Bronchiolitis and Non-Cystic Fibrosis Bronchiectasis

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Disclosure of Conflicts of Interest

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Bronchiolitis: Definition

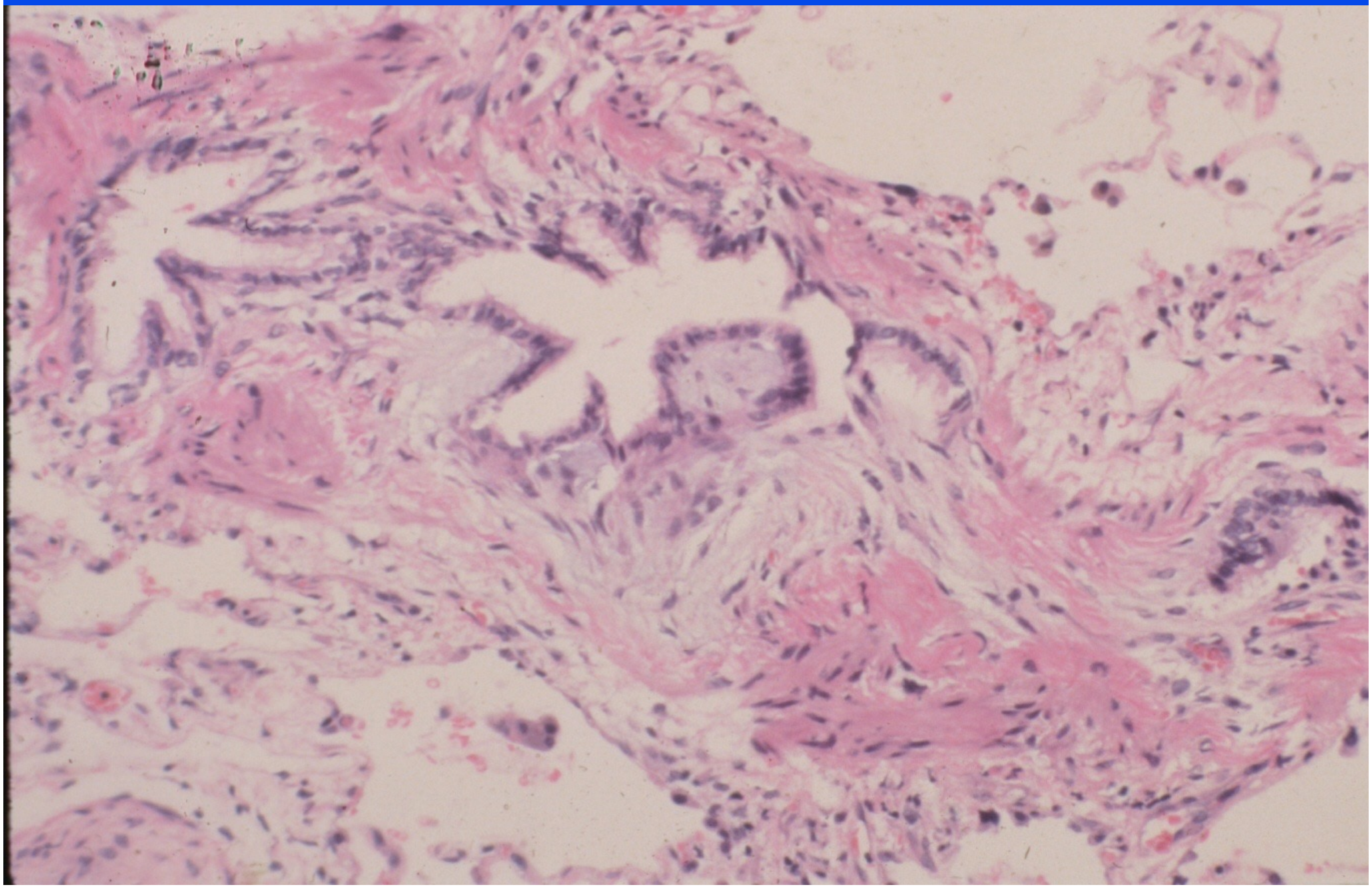
Acute or chronic cellular inflammation or fibrosis of the bronchiolar walls.

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; $\pm$ small patchy parenchymal infiltrates

