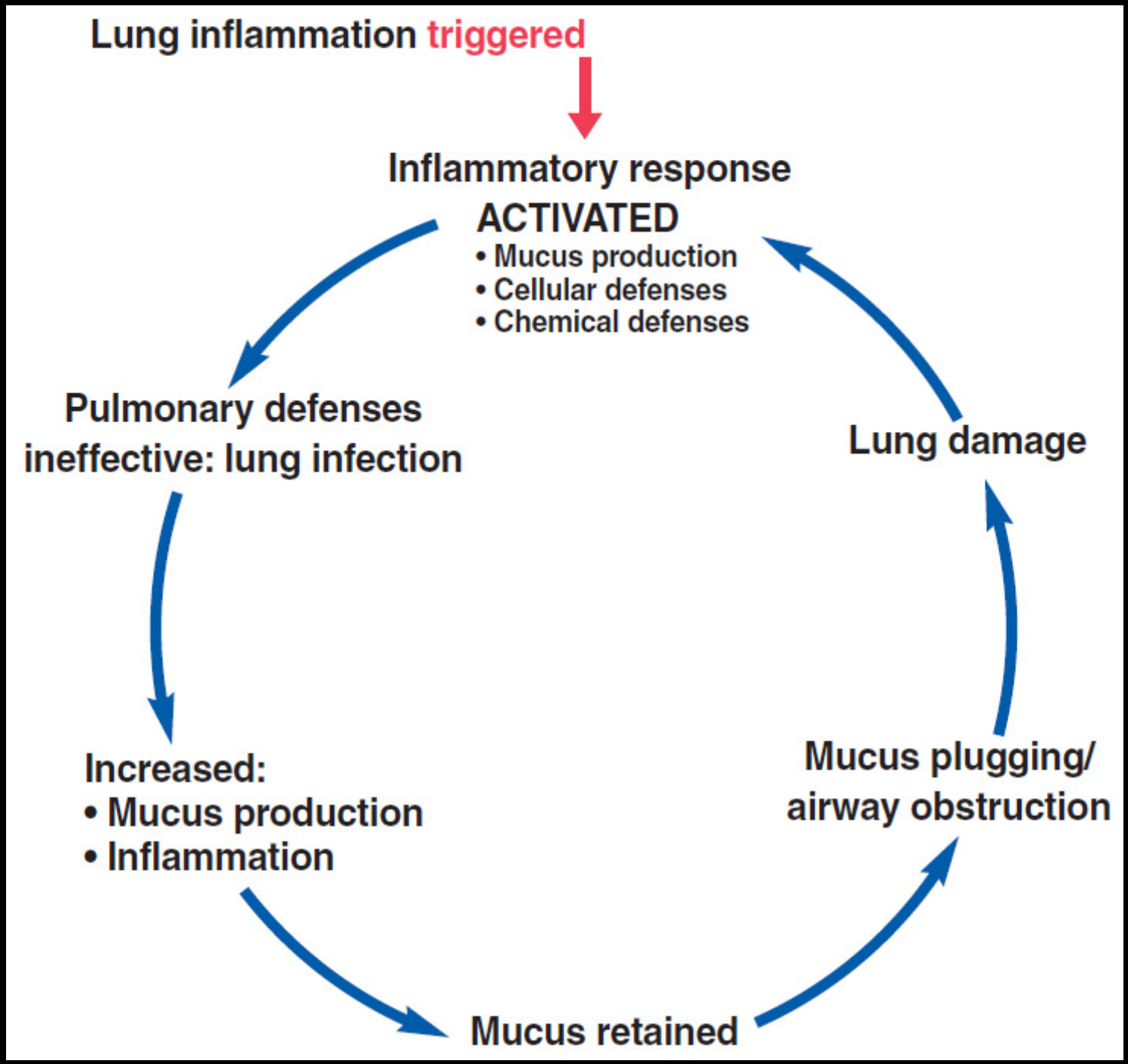
Useless Morphology Classification



- Bronchiectasis can be:
  - Focal (lobe/segment)
  - Diffuse
- Cylindrical: creates tram track lines
- Varicose: beaded bronchi.
- Cystic: occ large cysts imitate cavity or give grape cluster pattern

Vicious Cycle Hypothesis

- Microbial colonization initiates & perpetuates airway inflammation
- PMNs infiltrate lungs & cause structural airway damage
- Impaired mucociliary clearance.
- Optimal for bacterial growth & certain *spp*. Selection (eg, *S aureus*, *H flu*, *P aeruginosa*)


Lung inflammation triggered
Inflammatory response ACTIVATED
• Mucus production
• Cellular defenses
• Chemical defenses
Pulmonary defenses ineffective: lung infection
Increased:
• Mucus production
• Inflammation
Mucus retained
Mucus plugging/ airway obstruction
Lung damage

Bronchiectasis Differential Diagnosis

- **Idiopathic (50→10%...)**
- Airway obstruction
- Primary Ciliary Dyskinesia Syndrome (PCD)
- **Immunodeficiency (Ig Def, CLL/Rx, GVHD, HIV)**
- **Post-infectious**
- Diffuse Panbronchiolitis
- Inflammatory Disease
- Alpha-1-Antitrypsin Syndrome
- **Cystic Fibrosis**

Airway Obstruction

- Foreign Body Aspiration
  - Lower lobes, posterior segment upper lobe
- Obstruction broncholith, slow growing/B9 tumor
- Lymph nodes enlargement
  - Middle Lobe Syndrome

