

NTM Lecture Series for Providers

September 19-20, 2019
NATIONAL JEWISH HEALTH

Bronchiectasis

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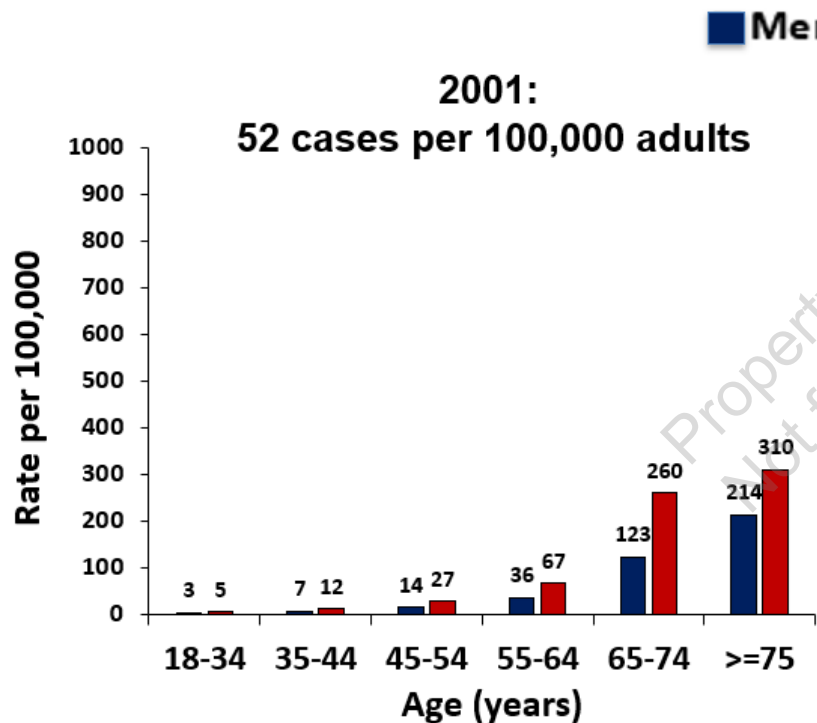
Disclosures

Speaker and advisory board member for Insmed

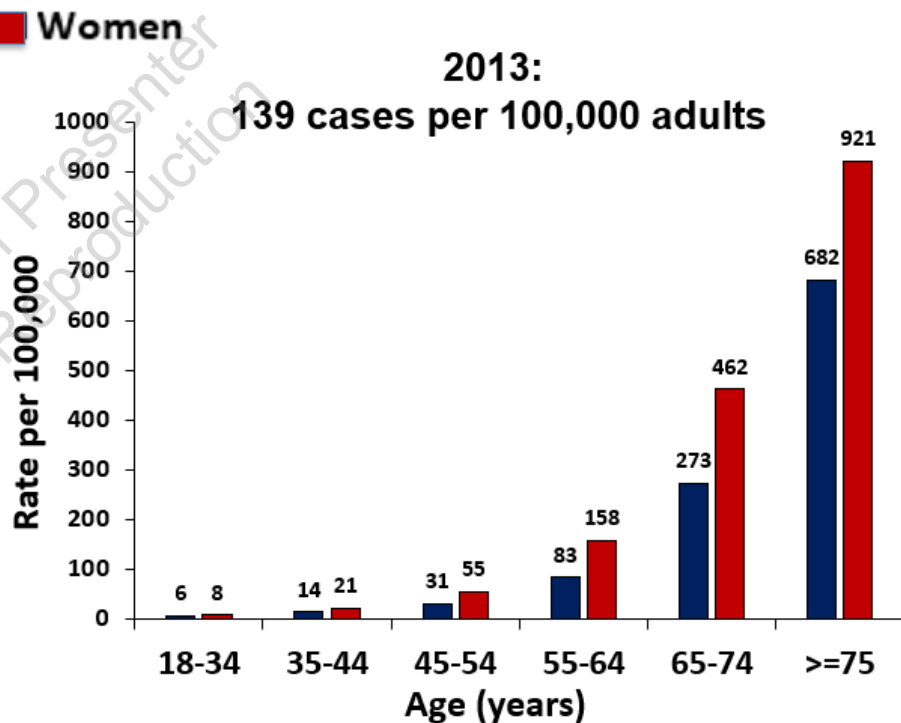
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Prevalence of Bronchiectasis in US