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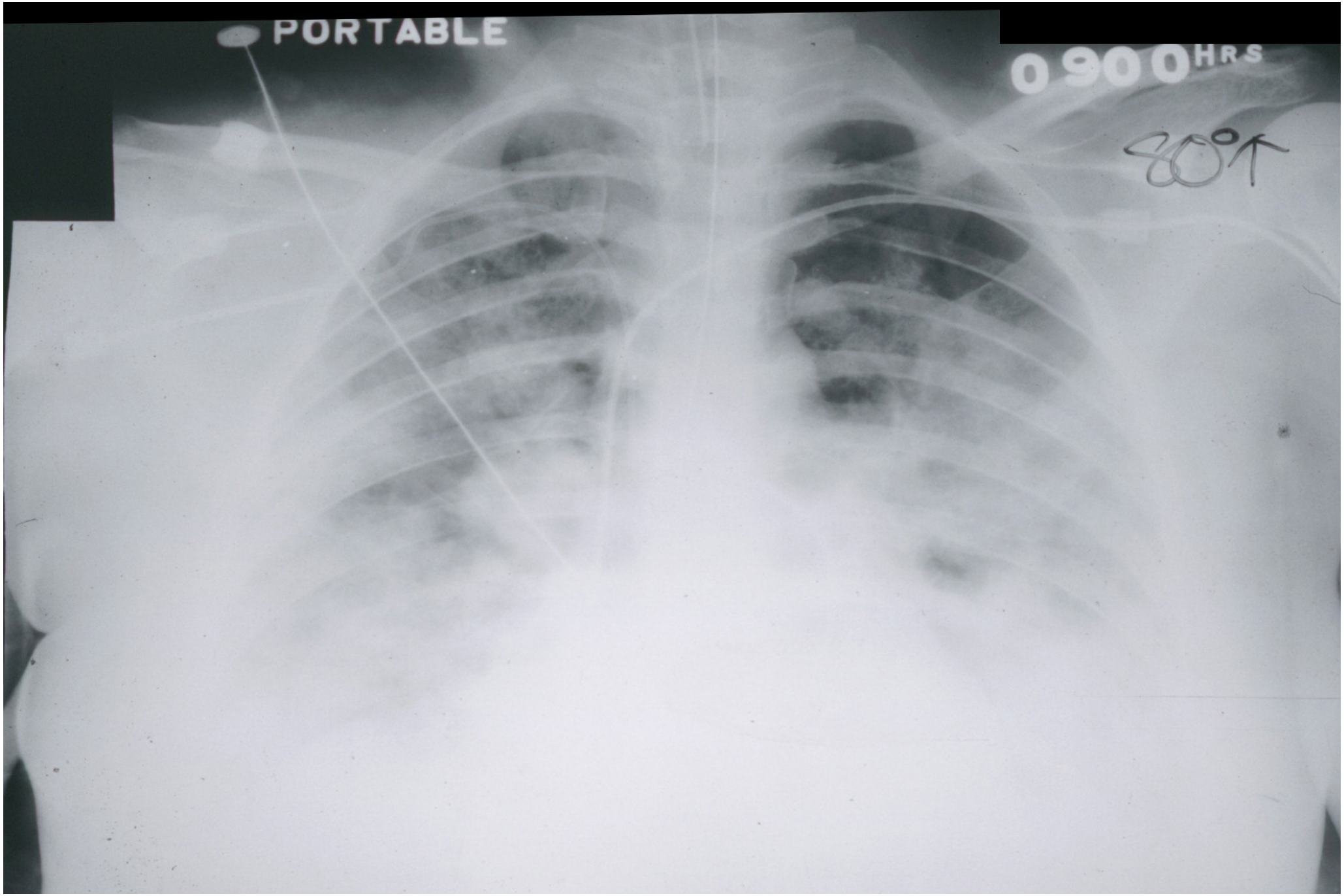
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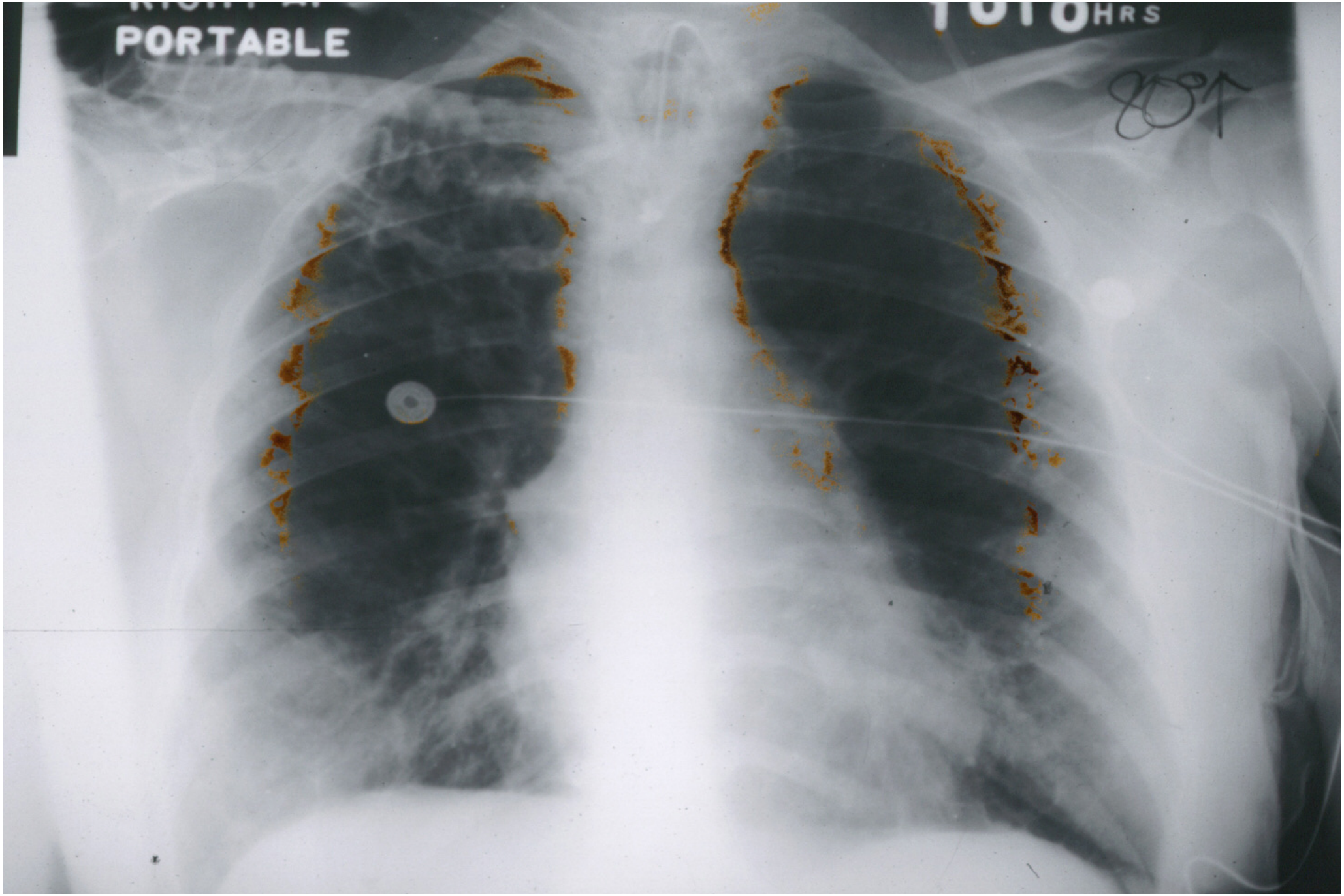
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Radiographic Findings on CT Imaging

