Bronchiolitis and Non-Cystic Fibrosis Bronchiectasis

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Disclosure of Conflicts of Interest

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Bronchiolitis: Definition

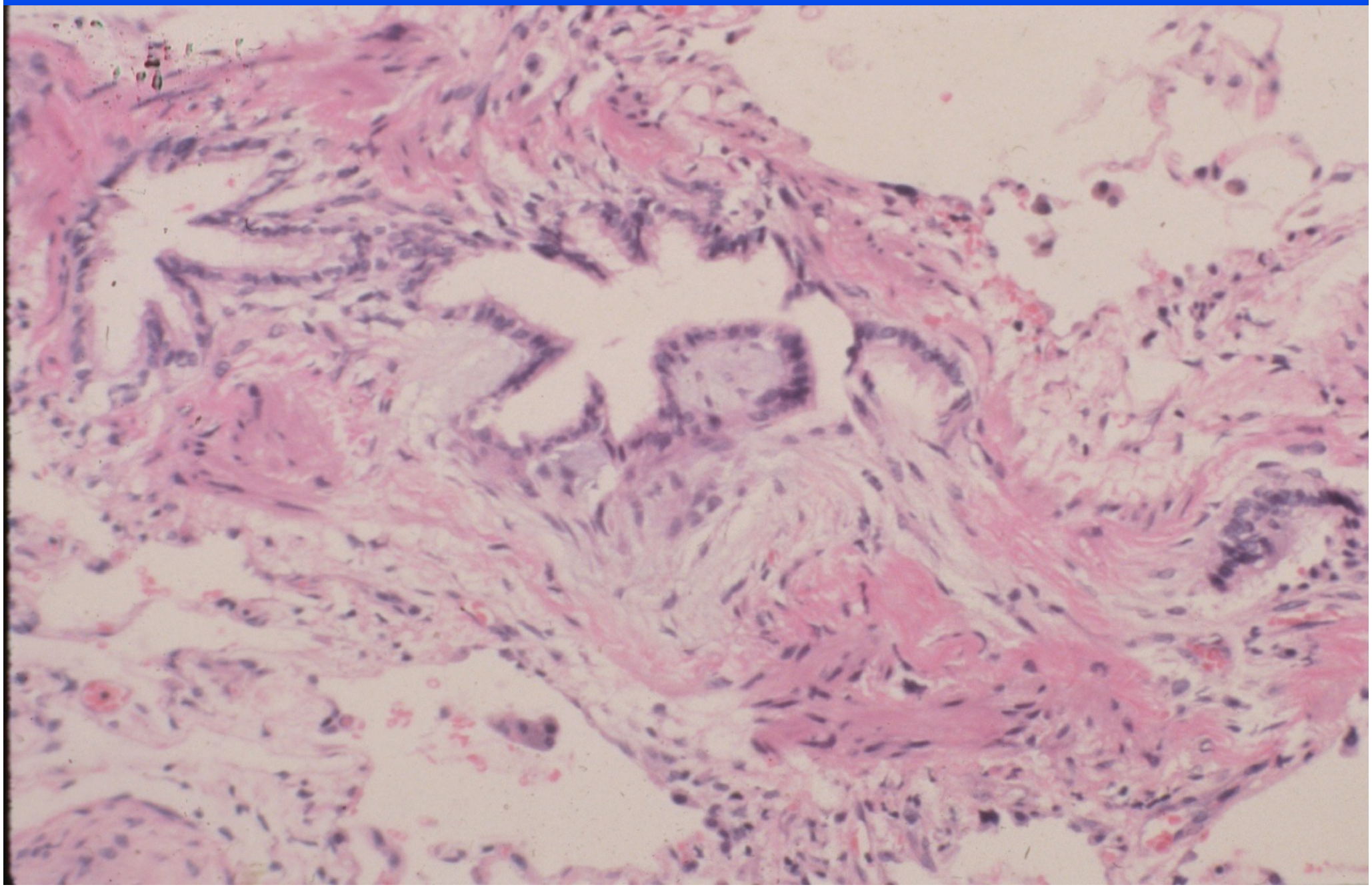
Acute or chronic cellular inflammation or fibrosis of the bronchiolar walls.

Acute: Viral (e.g., RSV), mycoplasma
Aspiration

Chronic: Follicular bronchiolitis (C-V diseases)
Mineral dust bronchiolitis
Cigarette smoke respiratory bronchiolitis
Diffuse panbronchiolitis (Japan)
Bronchiolitis obliterans

Bronchiolitis Obliterans: Etiologies

- Toxic fume inhalation (e.g., nitrogen oxides in silo filler's lung disease; diacetyl in workers exposed to artificial butter flavoring for popcorn; vaping)
- Post-infectious (e.g., viral, mycoplasma)
- Immune-mediated
  - Rheumatoid arthritis (± penicillamine)
  - Ulcerative colitis
  - Paraneoplastic pemphigus/other autoimmune blistering diseases
  - S/P transplantation (e.g., lung, allogeneic bone marrow)



Bronchiolitis Obliterans: Clinical Features

- Hx: dyspnea, non-productive cough
- P.E.: inspiratory crackles; mid-inspiratory squeak; expiratory wheezes
- CXR: hyperinflation; ± small patchy parenchymal infiltrates