Differential Diagnosis

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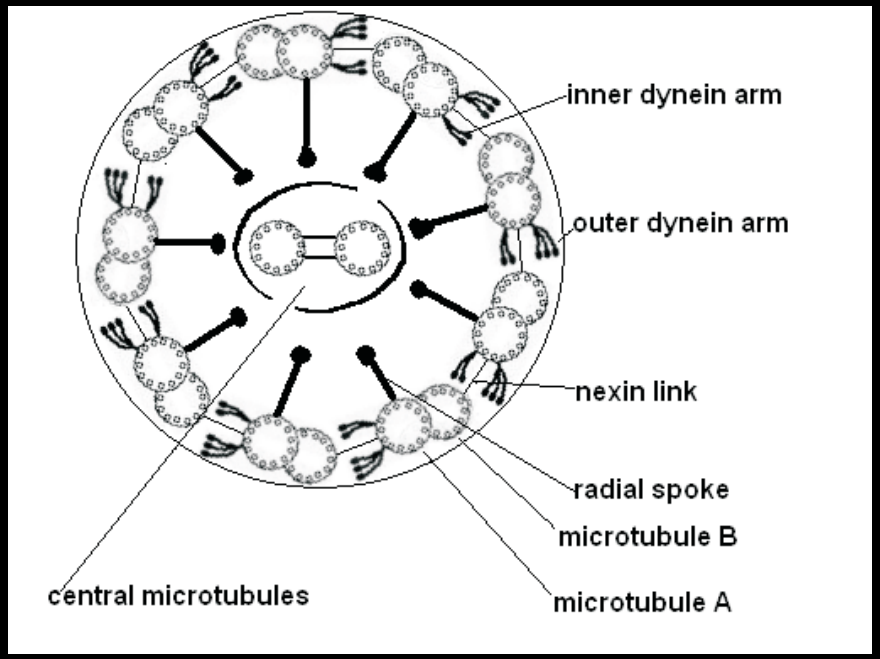
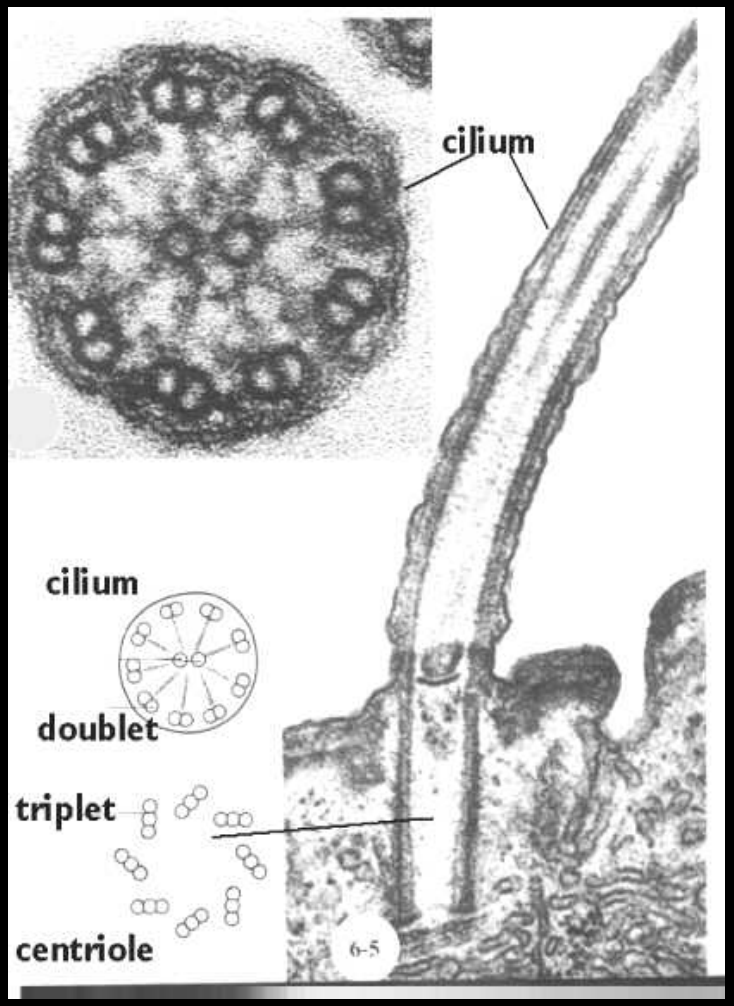
Primary Ciliary Dyskinesia (PCD)

- Incidence ~ 1/15000 – 1/60000
- Autosomal recessive (some DNAH11)
- Classic triad
  - Bronchiectasis
  - Sinusitis
  - Variable male sterility
- Situs inversus (50%) = Kartagener's
- Classic ultrastructure defect…





Nasal NO for PCD Diagnosis

	Subjects:	Measurements*	Age in Years†		nNO (nl/min)	
	Total No. (No. Females)	No.	Mean (SD)	(min, max)	Mean (SD)	(min, max)
UNC						
PCD (with PCD-specific EM defect)						
Subjects with cross-sectional data only	103 (61)	103	29.3 (17.6)	(5.2, 73.0)	20.0 (19.8)	(1.5, 125.3)
Subjects with longitudinal data	40 (21)	132	9.0 (3.2)	(5.1, 16.7)	21.0 (27.5)	(1.8, 207.3)
PCD (with biallelic *DNAH11* mutations)						
Subjects with cross-sectional data only	4 (2)	4	26.2 (9.2)	(12.4, 31.9)	21.0 (7.4)	(9.8, 24.5)
Subjects with longitudinal data	2 (2)	6	14.2 (0.3)	(13.9, 14.4)	25.9 (19.4)	(12.3, 65.0)
All PCD measurements at UNC	149 (86)	245	19.1 (14.8)	(5.1, 73.0)	20.7 (24.1)	(1.5, 207.3)
Healthy control subjects	78 (45)	78	20.9 (15.7)	(5, 73.6)	304.6 (118.8)	(125.5, 867.0)
Disease control subjects						
Subjects with asthma	37 (16)	37	14.8 (11.5)	(5.4, 53.5)	267.8 (103.2)	(125.0, 589.7)
Subjects with cystic fibrosis	77 (41)	77	16.0 (9.4)	(5.5, 56.0)	134.0 (73.5)	(15.6, 386.1)
Subjects with COPD	32 (10)	32	61.1 (8.9)	(43.2, 77.8)	223.7 (87.1)	(109.7, 449.1)
Validation subgroups (non-UNC sites)						
Confirmed PCD‡	71(45)	71	23.3 (18.0)	(5.1, 69.0)	19.6 (16.6)	(0.66, 31.3)
Indeterminate§	84 (46)	84	31.8 (22.3)	(5.5, 79.6)	216.4 (174.5)	(1.8, 991.7)

- Proper SOP, nNO <77: Sensitivity 98%, Spec 99%
- 6 other centers: Identified correctly 70 out of 71 PCD
- Technology more user friendly
- nNO for screening then confirm by EM, *in vitro*/*vivo* assess

Leigh et al. *Ann ATS* 2013;10:574-81

Differential Diagnosis

- Idiopathic (50→10%...)
- Airway obstruction
- Primary Ciliary Dyskinesia Syndrome (PCD)
- Immunodeficiency (Ig Def, CLL/Rx, GVHD, HIV)
- Post-infectious
- Diffuse Panbronchiolitis
- Inflammatory Disease
- Alpha-1-Antitrypsin Syndrome
- Cystic Fibrosis

Immunodeficiency

- Hypogammaglobinemia presents in children
  - Recurrent sinopulmonary infections (middle ear)
  - Can be acquired in elderly
  - Measure IgA, IgG, and IgG subclasses
  - Measure response to protein, polysaccharide vaccine
  - NB: D/t dysregulated T-cell function lung/LN bx may show granuloma $\rightarrow$ misDx sarcoid/TB/NTM
  - Treatment: IVIG infusion q mo.
- Heme-Malig: CLL, post rituximab, GVHD
- AIDS associated bronchiectasis (recurrent infection)
- Jobs Syndrome

Differential Diagnosis

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Post-Infectious

- Viral, Mycoplasma
- TB
- Pertussis
- Nontuberculous mycobacteria & Nodular Bronchiectasis
- Aspergillus
- Severe/recurrent bacterial pneumonia
  - Post-op. nosocomial pneumonia
  - Associated with kyphoscoliosis

What do you know about Nodular/Bronchiectasis Form of MAC Lung Infection?
What about Rapid Growers?
NTM Lung Infection a/w Pre-existing Bronchiectasis or CF?