Retrospective Analysis of Health-care Claims for Bronchiectasis



Weycker, et al. *Clin Pulm Med.* 2005;12:205



Weycker, et al. *Chron Respir Dis.* 2017; 14: 277

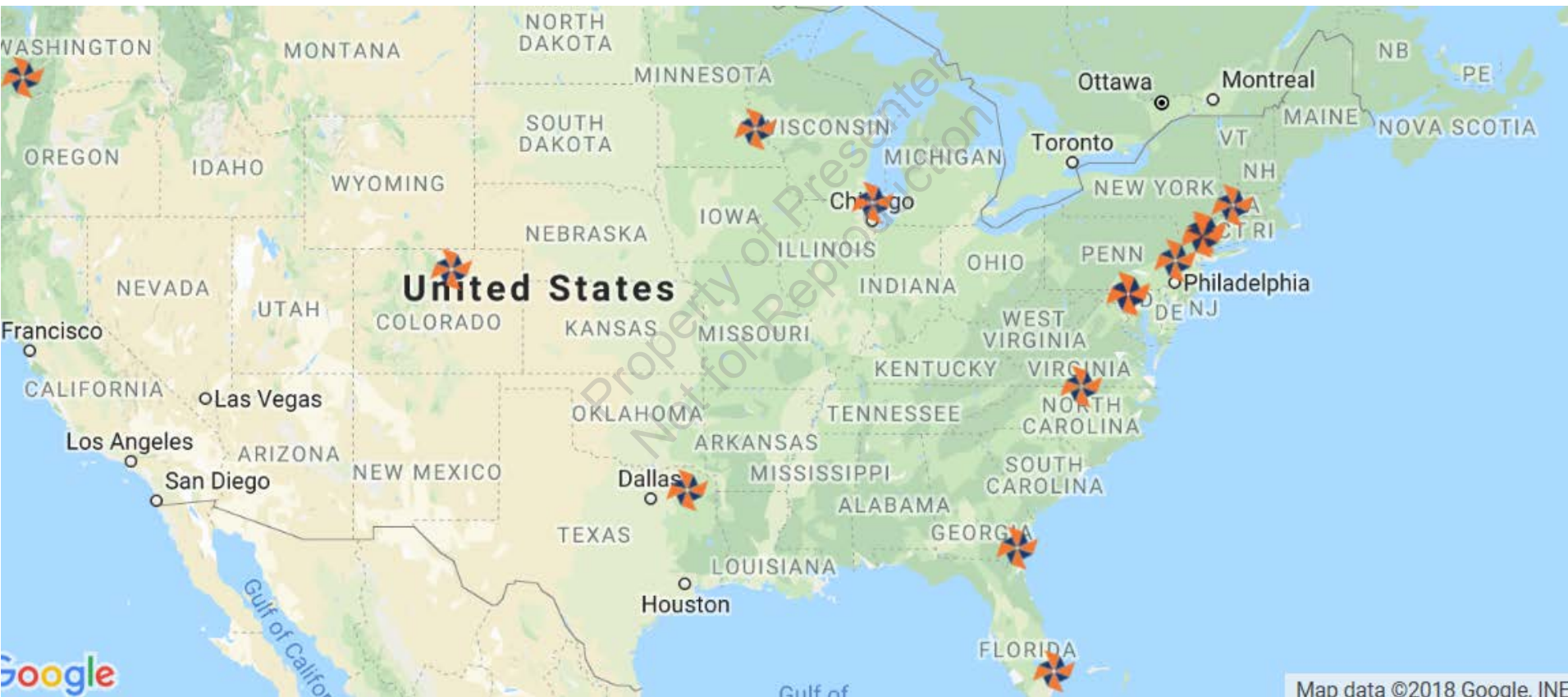


BRONCHIECTASIS AND NTM RESEARCH REGISTRY

A COPD Foundation Initiative

NTM Lecture Series for Providers

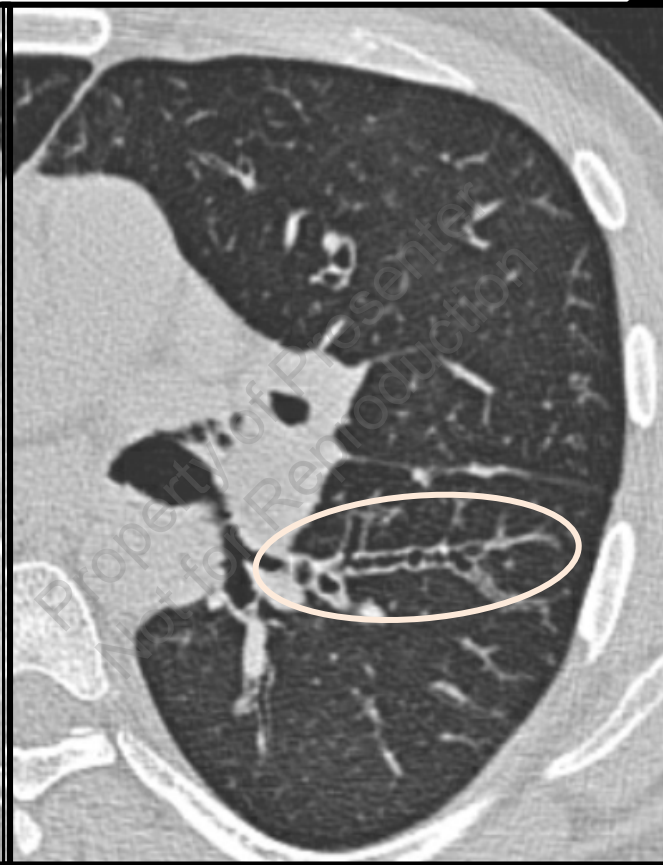
<https://www.bronchiectasisandntminitiative.org>