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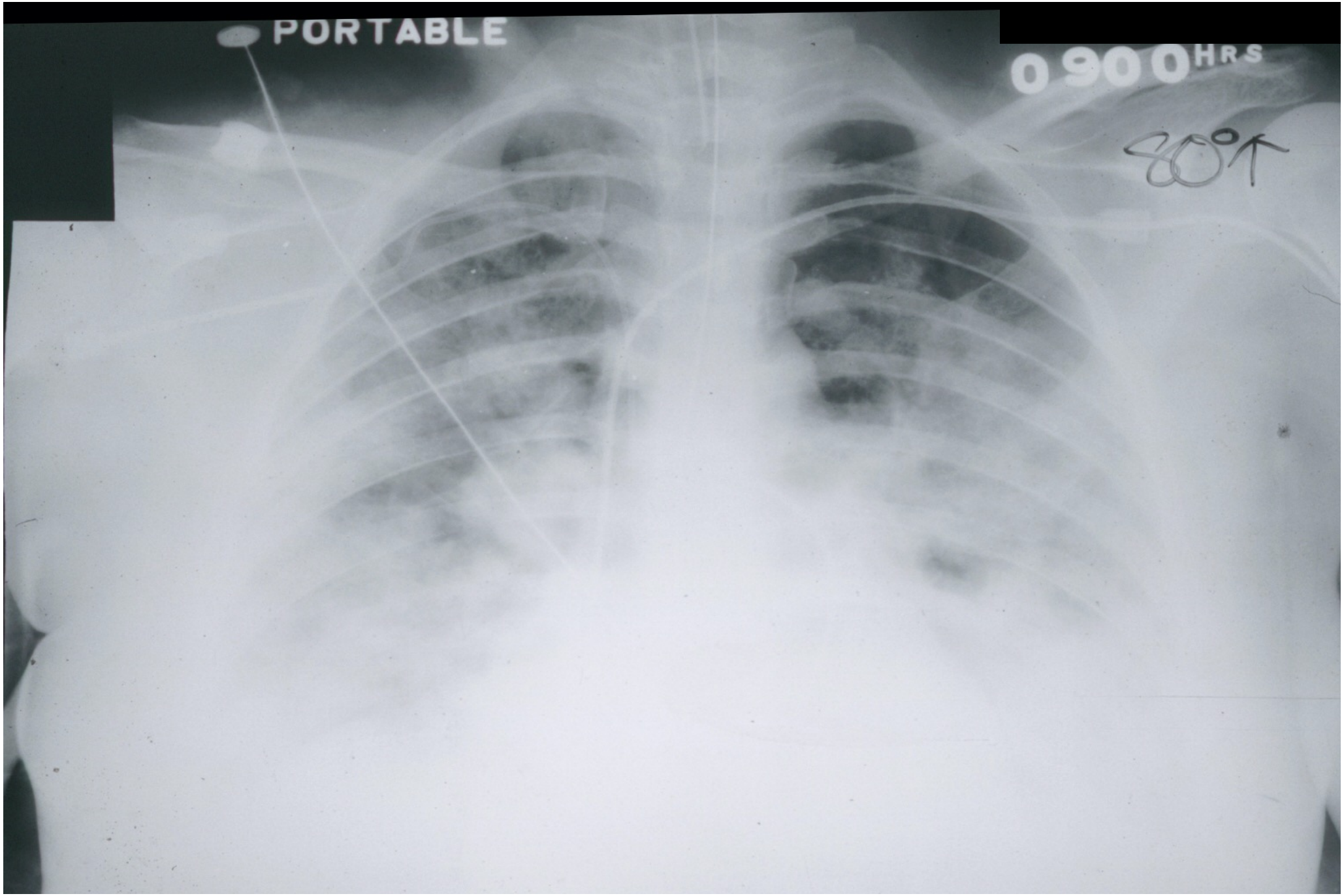
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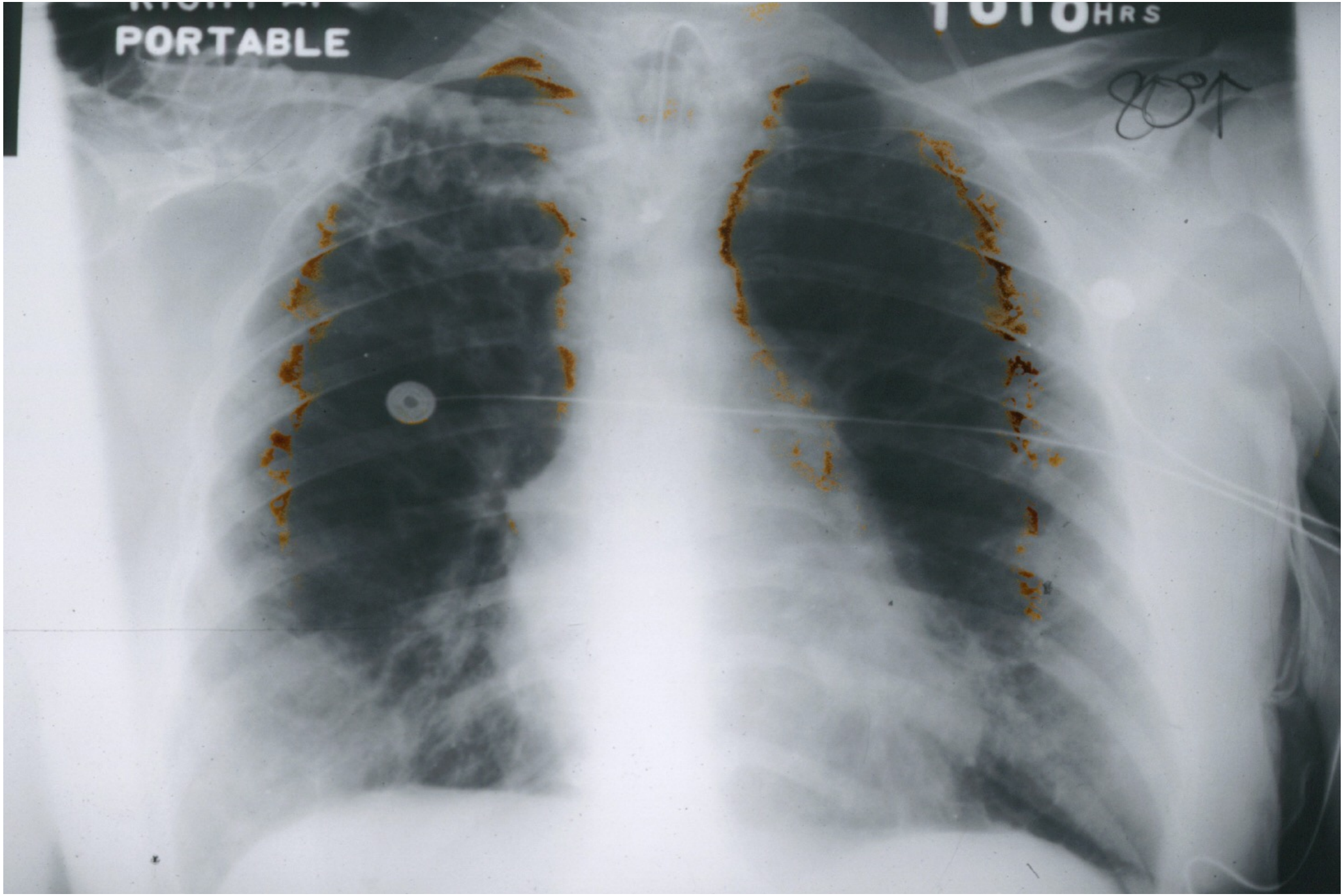
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Radiographic Findings on CT Imaging

- Centrilobular micronodules (often tree-in-bud distribution)
- Bronchiolectasis
- Bronchial wall thickening
- Mosaic attenuation

Winningham PJ, et al., *RadioGraphics* 2017; 37:777–94.