Fascinating Stuff???…

Post-Infectious

- Viral, Mycoplasma
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Allergic Bronchopulmonary Aspergillosis (ABPA)

1. Asthma
2. Skin test reactivity to *Aspergillus fumigatus*
3. Serum precipitins to *Aspergillus fumigatus*
4. IgE elevation (>1000 ng/ml or >500 IU/ml)
5. Specific IgE (IgG) antibodies to *Aspergillus fumigatus*
6. Proximal Bronchiectasis
7. Pulmonary Infiltrates (eg. fleeting, upper lobes, mucoid impaction)
8. Eosinophilia with pulmonary infiltrates

Note: Positive sputum culture not essential for diagnosis

Allergic Bronchopulmonary Mycosis (other Aspergillus spp, Candida, other fungi)

Adapted from Patterson & Greenberger

Post-Infectious

- Viral, Mycoplasma
- TB
- Pertussis
- NTM and nodular bronchiectasis
- Aspergillus
- Severe/recurrent bacterial pneumonia
  - Post-op. nosocomial pneumonia
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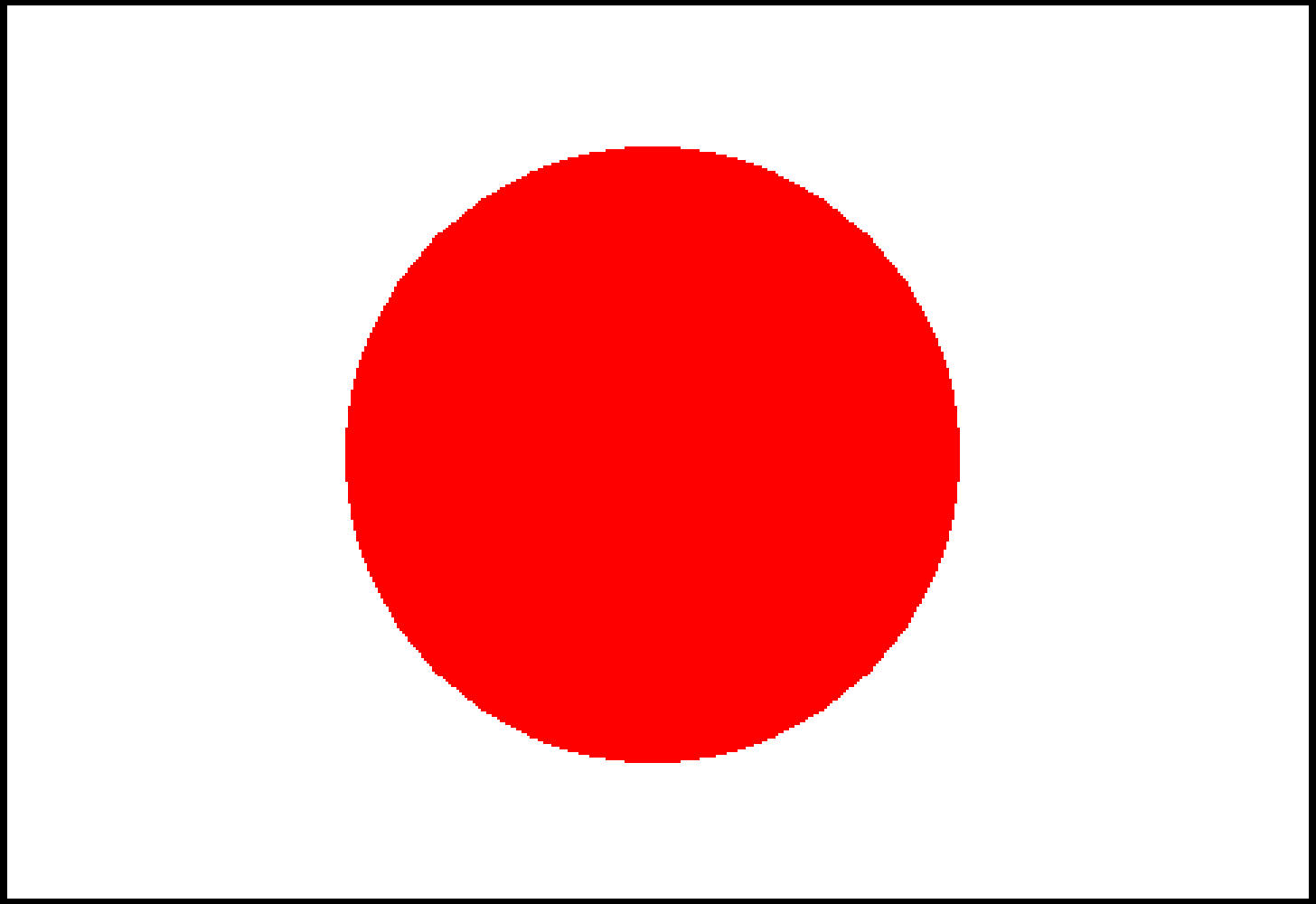
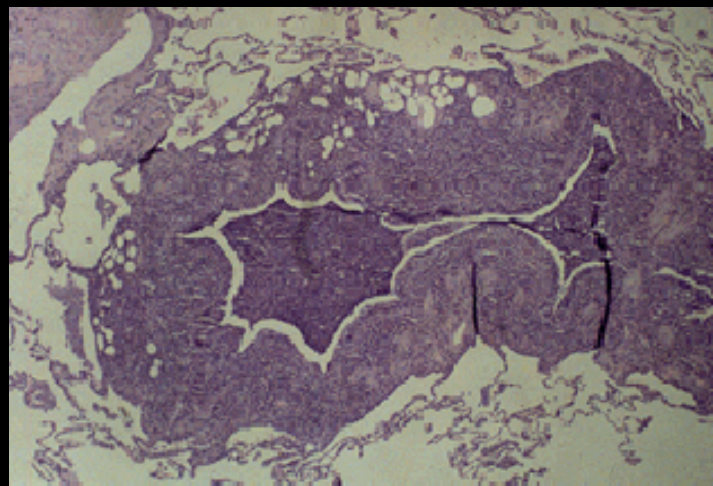
Differential Diagnosis

- Idiopathic
- Airway obstruction
- Dyskinetic Cilia Syndrome
- Immunodeficiency (Agammaglobulinemia)
- Post-infectious
- Diffuse Panbronchiolitis
- Inflammatory Disease
- α-1 Antitrypsin Syndrome
- Cystic Fibrosis