- 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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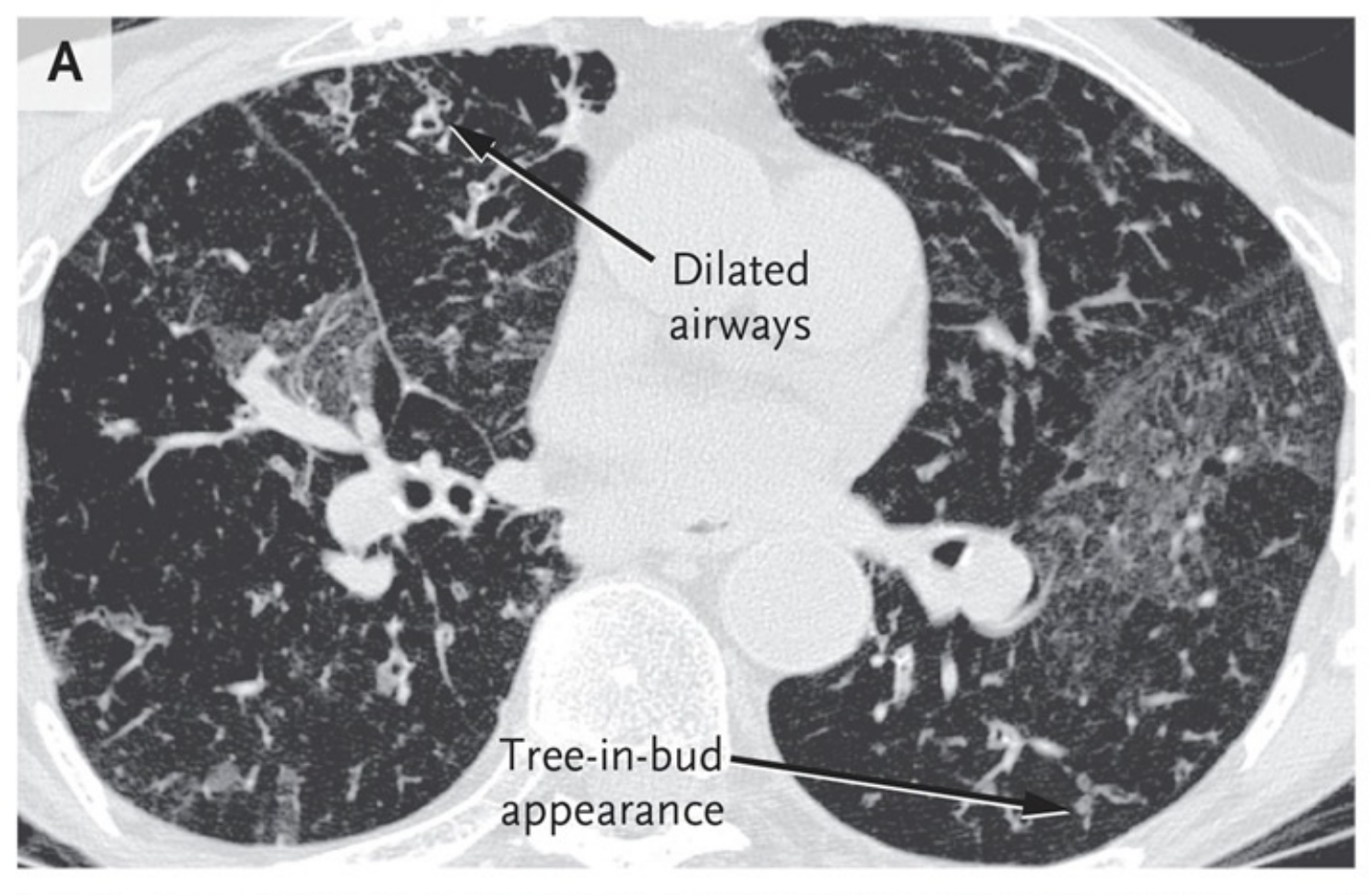
CT Scan in Bronchiolitis



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).

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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.

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

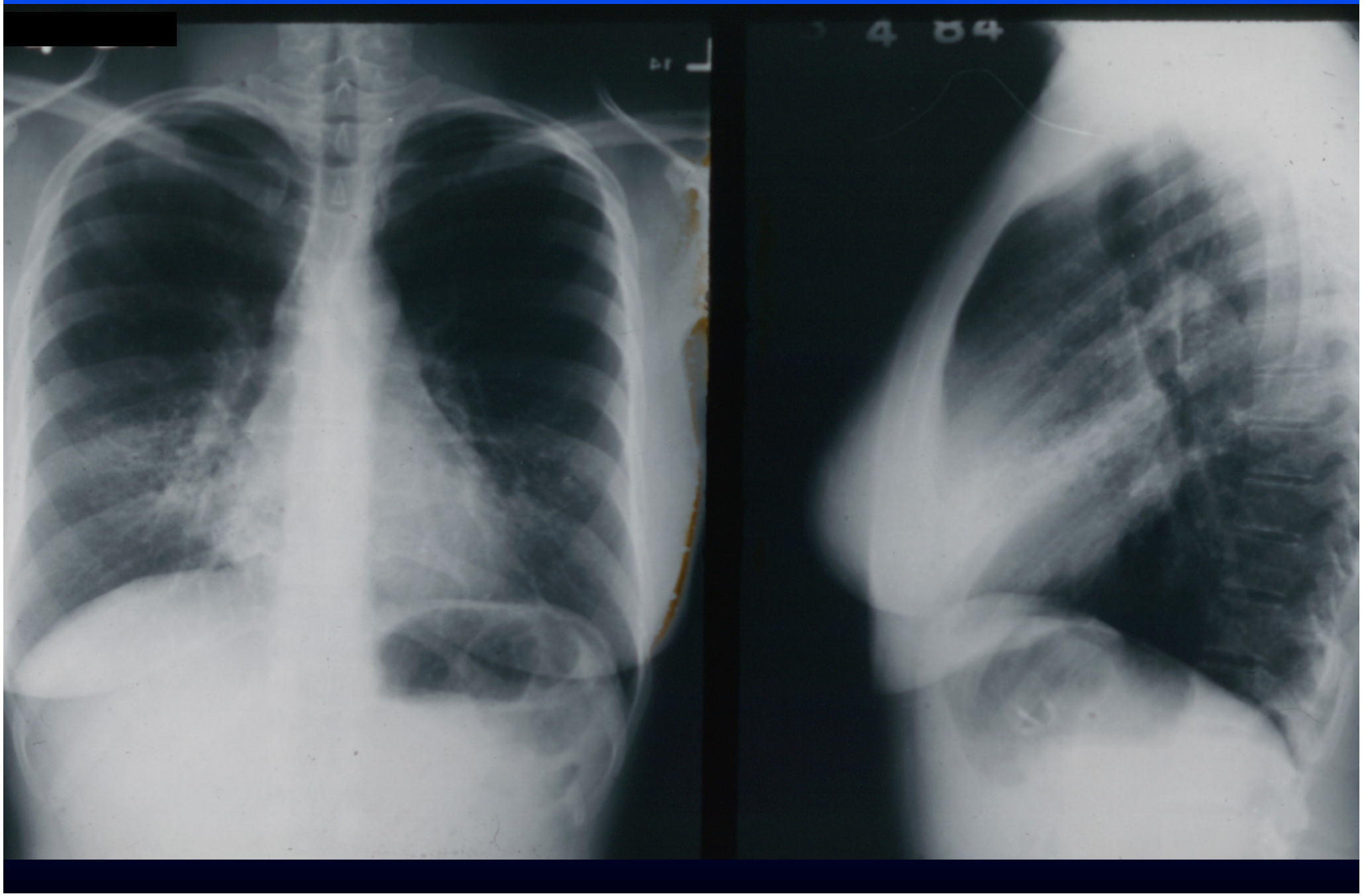
- Focal inspiratory crackles
- Low-pitched wheezing ("rhonchi")
- Clubbing