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Tree-in-Bud

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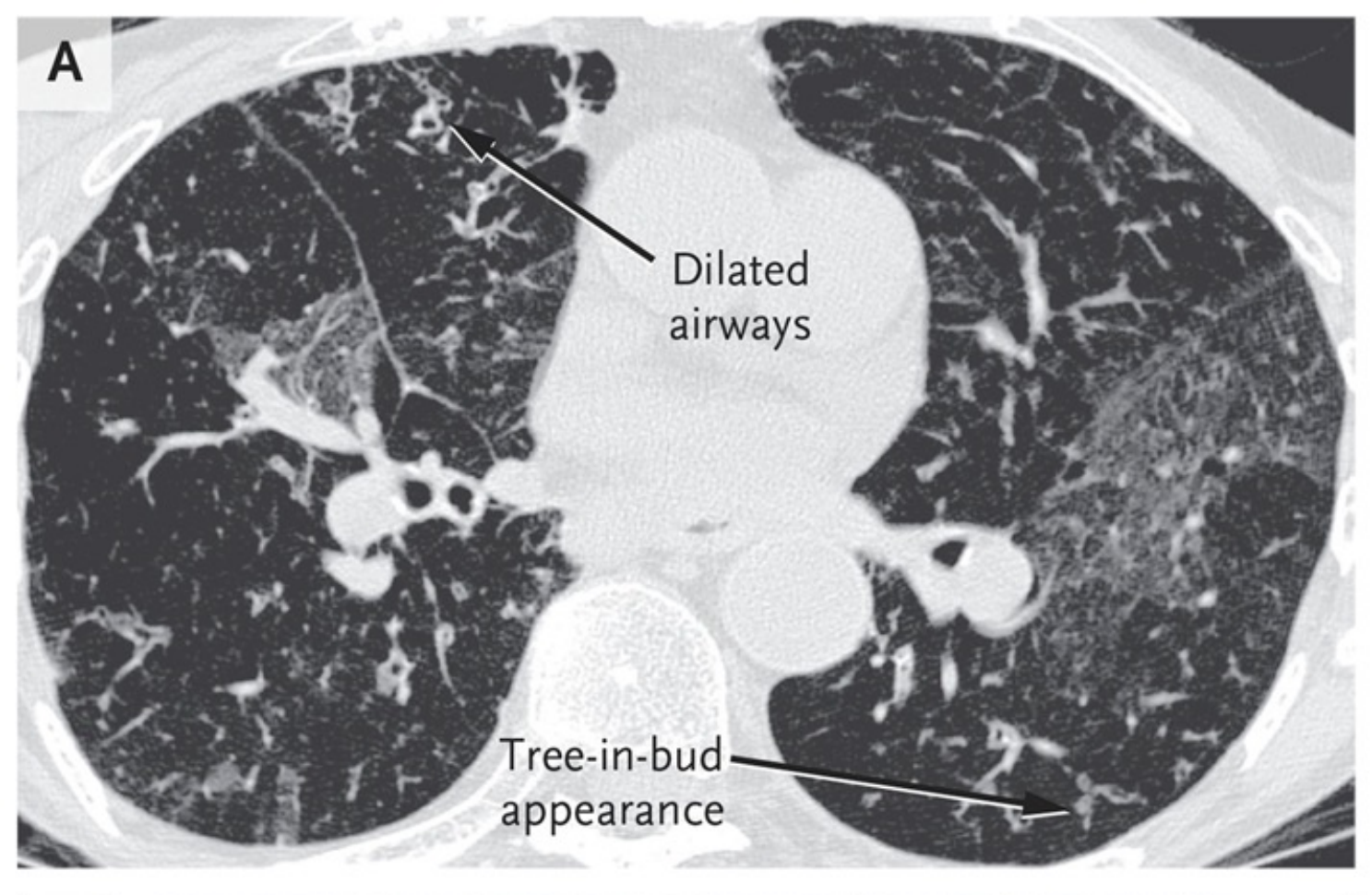
CT Scan in Bronchiolitis



Barker AF et al.
N Engl J Med
2014;370:1820-28.

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Bronchiolitis Obliterans: Diagnosis

- Typically, a clinical diagnosis (without biopsy).
- Based on airflow obstruction in the appropriate setting and in the absence of alternative etiologies (such as asthma or COPD).
- Lung biopsy infrequently employed (exception = s/p lung transplantation).

Bronchiolitis Obliterans: Treatment

- Corticosteroids (systemic/inhaled); bronchodilators; O_2 as needed.
- (Post-transplant: extracorporeal photopheresis; etanercept; montelukast)
- Experimental: anti-IL-1R; inhaled liposomal cyclosporine A

Bronchiolitis obliterans is often refractory to therapy.

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Bronchiolitis: Key Points

- Consider bronchiolitis obliterans in patients with unexplained chronic airflow obstruction (not asthma or COPD).
- Imaging varies considerably and is often non-specific.
- Etiologies include infection, toxic exposures, and underlying immune disorders.
- Treatment generally involves corticosteroids and other immunosuppression.

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Bronchiectasis: Definition

Irreversible airway wall damage and dilatation (-ectasis) of the bronchi, usually associated with chronic airway infection

Clinical Presentations: Historical Features

- Chronic productive cough
- Recurrent hemoptysis
- Recurrent focal pneumonia
- Associations: sinusitis, infertility

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Clinical Presentations: Physical Examination

- Focal inspiratory crackles
- Low-pitched wheezing (“rhonchi”)
- Clubbing

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Clinical Presentations: Laboratory Data

- Purulent sputum
- Typical bacterial isolates, especially *Pseudomonas*
- Abnormal chest radiograph / CT scan
- Pulmonary function:
  - variable: obstruction, restriction, mixed obstructive and restrictive patterns

Chest Radiography

- Focal non-homogeneous infiltrate with orientation of markings in direction of bronchovascular bundles
- Volume loss
- “Tram lines”
- Other: cyst formation; mucoid impaction

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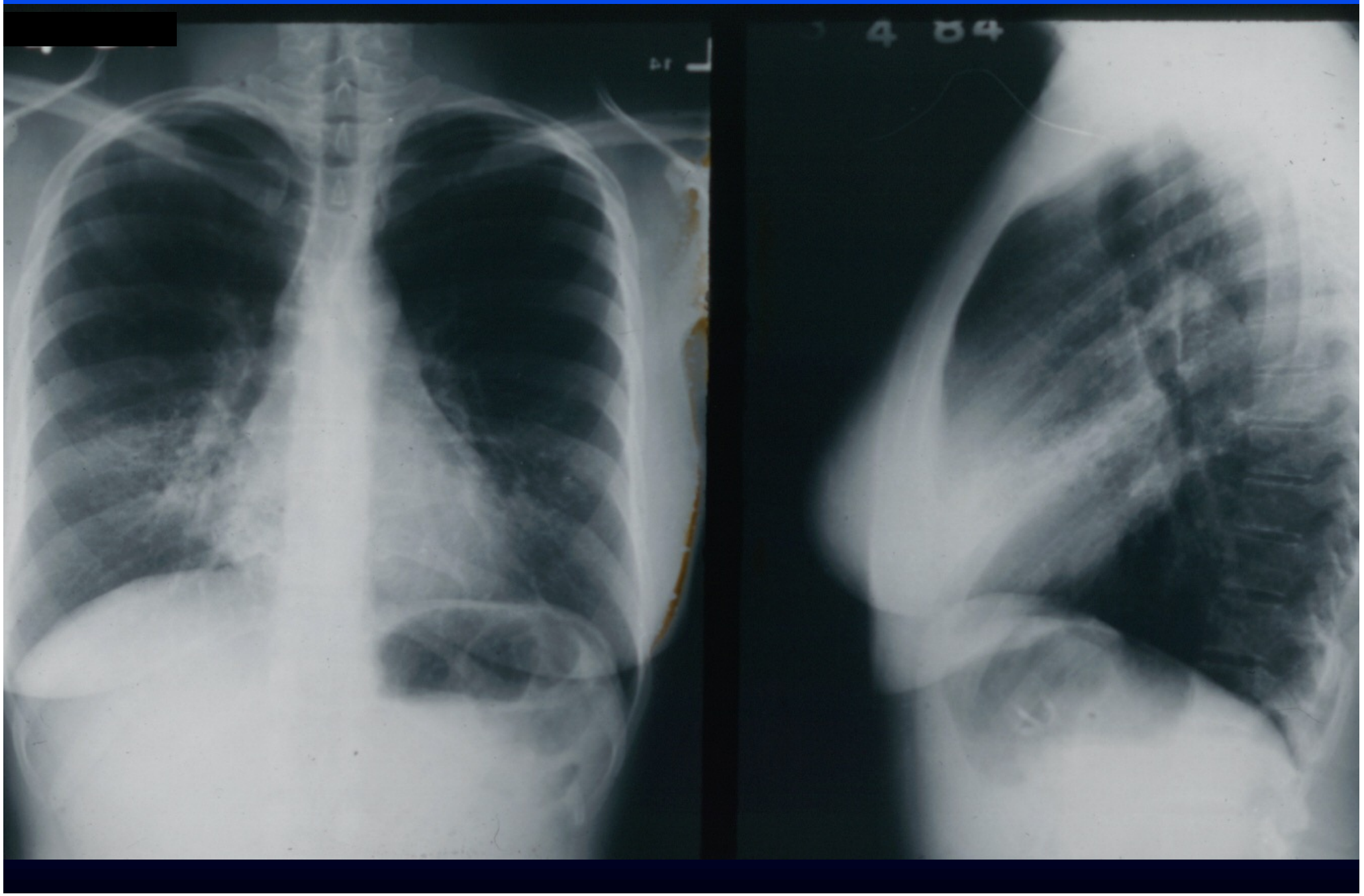