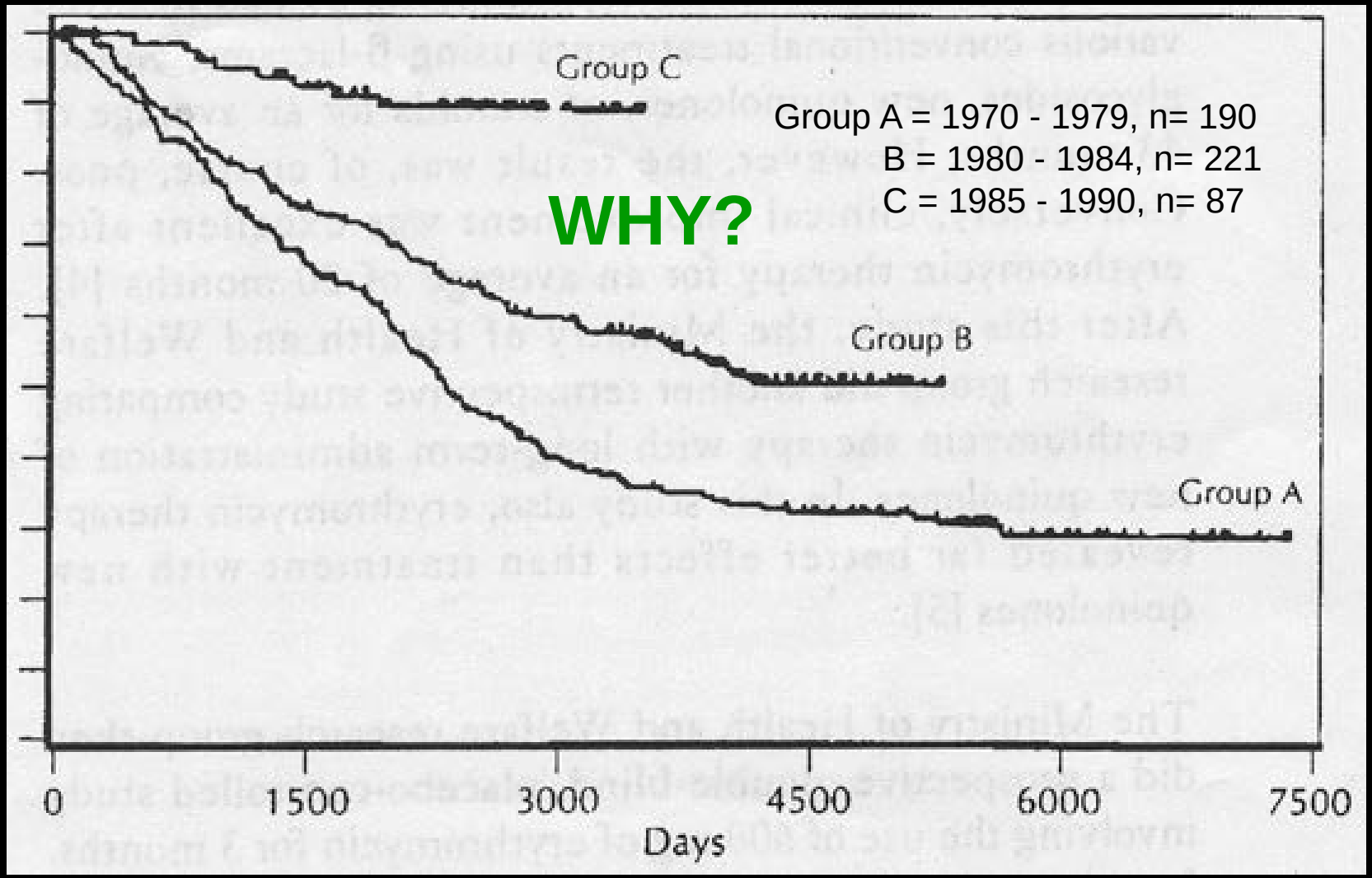


Diffuse Panbronchiolitis (DPB)

- Japanese, Korean, M:F 2:1, onset 20-80 y.o
- Clinical characteristics
  - Chronic sinusitis 75%, precedes lung disease (yrs or decades)
  - Productive cough, dyspnea, wheezing, weight loss, clubbing uncommon
  - Sputum: *H. influenzae*, *S. aureus*, *P. aeruginosa*
  - Acquisition of Psa→poor survival (8%@ 5 yr)
  - PFTs: obstructive, mixed obstructive/restrictive
  - Histopath: localized to resp bronch. transmural inflammation (lymphocytes, foamy macrophages)
  - **No:** exocrine dysfunction, ↑ sweat Cl, CFTR abnormality



Survival Curves According to Year of Diagnosis



Kudoh S. *Curr Opin Pulm Med* 1998

DPB and Macrolide Rx

- Serendipitous discovery 1982
- Standard: E-mycin 400-600 mg/day continuous
- No significant change in bacterial flora & serum levels (1 μg/ml) don't exceed MICs
- Clinical factors improved
  - Randomized blinded trial (Yamamoto et al, 1991)
    - 3 mos E-mycin vs. placebo
    - Improved DOE, sputum volume, CRP, PFTs, CXR)
  - PFTs
  - *P. aeruginosa* infected group improves also
  - Mortality rates decreased
- Other macrolides tested (clari-, roxi-, azithromycin)

In vitro data: Macrolides modulate inflammatory response & Inhibit *P. aeruginosa* virulence factors (eg, biofilm)

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Young's Syndrome

- Similar to CF
- Sinusitis, bronchiectasis, azoospermia
- Nl Sweat Cl, NPD
- Nl pancreas function
- No genetic link yet found
- Infertile middle age males
- Decreasingly found (toxic exposure births/prior era?)

Inflammatory Diseases & Bronchiectasis

- Sjogren’s Syndrome
- Rheumatoid Arthritis
- Ulcerative Colitis >> Crohn’s disease

Alpha-1-Antitrypsin Deficiency

- Radiographic:
  - Cystic bronchiectasis 10-20%
  - Emphysema co-exists or overshadowed
  - No other predisposing illness
- Uncertain clinical correlation (sputum production)
- No pathophysiologic association
  - All causes bronchiectasis: no increase in AAT alleles (Cuvilier et al: *Chest* 2000)

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How can one remember this list???

Differential Dx
(Mnemonic: IA_SPICE)

- **I**diopathic
- **A**irway Obstruction
- **S**jogren's & other Inflammatory (RA, IBD)
- **P**ost-Infectious (TB, non-tuberculosous mhycobacteria, Aspergillus, Pertussis, NP, virus)
- **I**mmunodeficiency (Ig, AIDS)
- **C**F & other genetic/congenital (Primary Ciliary Dyskinesia, Sequestration, α-1 Anti-trypsin)
- **E**soteric (Diffuse Panbronchiolitis, Yellow Nail Syn., Tracheobronchomegaly [Mounier-Kuhn], Cartilage deficiency [Williams-Campbell], Swyer James)

How do you evaluate a patient for bronchiectasis?

Evaluation for Bronchiectasis

- History
  - Poorly resolving/recurrent pneumonia
  - Purulent sputum (quantify)
  - H/O of difficult asthma management
  - Family history/GI problems/infertility
- Exam
  - nasal polyps
  - localized rales, wheezes, or rhonchi
  - clubbing