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



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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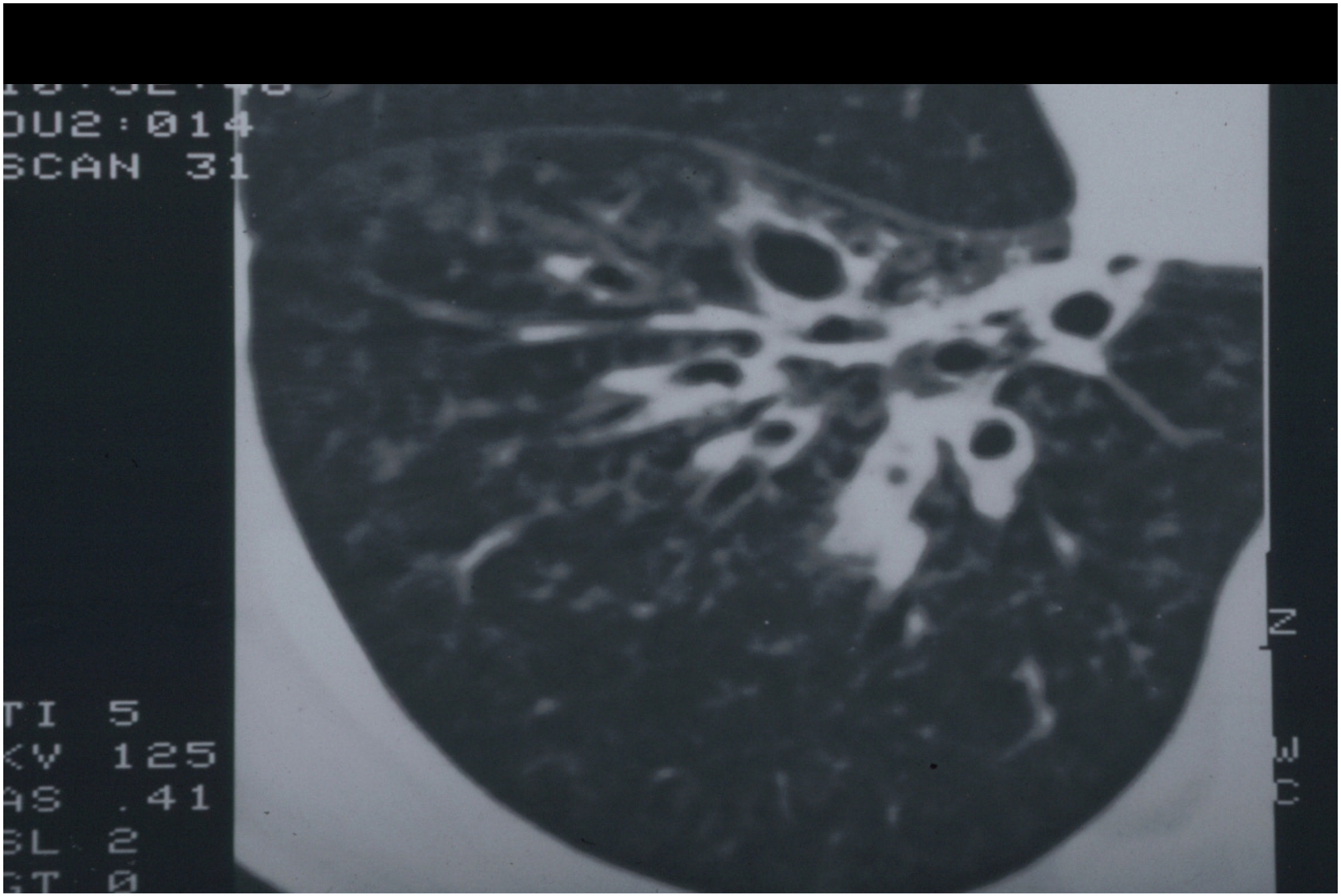
Chest CT Appearance