Primary Ciliary Dyskinesia (Immotile Cilia Syndrome) (Kartagener's Syndrome)

- Bronchiectasis
- Sinusitis
- Situs inversus (50%)
- Immotile sperm

Classic description: ultrastructural abnormality of cilia (e.g., absence of dynein arms)

Diagnostic Techniques in Primary Ciliary Dyskinesia

- Transmission electron microscopy
- Videomicroscopy
- Immunofluorescence labeling
- Nasal exhaled nitric oxide
- Genetic analysis

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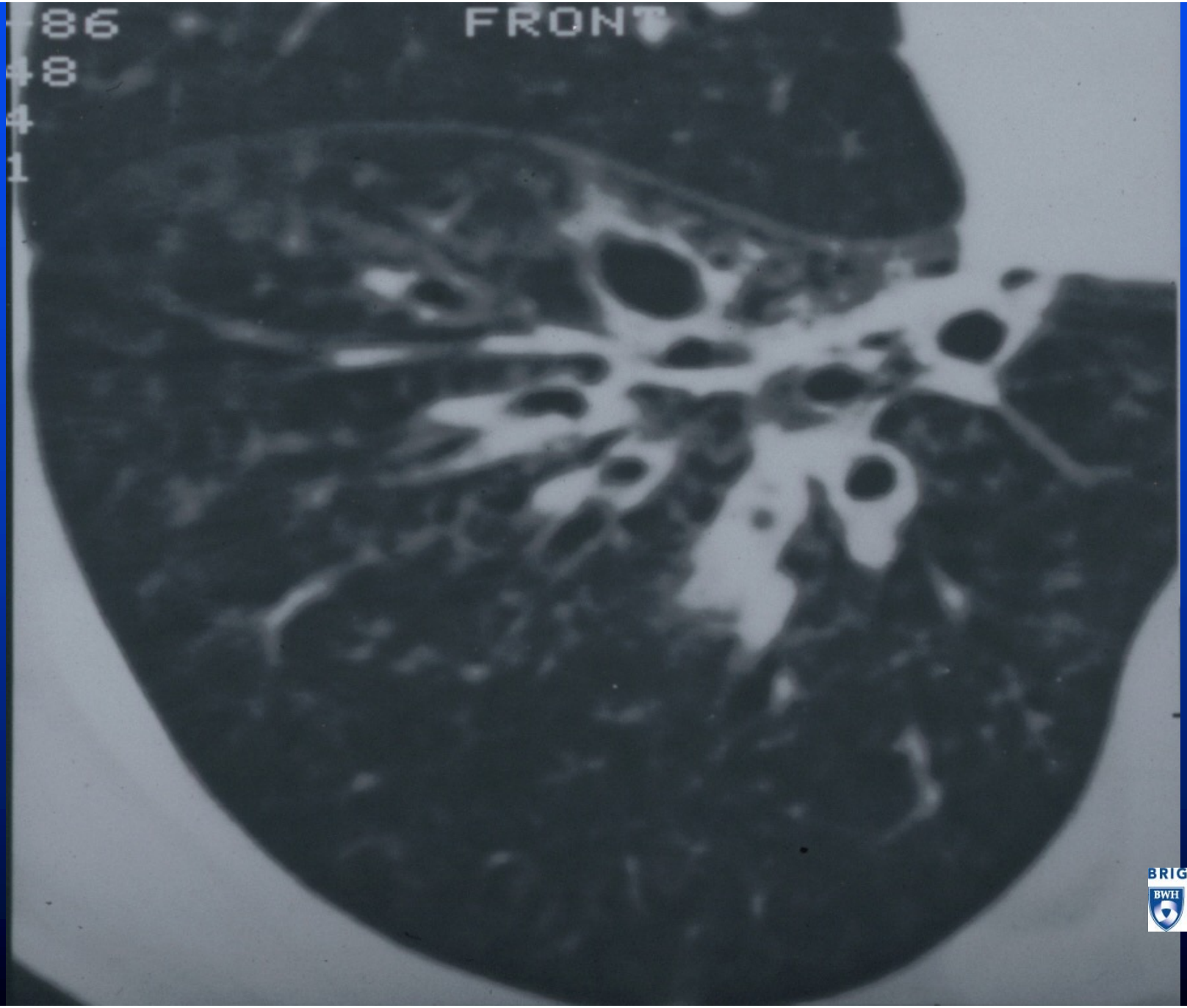
Chest CT Appearance

- Lack of bronchial tapering
- Bronchial dilatation (internal diameter > 1.5 x diameter of accompany vessel)
- Visualization of bronchi in lung periphery (within 1 cm of pleura)
- Often with bronchial wall thickening