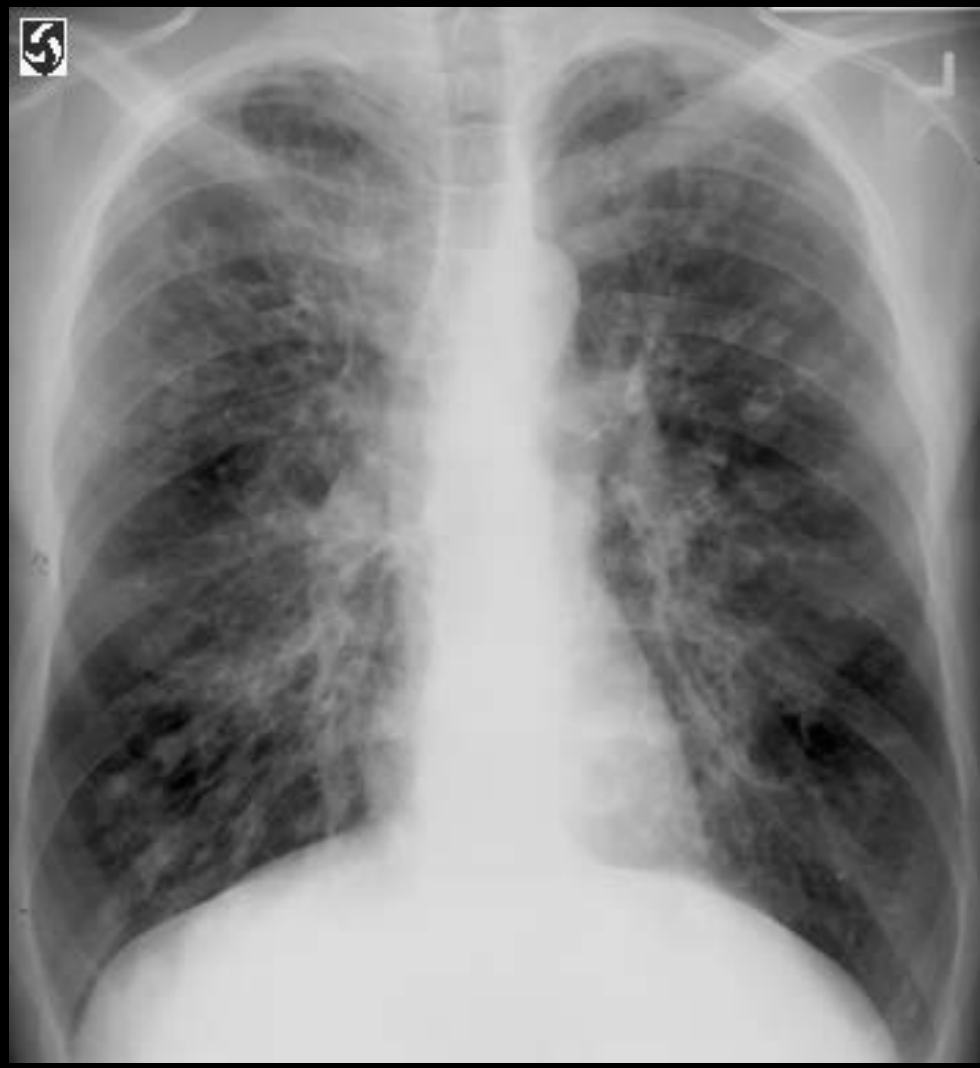
Evaluation for Bronchiectasis
Lab Data

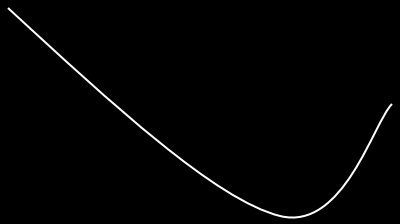
- Spirometry
- Sputum Gram Stain & Culture (quantitative)
  - *S. aureus*, *H. influenzae*
  - *P. aeruginosa* (mucoid?)
  - AFB smear/culture (AM x3 Mail Back)
- Consider:
  - Immunoglobulin electrophoresis & quantification of IgG subclasses; pre/post PVX/DT titers
  - Sweat Chloride, CF genetics (Ambry lab), NPD
  - RF, CCP, ANA, SSA, SSB antibodies
  - Exhaled nasal Nitric Oxide screen, then EM, genetics,
  - Asthma?, Eos?, Aspergillus skin test, IgE (ARUP ABPA panel)
  - Bronchoscopy for cultures (eg, elderly: NTM, other bacteria)
- Radiology Evaluation
  - Chest x-ray & High Resolution Chest CT
  - Sinus CT

What are the radiographic features of bronchiectasis?

Radiography

- Bonchograms (history of medicine)
- CXR and High Resolution CT
  - Signet Ring — Engagement Ring
  - Tram Tracks — Railroad tracks





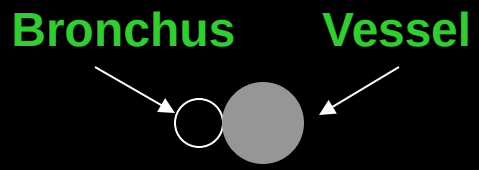
Normal Airway

Air in dilated airway

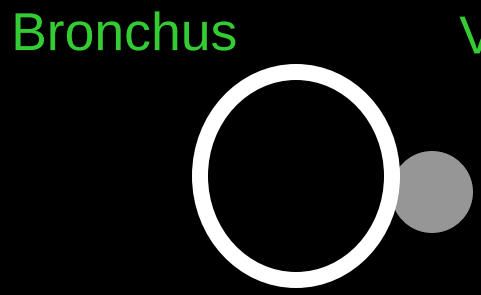
Swollen airway wall

CT Characteristics:

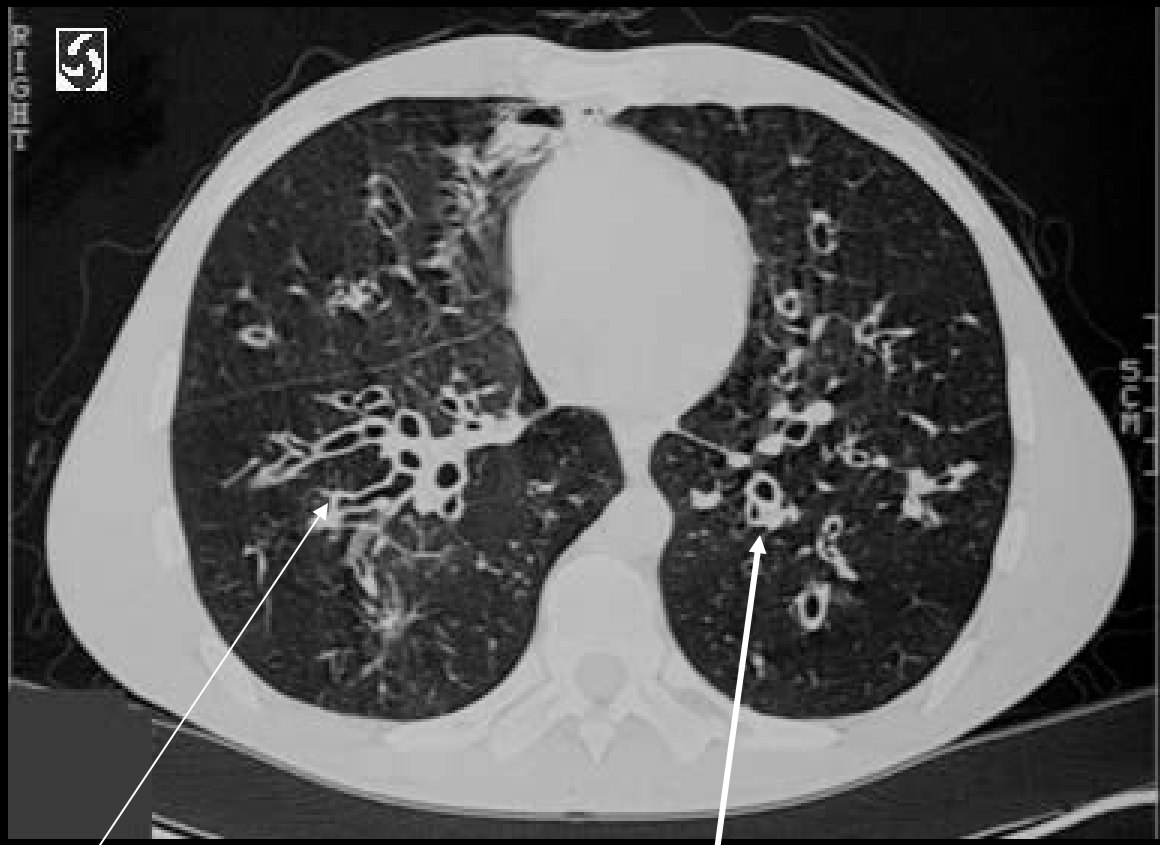
- High resolution= Thin sections (1.5-3 mm)
- Normal:



- Engagement (Signet) ring:



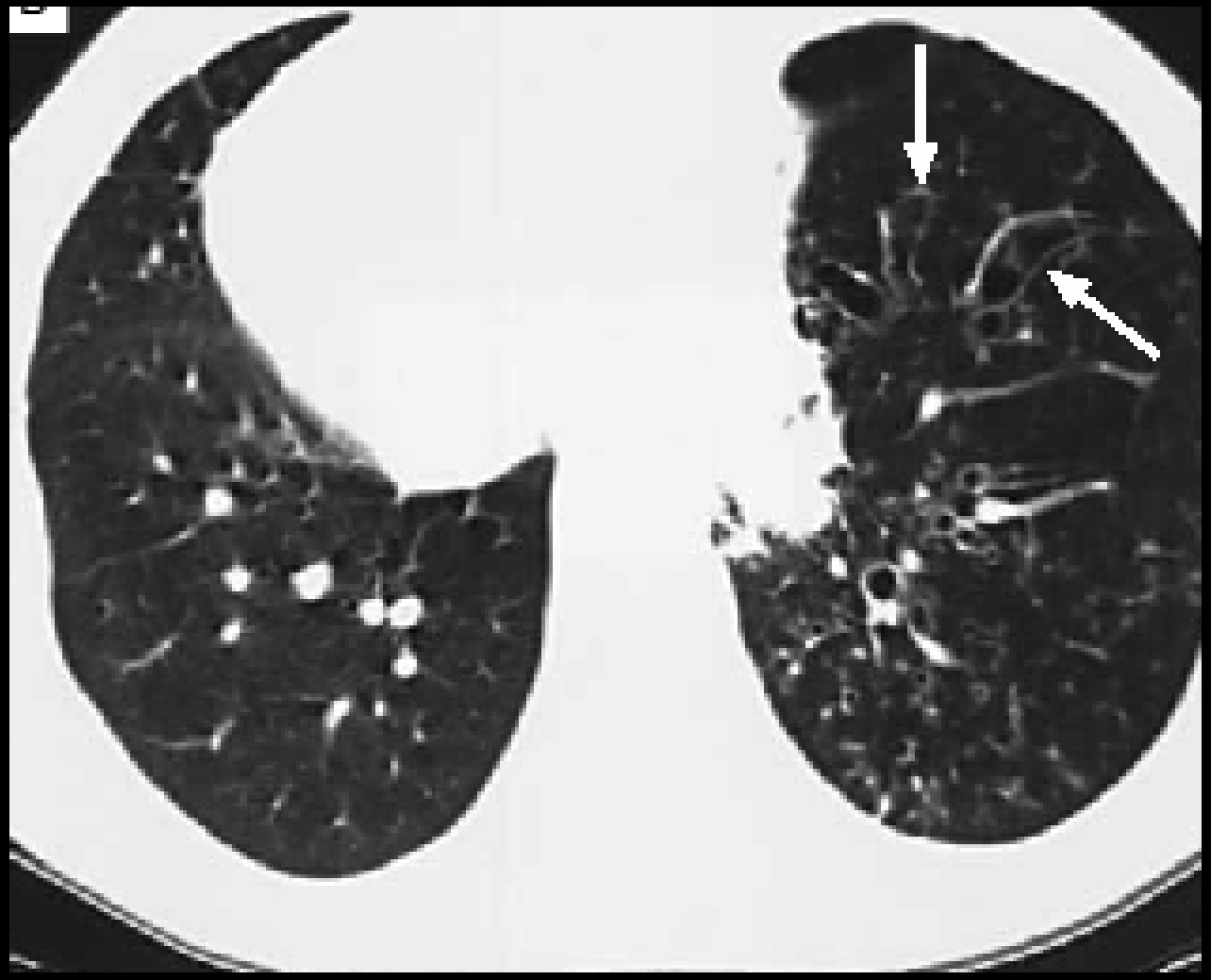
- Railroad tracks



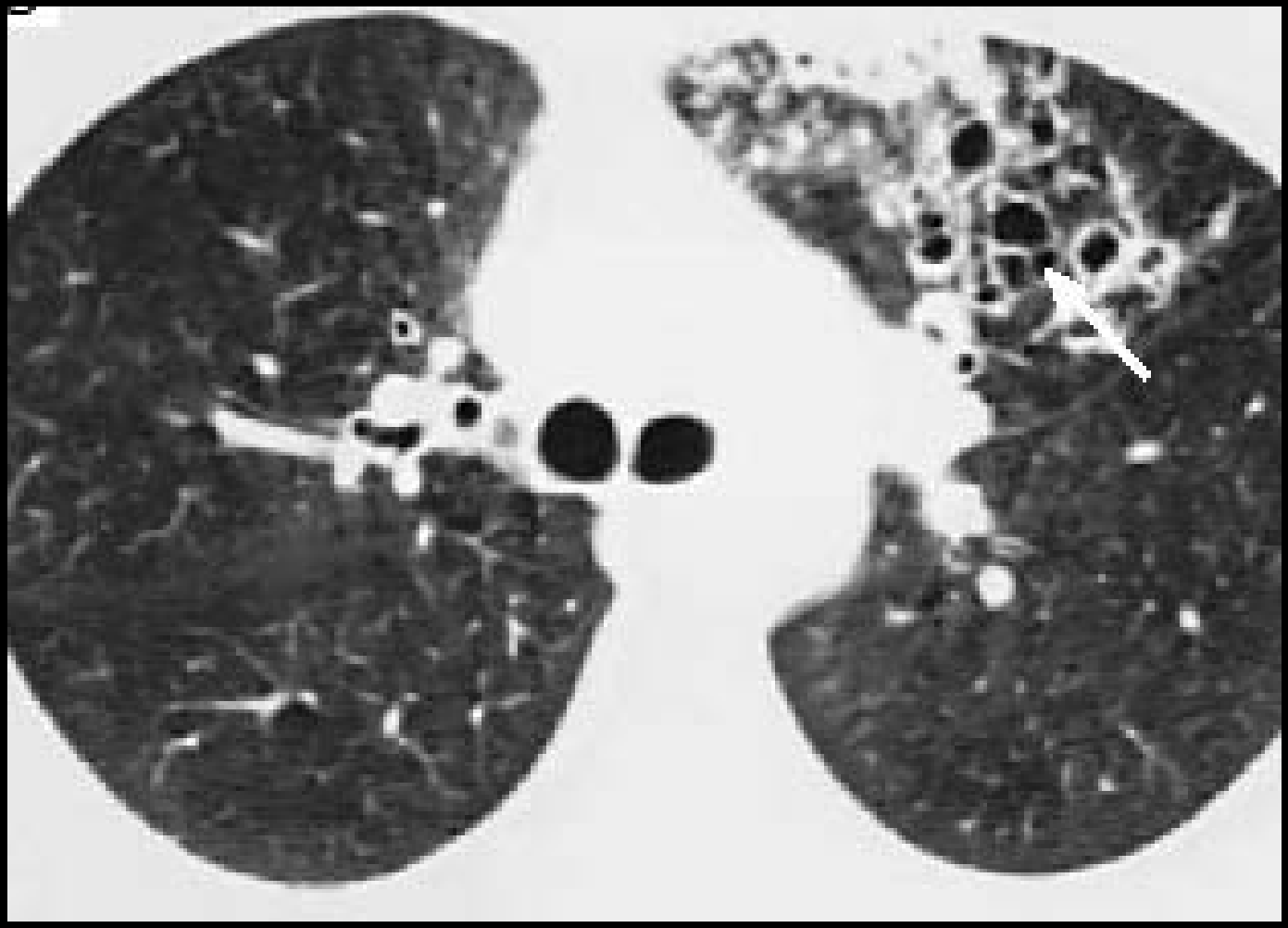
HRCT: Other Characteristics

- Lack of tapering bronchi
- Clusters = Grape-like appearance
- Enlarged bronchi can appear cystic vs. Blebs of emphysema (thinner walls)