- 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)
- Bronchial wall thickening may be present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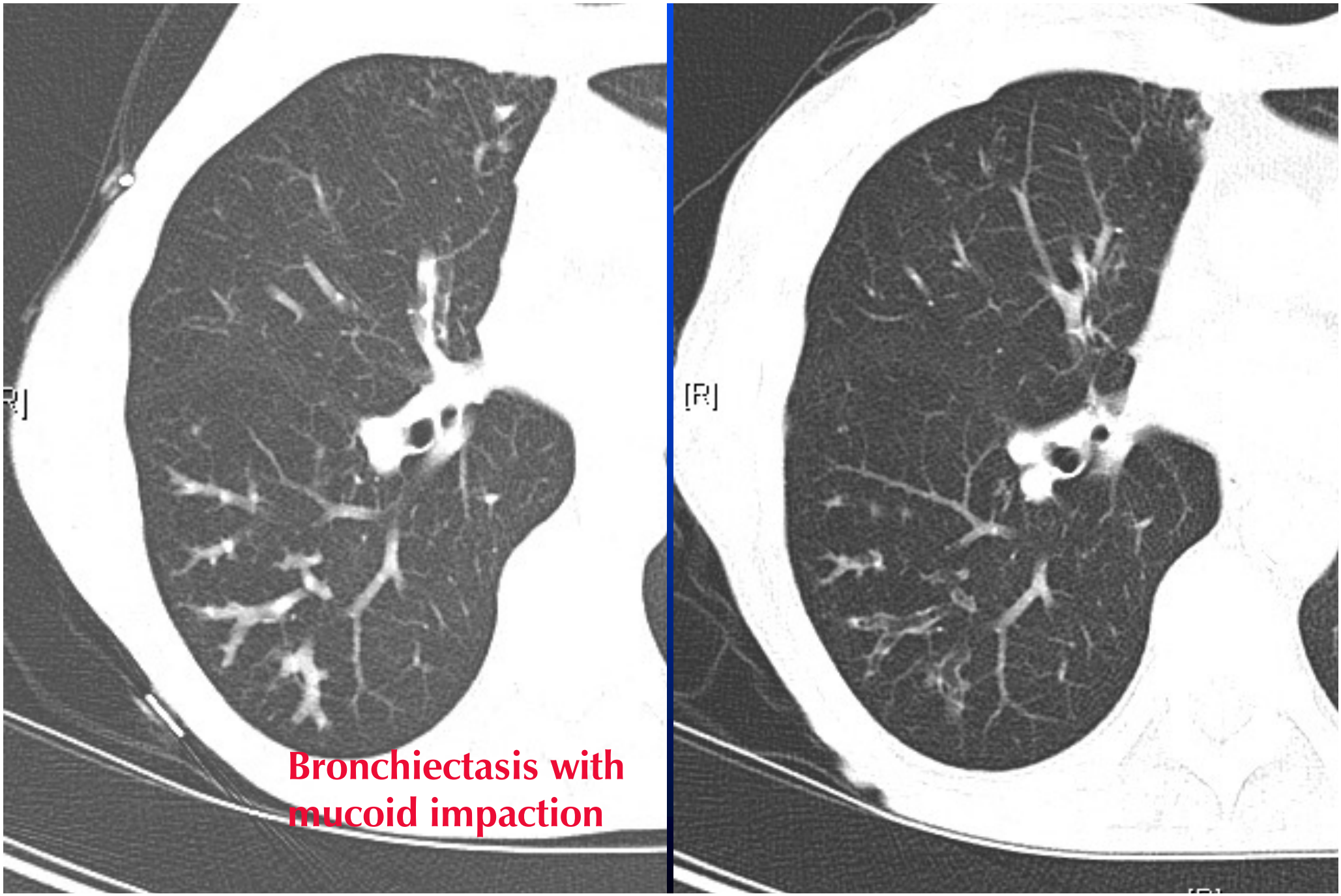
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Bronchiectasis with
mucoid impaction

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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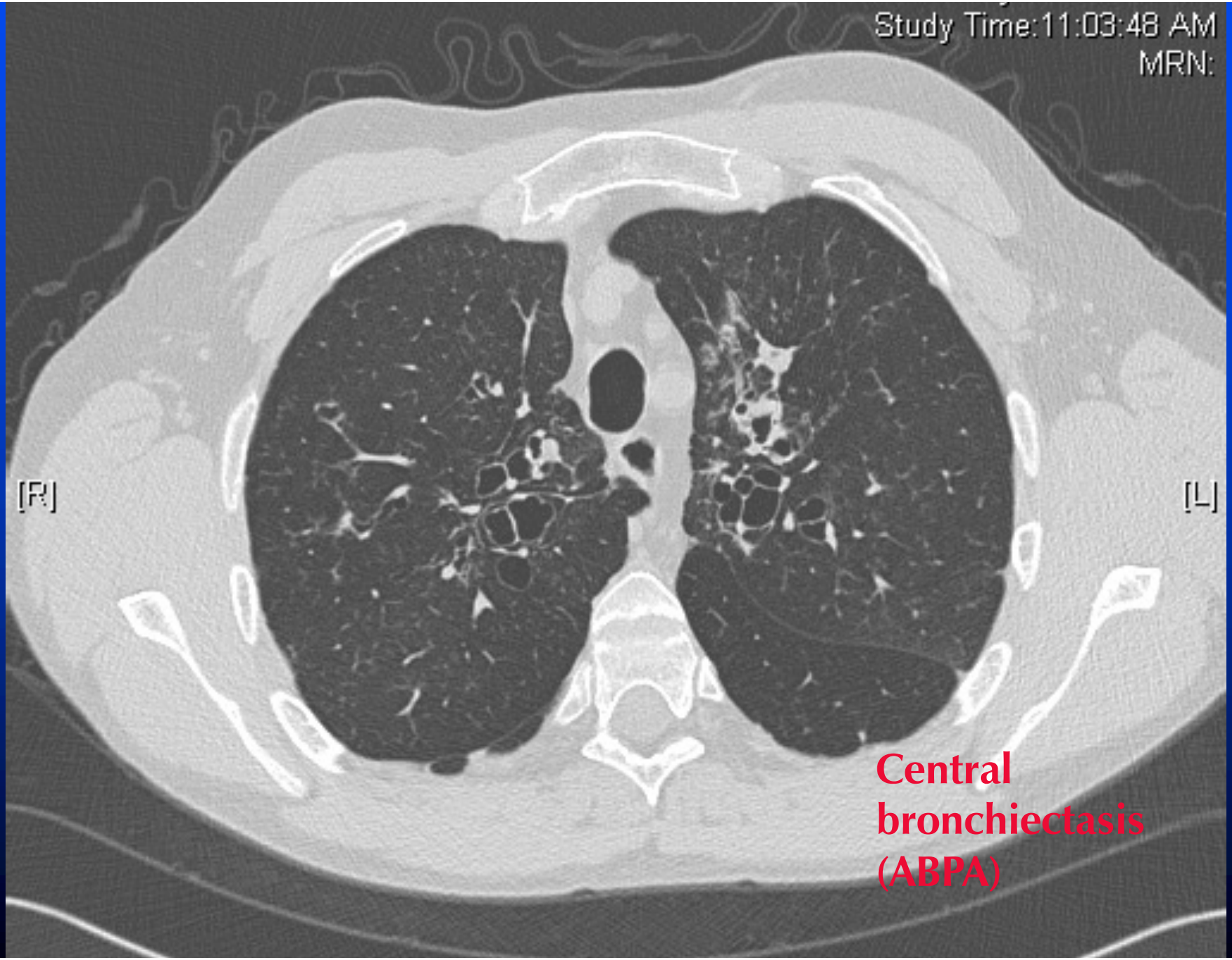
Etiologies:
Other Observations