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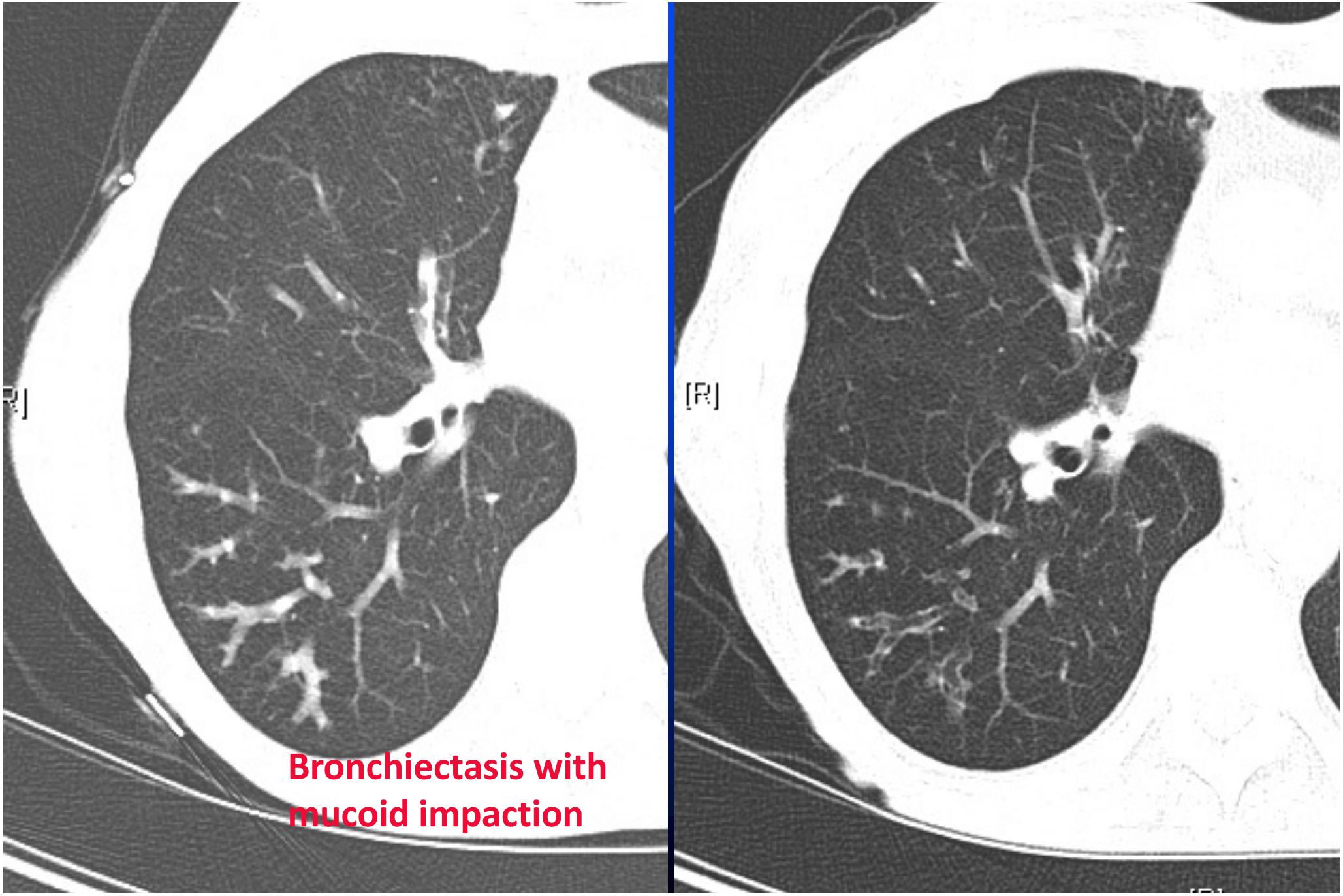
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Bronchiectasis with
mucoid impaction

Etiologies

- **Localized**
  - Post-pneumonic
  - Distal to bronchial obstruction
- **Widespread**
  - Cystic fibrosis
  - Primary ciliary dyskinesia
  - Hypogammaglobulinemia

Etiologies:
Special Syndromes

- Congenital anatomic defects
  - Williams-Campbell syndrome (bronchial cartilage deficiency)
  - Yellow nails syndrome (lymphatic hypoplasia)
  - Young's syndrome (bronchiectasis and azospermia)
  - Munier-Kuhn syndrome (tracheobronchomegaly: trachea >30 mm; right mainstem >20 mm, left mainstem >18 mm)
- Alpha-1 antitrypsin deficiency

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Etiologies:
Other Observations

- AIDS
- Ulcerative colitis
- Rheumatoid arthritis
- Allergic bronchopulmonary aspergillosis
- Non-tuberculous mycobacterial infection

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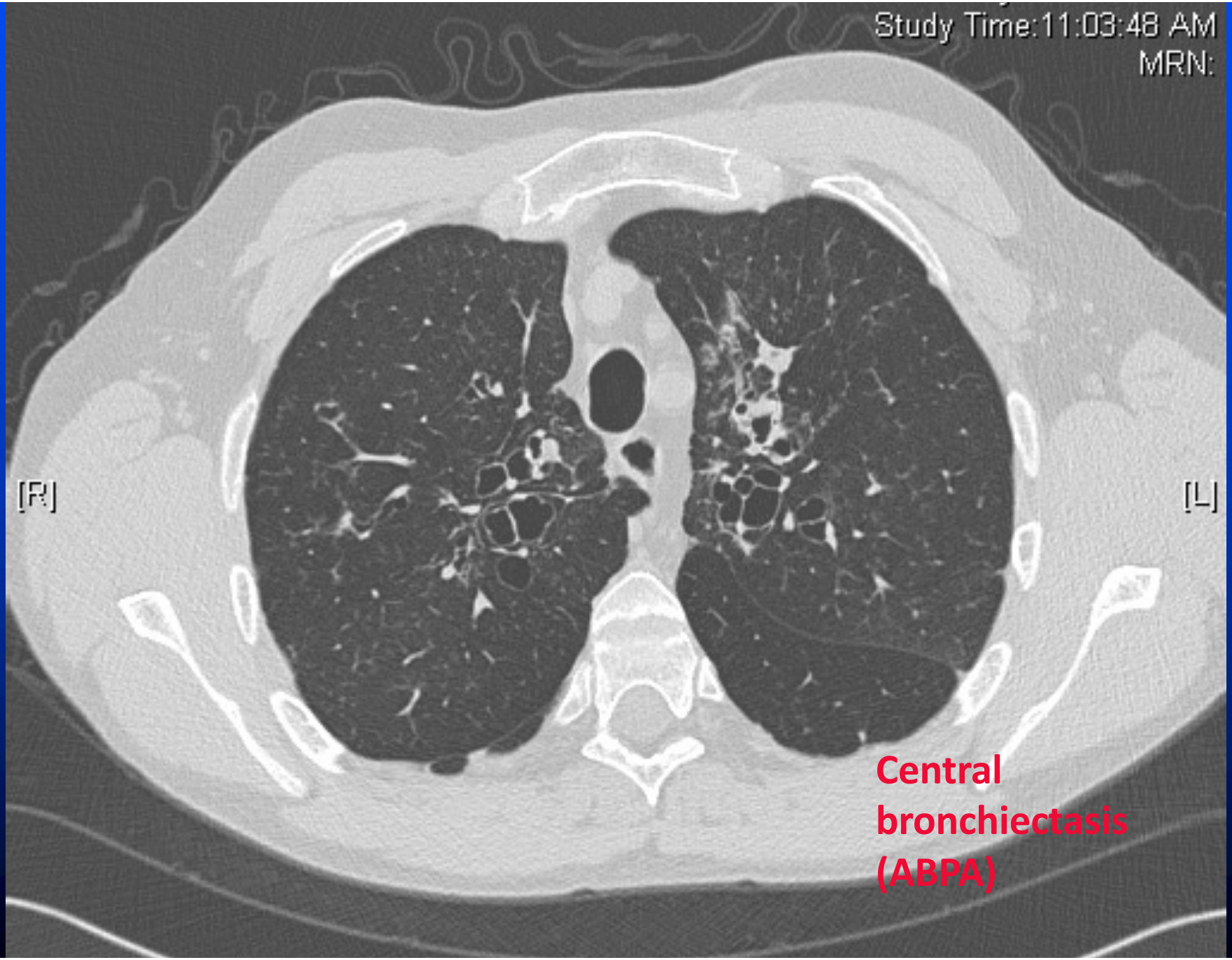
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Central bronchiectasis (ABPA)