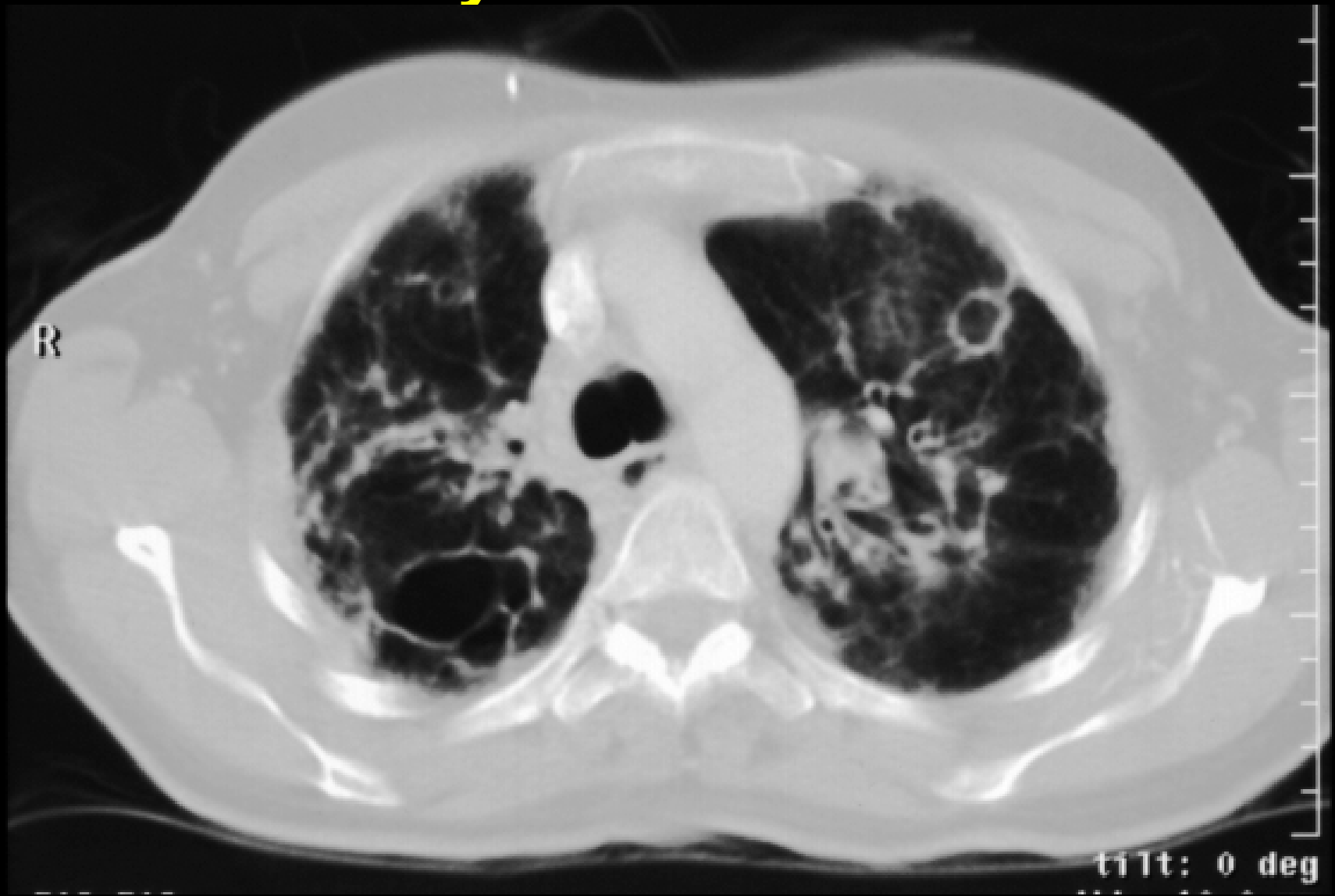
Lack of Tapering Bronchi



Grape-like Clusters



Cystic Bronchi

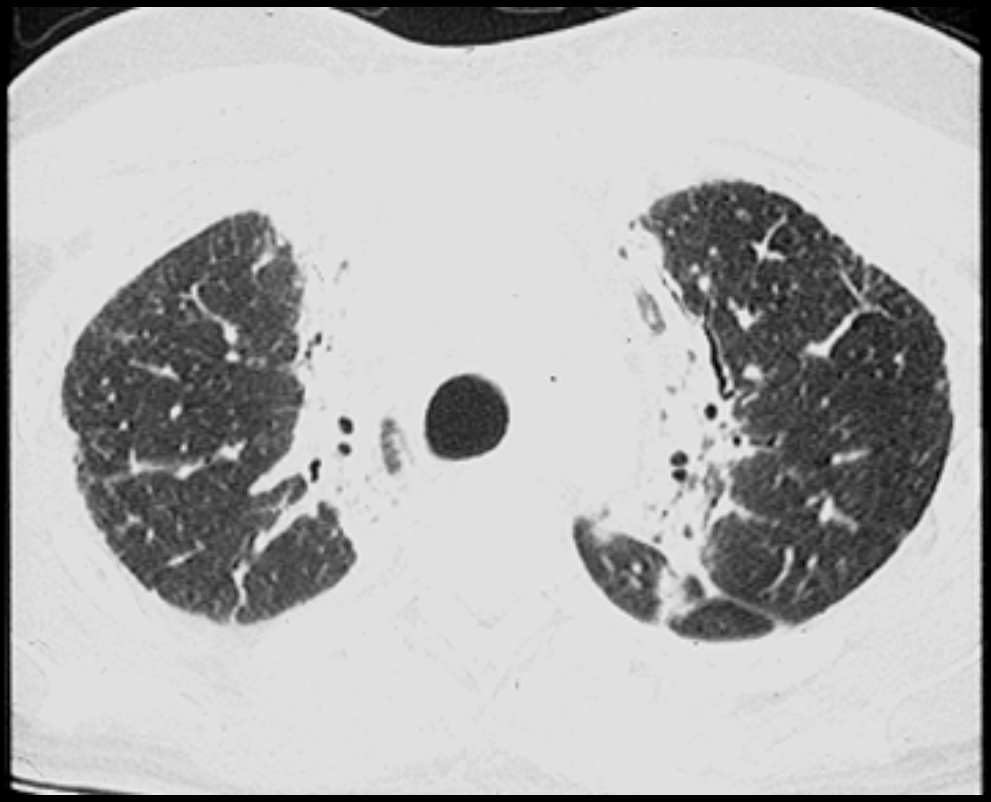


HRCT bronchiectasis Dx

- Central→ABPA
- Upper lobe → CF
- Lobar → Post-infectious; obstructive (eg, LN, FB)
- Correlation: # abnormal airways and severity