- AIDS
- Ulcerative colitis
- Rheumatoid arthritis
- Allergic bronchopulmonary aspergillosis
- Non-tuberculous mycobacterial infection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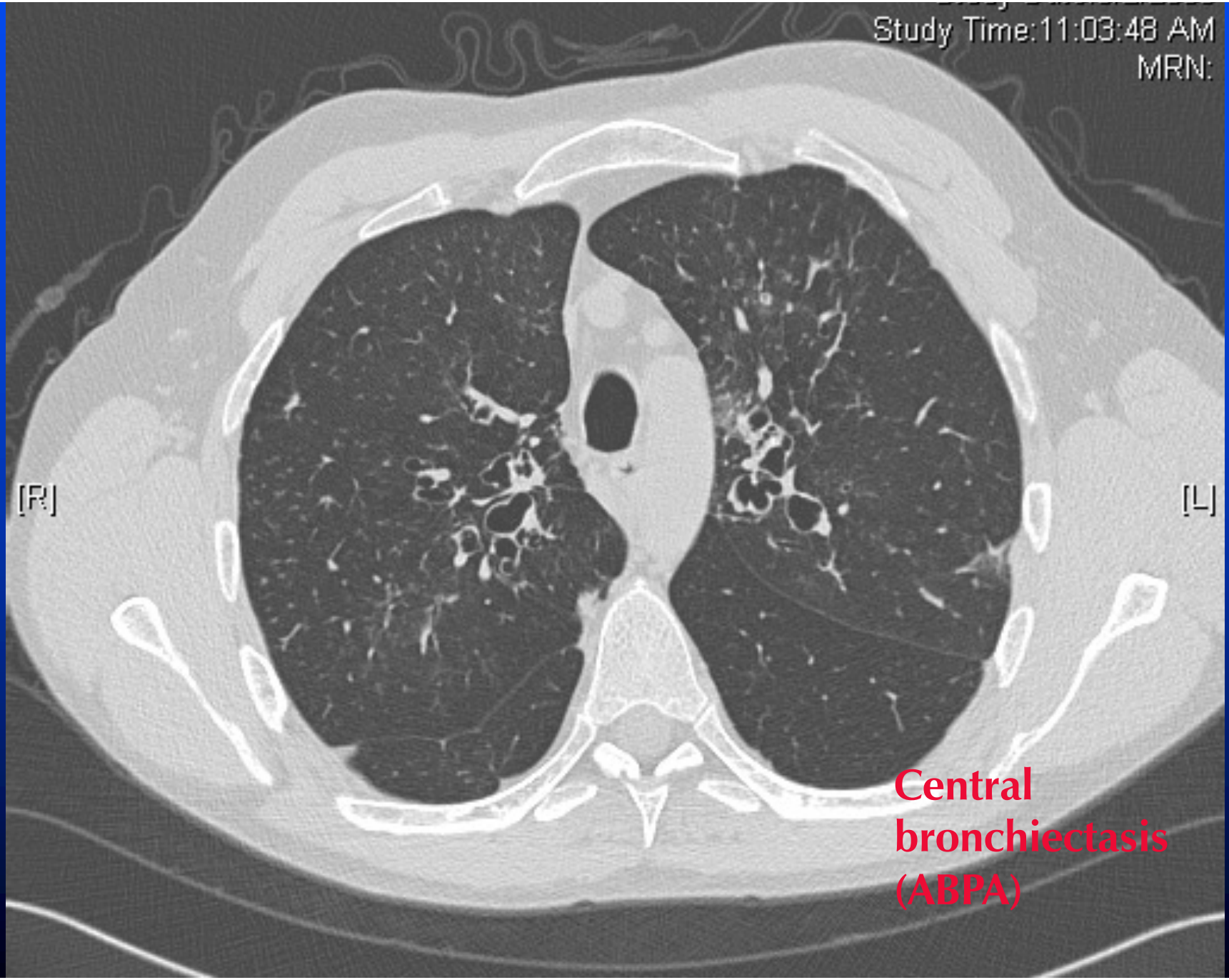
Central bronchiectasis (ABPA)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Central bronchiectasis (ABPA)