Diagnosis of ABPA

- Asthma or cystic fibrosis
- ↑IgE (>1000 ng/ml)
- Aspergillus-specific IgE (or skin test)
- Aspergillus-specific IgG
- Peripheral blood eosinophilia
- Aspergillus isolated from sputum

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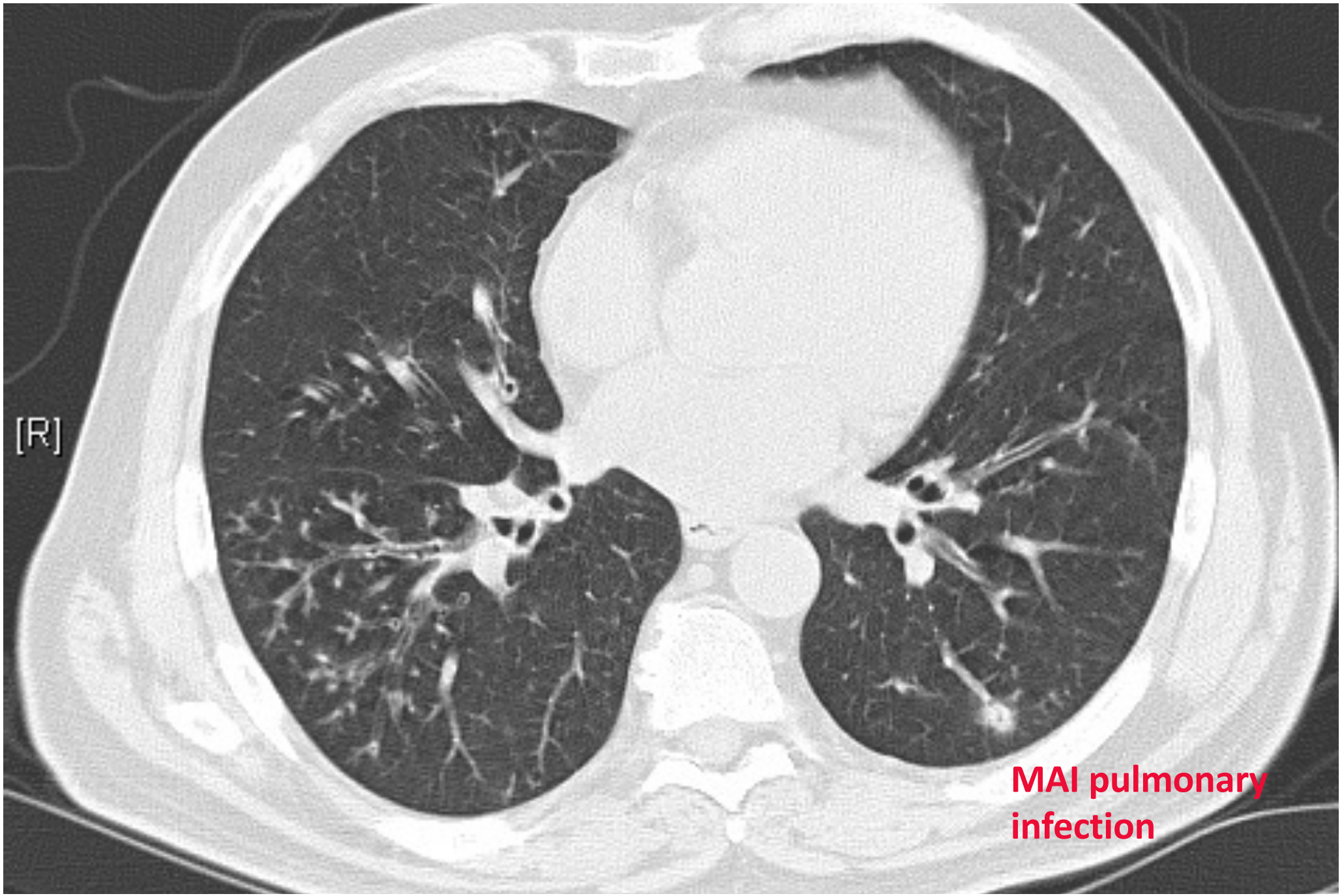
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MAI pulmonary infection

Tree-in-Bud: Differential Diagnosis

- Infections
  - Mycobacterial
  - Fungal (aspergillus)
  - Viral (CMV)
  - Bacterial *(H. influenzae*)
- Bronchiolitis obliterans
- Aspiration pneumonitis
- Sarcoidosis

Therefore, Dx of NTM = history, imaging, and sputum isolates X2 or bronchoscopic X1

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Patient Evaluation

- Chest X-ray/CT scan
- Pulmonary function/gas exchange
- Sputum culture
- Immunoglobulin analysis
- Other: sweat chloride; CF genotyping; semen analysis; nasal or bronchial biopsy; alpha-1 antitrypsin level; IgE and aspergillus-specific IgE
- Bronchoscopy (new, local disease)

Treatment

- Predisposing condition
  - Gammaglobulin replacement
  - Systemic corticosteroids/antifungals in ABPA
  - (?) α_1-antitrypsin replacement in AAT deficiency
  - CFTR modulators

Therapeutic Options

- Antibiotics
- Mucolytics
- Clearance of secretions
- Bronchodilators
- Anti-inflammatory Rx:
  macrolide antibiotics; ? corticosteroids

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Antibiotic Therapy

- Intermittent antibiotics
- Chronic, rotating antibiotics
- Inhaled antibiotics
- Intravenous antibiotics (for refractory infections or resistant pathogens)

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Randomized Trials of Suppressive Antibiotics

520 patients with cystic fibrosis randomized to inhaled tobramycin 300 mg BID vs. placebo every other month for 6 months.