Traction Bronchiectasis

- Radiographic finding w/o clinical features of bronchiectasis
- Pulmonary Fibrosis
- Radiation injury



How do you identify acute exacerbation of bronchiectasis?

Sypmtoms of Acute Exacerbation of Bronchiectasis

- Change in sputum production
- Increased dyspnea
- Increased cough
- Increased wheezing
- Malaise, fatigue, lethargy, decreased exercise tolerance
- ± Fever (T>38)
- Changes in chest exam
- Reduced pulmonary function
- Radiographic changes (subtle vs. new infiltrate)

Adapted from Odonnell et al: *Chest* 1998

How do you treat bronchiectasis?

Rx Extrapolated from CF…

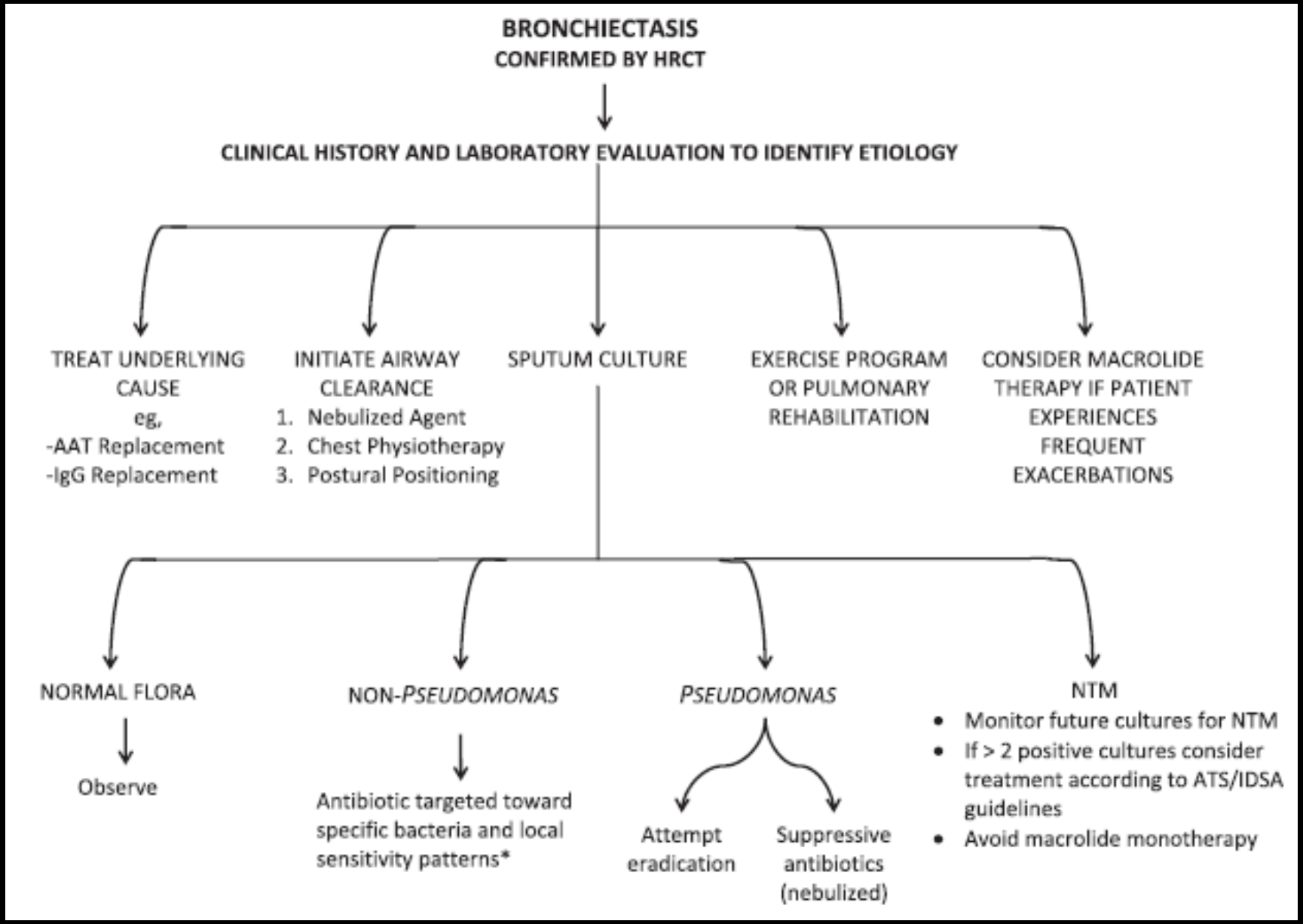
- Antibiotics generally effective for chronic Rx
  - Suppress bacteria burden: ↓ bacteria = ↓ evil cytokines
    - Nebulized tob, gent, colistin effective, small trials
    - Nebulized aztreonam (Cayston) not effective
  - Eradication Rx for *P aeruginosa* likely effective
  - Cycling antibiotics: no supportive data, but often done
- Exacerbation: IV antibiotics aimed at predom *spp* …little supportive data
- Pulmozyme trial…not good, maybe harmful
- Anti-inflammatory Rx
  - Avoid long term steriods except ABPA
  - ICS weak data; ICS/LABA no supportive data (ex. Asthma too)
  - Macrolide randomized control trial data supportive
    Azithro MWF (EMBRACE, BAT trials) & E-mycin 250 bid (BLISS)

Brodt et al. *Eur Resp J* 2014;44:382-93; Barker AF et al. *Lancet Resp Med* Aug 2014; O'Donnell AE et al *Che*st 1998
Wong C et al. *Lancet* 2012;380:660-67; Altenburg J et al. *JAMA* 2013;309:1251-1259; Serisier JD et al. *JAMA* 2013;309:1260-67

Bronchiectasis Treatment Overview

- Manage/alter underlying cause
- Antibiotics
  - Acute exacerbation, parenteral abx based on culture & susceptibilities
  - Preventive strategies-uncertain benefit
    - Cycling Abx (no real data to support)
    - Inhaled Abx (tobramycin [gent], colistin, not aztreonam)
- 7% saline neb bid
- Bronchodilators (widely used…no good data)
- Chest physiotherapy (various modalities) & Aerobic exercise
- Pulmozyme…No
- ICS (minimal if any benefit)
- Macrolides (must r/o NTM)
- Nutrition
- Surgery

Comprehensive Overview



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