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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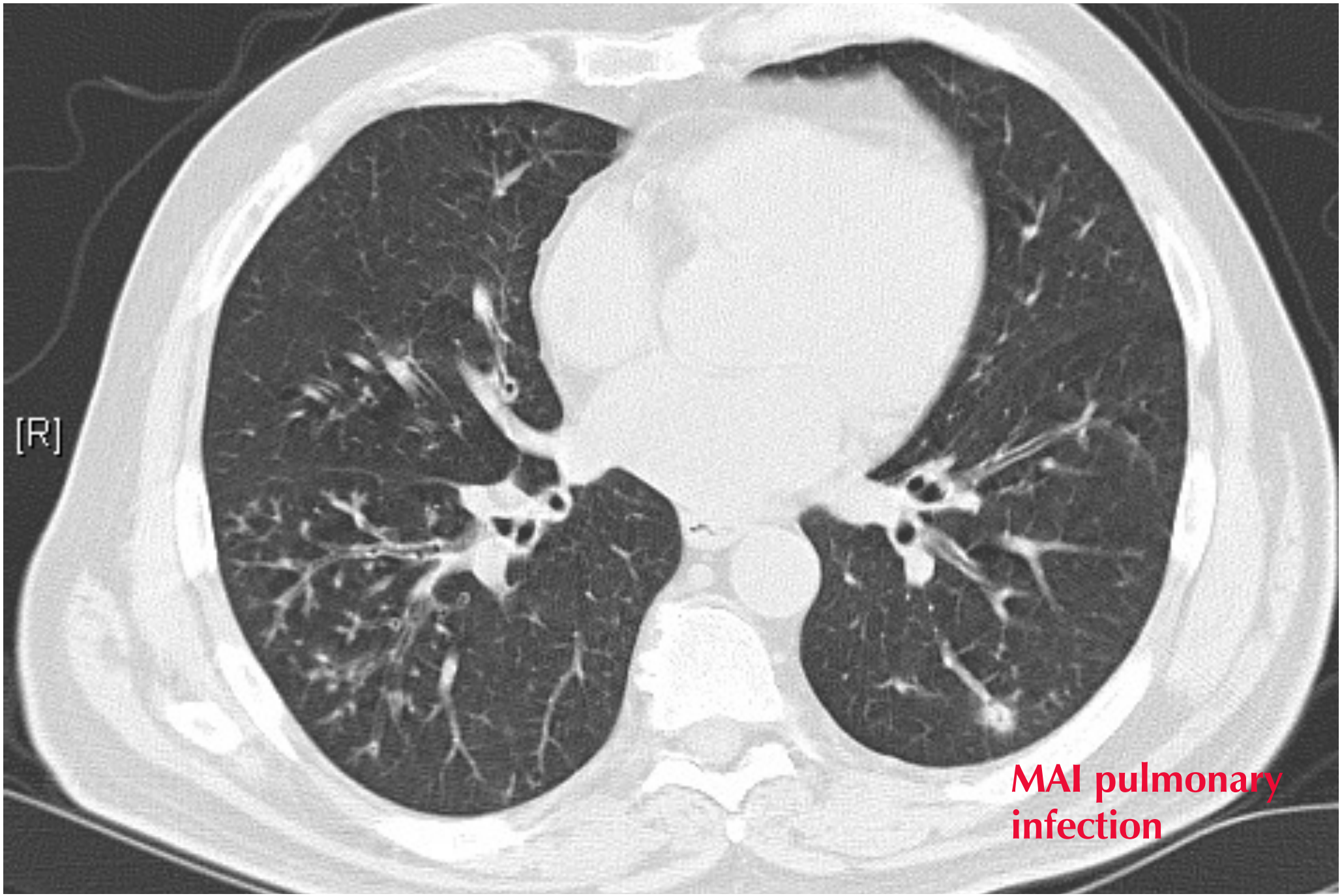
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MAI pulmonary infection

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; genetic typing; semen analysis; nasal or bronchial biopsy; alpha-1 antitrypsin level; IgE and aspergillus-specific IgE
- Bronchoscopy (new, local disease)

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Treatment

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

Treatment

- Bronchiectasis itself
  I. Mild, intermittently symptomatic
  II. Persistent symptoms and morbidity
  III. Acute-on-chronic exacerbations

Therapeutic Options

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

Antibiotic Therapy

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

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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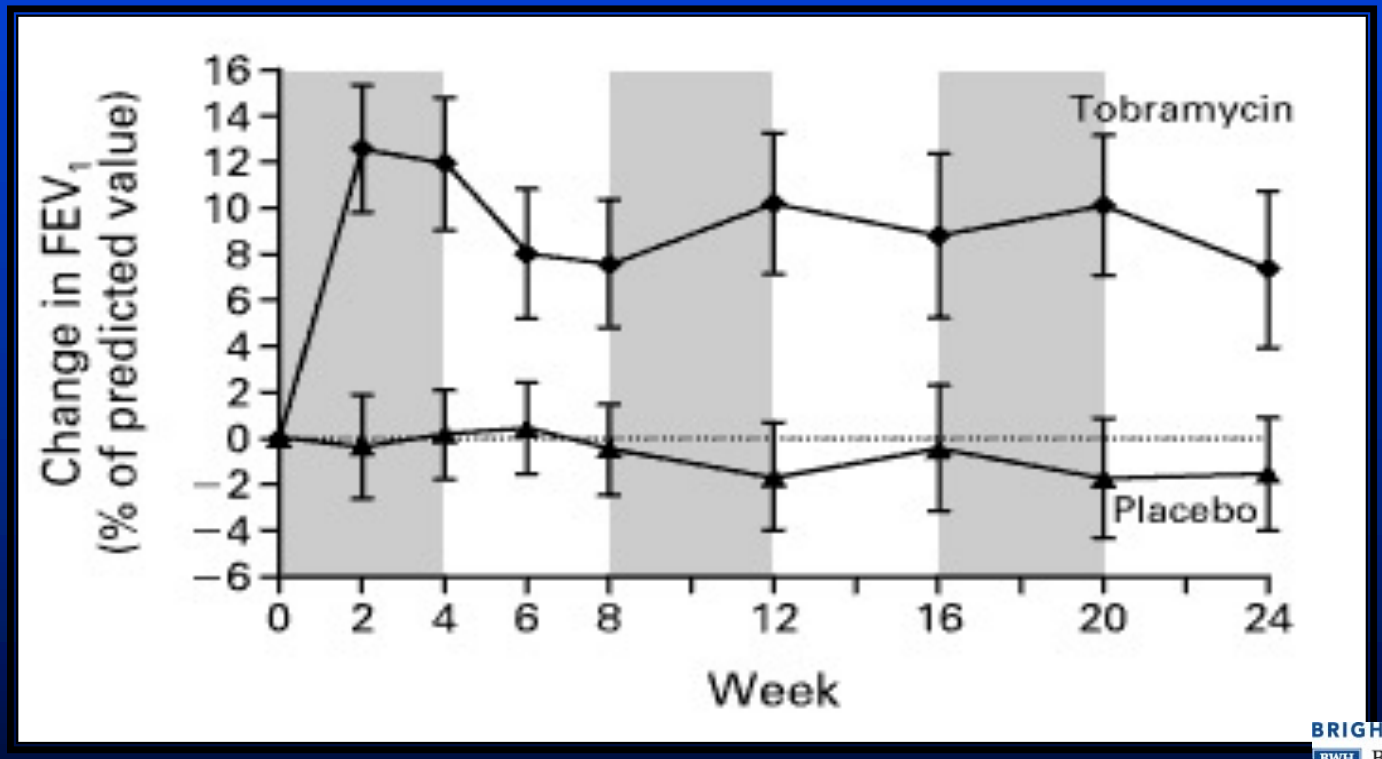
Randomized Trial of Nebulized Tobramycin in CF