Outcomes: Lung function (FEV_1)

Density of *Ps. aeruginosa* in sputum

Need for hospitalization/intravenous antibiotics

Ramsey BW, et al., *N Engl J Med* 1999; 340:23-30

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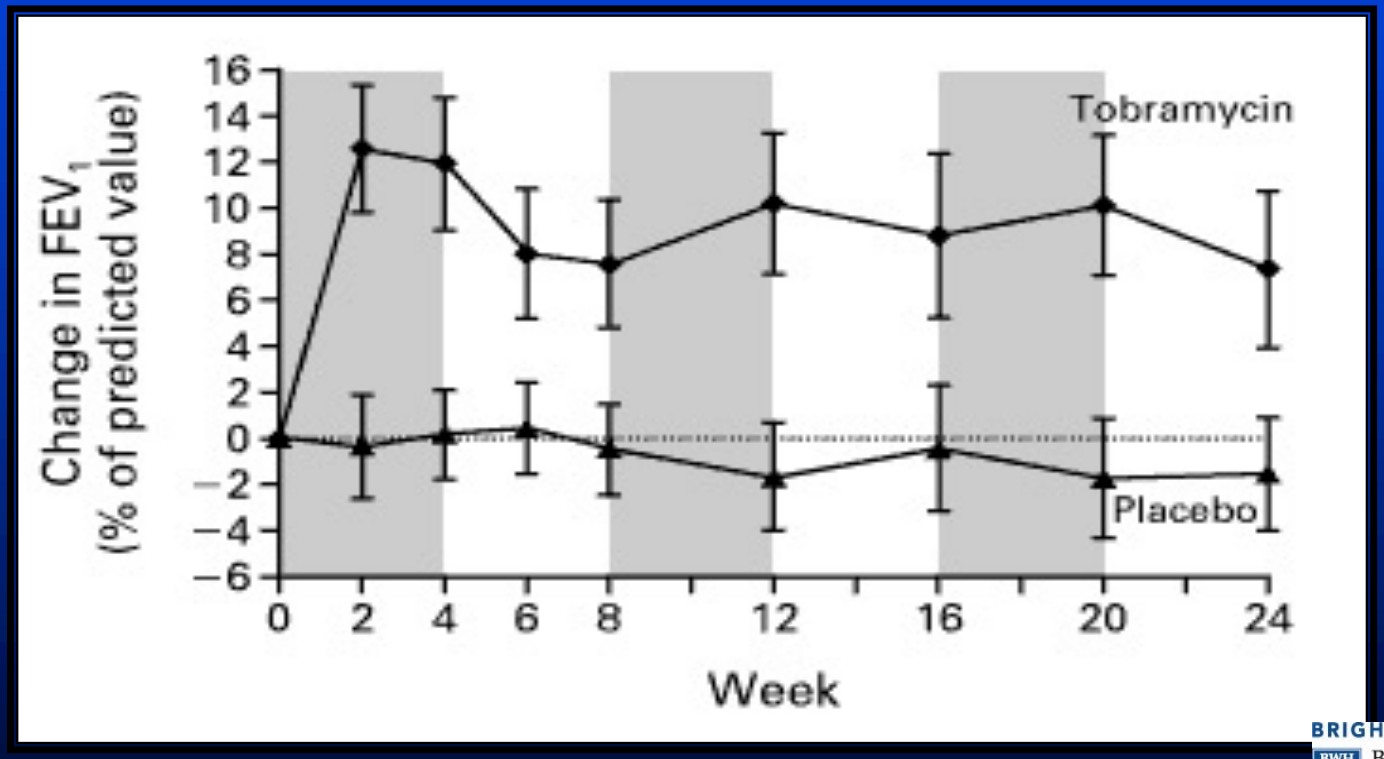
Randomized Trial of Nebulized Tobramycin in CF

Change in Lung Function



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Ramsey BW, et al., *N Engl J Med* 1999; 340:23-30

Randomized Trial of Nebulized Tobramycin in CF

	Tobramycin	Placebo	
% of pts. hospitalized at least once	37	45	(26%) ↓
% of pts. receiving i.v. antibiotics at least once	39	52	(36%) ↓

Ramsey BW, et al., *N Engl J Med* 1999; 340:23-30

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Other Inhaled Antibiotics

- Tobramycin Podhaler
- Colymycin
- Aztreonam

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Therapeutic Options

- Mucolytics
  - Iodides
  - Guaifenesin
  - Acetylcysteine (Mucomyst®)
  - rh-DNase (Pulmozyme®)
  - Hyperosmolar aerosols (3%-7% NaCl)

Mucolytics:
rh-DNase in "Idiopathic" Bronchiectasis

349 patients recruited from 23 centers, randomly assigned to rh-DNase or placebo twice daily for 6 months.

Outcomes: Number of exacerbations
Lung function (FEV_1)
Quality of life

O'Donnell AE, et al., *Chest* 1998; 113:1329-34

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Mucolytics:
rh-DNase in "Idiopathic" Bronchiectasis

	rh-DNase	Placebo	
No. of exacerbations/pt.	0.66	0.56	
% change in FEV_1	-3.6	-1.7	$p \leq 0.05$
Antibiotic use (days)	56.9	44.1	$p \leq 0.05$
No. of hospitalizations/pt.	0.39	0.21	

O'Donnell AE, et al., *Chest* 1998; 113:1329-34

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Mucolytics:
rh-DNase in "Idiopathic" Bronchiectasis

Observations from this large-scale, prospective study of bronchiectasis (placebo group):

- Average annualized decline in FEV_1 = 53 ml/yr.
- No. of pulmonary exacerbations ≈ 1 every 8 mos.

O'Donnell AE, et al., *Chest* 1998; 113:1329-34

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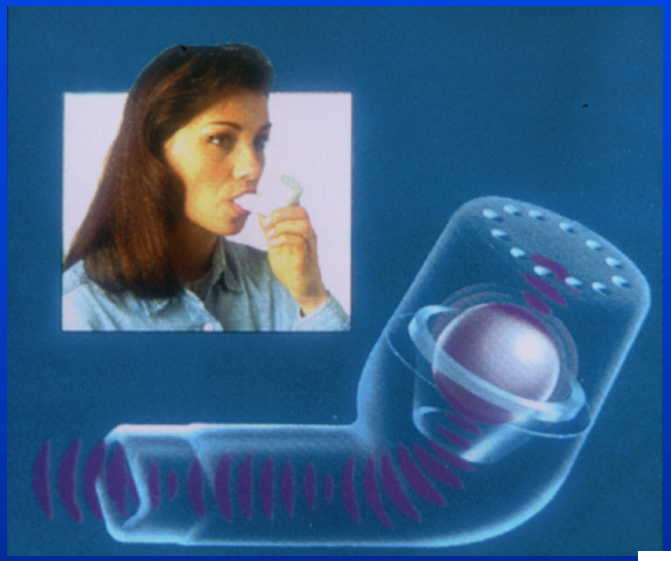
Therapeutic Options

- Clearance of secretions
  - Chest physiotherapy and postural drainage
  - PEP bronchial vibrating device
  - External electric vibrator
  - Pneumatic vest
  - Exercise