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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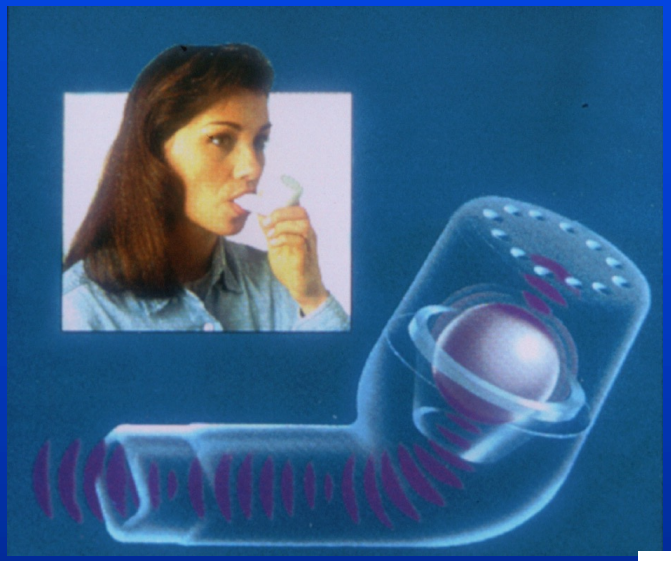
Therapeutic Options

- 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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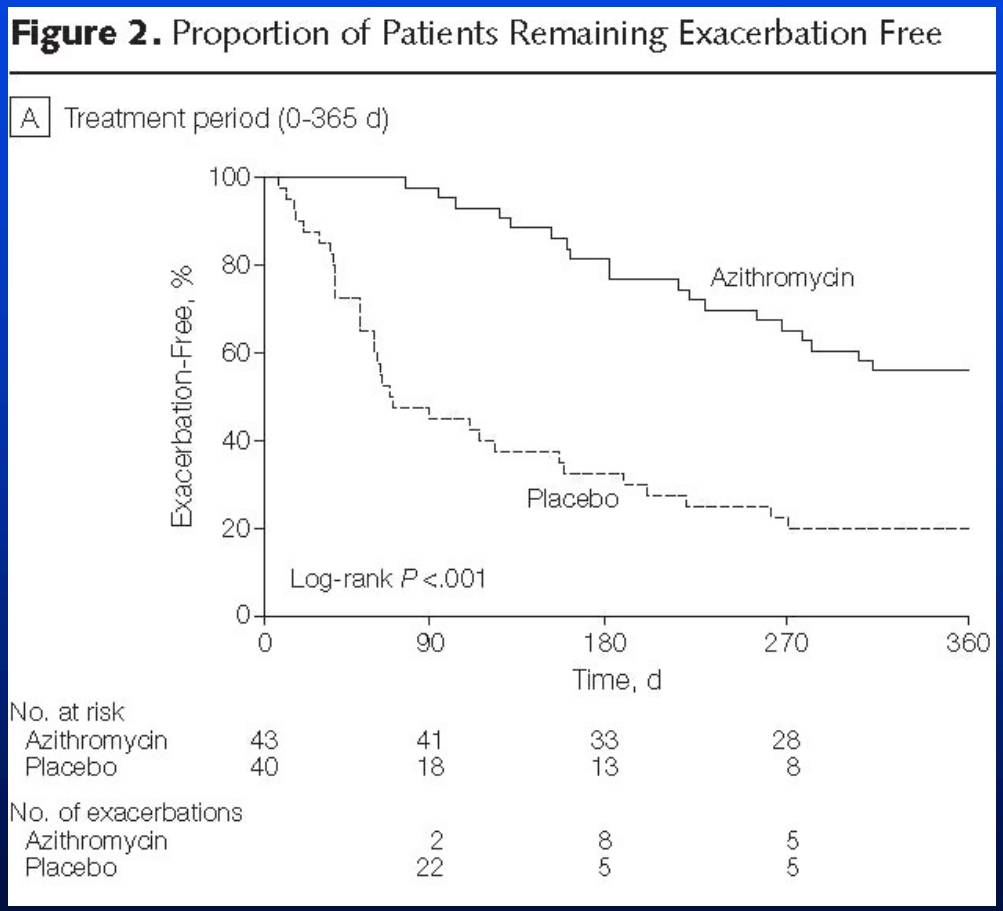
Anti-Inflammatory Therapy

- 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.

Complications

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

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Bronchiolitis: Key Points

- Bronchiolitis is a mixed group of disorders, both acute and chronic, involving respiratory bronchioles.
- Etiologies include infection, toxic exposures, and underlying immune disorders.

Bronchiolitis: Key Points

- Imaging varies considerably and is often non-specific.
- Biopsies are infrequently performed, leading to clinical diagnosis based on exclusion of other disorders.
- Treatment generally involves corticosteroids and other immunosuppression.

Key Points

- Bronchiectasis is a structural abnormality of the airways that predisposes to chronic airway infection.
- Symptoms may be intermittent or daily and include productive cough and periodic hemoptysis.

Key Points

- Etiologies include structural, immunologic, rheologic, and infectious causes.
- Chest CT scan is both sensitive and specific for diagnosis.
- Sputum culture is useful to guide treatment.

Key Points

- Treatment focuses on antibiotic treatment and airway clearance.
- Chronic suppressive antibiotics are effective but pose risk for emergence of resistant organisms.

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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

Correct Answer:

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

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