Cough-Assist Devices



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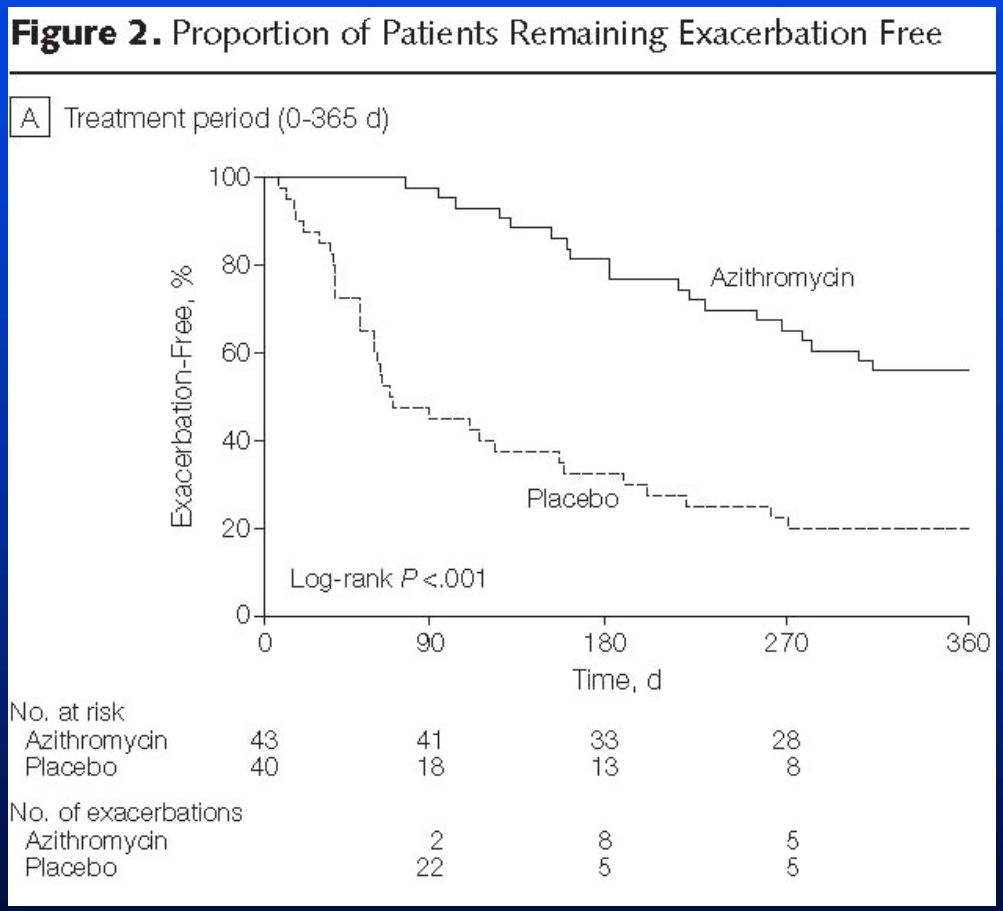
Anti-Inflammatory Therapy

- Inhaled corticosteroids
- Macrolide antibiotics
  - Two randomized, placebo-controlled trials of azithromycin found fewer exacerbations over 1 year of observation compared with placebo.

Altenburg J, et al. *JAMA* 2013; 309:1251-9.
Wong C, et al. *Lancet* 2012; 380:660-7.

BAT Trial

Figure 2. Proportion of Patients Remaining Exacerbation Free



No. at risk				
Azithromycin	43	41	33	28
Placebo	40	18	13	8
No. of exacerbations				
Azithromycin		2	8	5
Placebo		22	5	5

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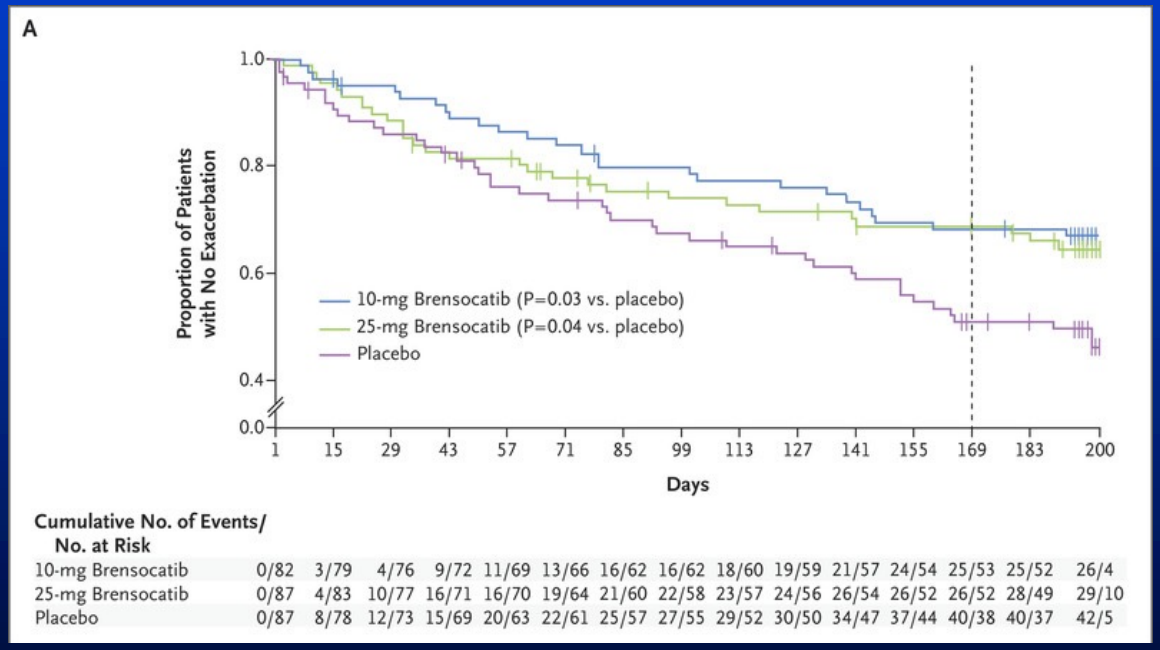
Altenburg J, et al. *JAMA* 2013; 309:1251-9.

Bensocatib

Oral reversible dipeptidyl peptidase 1 inhibitor, leading to decreased neutrophil elastase activity.



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

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Chalmers JD, et al. *NEJM* 2020; 383:2127-37.

Complications

- Hemoptysis, including massive hemoptysis
- Infection with resistant organisms
- Hypercapnic respiratory failure
- Other: weight loss, mycetoma

Bronchiectasis: Key Points

- Bronchiectasis is a structural abn'ty of the airways that predisposes to chronic airway infection.
- Symptoms may be intermittent or daily and include productive cough and periodic hemoptysis.
- Sputum culture is important in guiding treatment, which focuses on antibiotic Rx and airway clearance.
- Chronic suppressive antibiotics are effective but pose risk for emergence of resistant organisms.

Multiple-Choice Question:
48-year-old cigarette smoker with productive cough.

Multiple-Choice Question: Close-Up of left base

Question:

Which of the following blood tests is most likely to be helpful in assessment of this patient?

A. Cystic fibrosis gene mutation
B. ANCA
C. Alpha-1 antitrypsin level
D. VEGF-D
E. Serum immunoglobulin E

References

- Brodt AM, et al. Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis. *Eur Resp J* 2014; 44:382-93.
- McShane PJ, et al. Non-cystic fibrosis bronchiectasis. *AJRCCM* 2013; 188;647-56.
- Pulverino E, et al., European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Resp J* 2017; 50: 1700629.
- Barker AF, et al. Obliterative bronchiolitis. *NEJM* 2014; 370:1820-28.
- Ryu JH, et al. Bronchiolar disorders. *AJRCCM* 2003; 168:1277-92.