Cylindrical

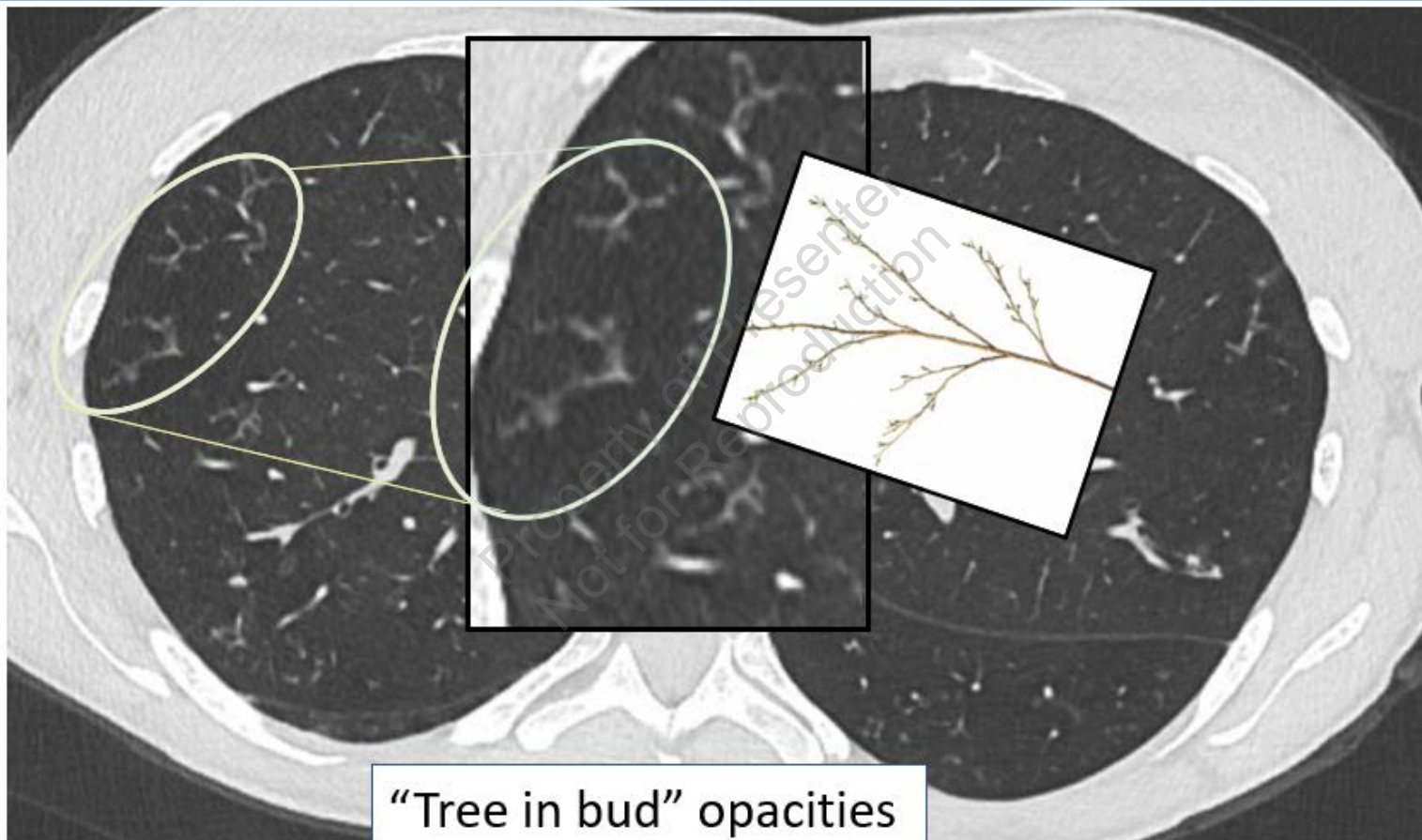


Varicose



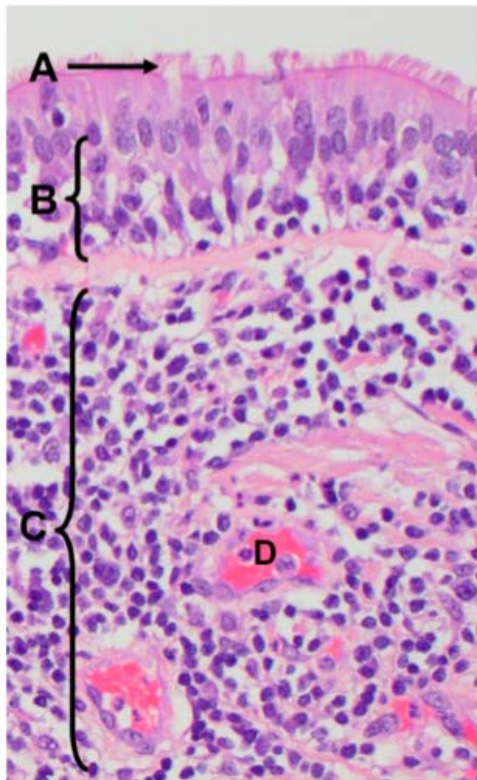
Cystic



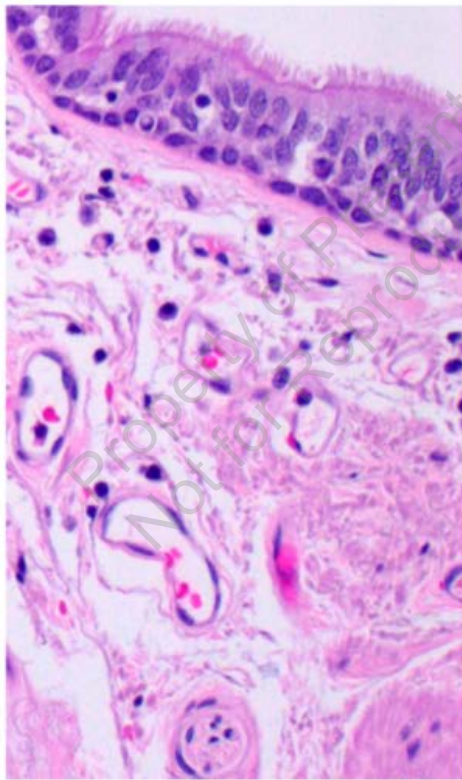


“Tree in bud” opacities

Histopathology of Bronchiectasis



Bronchiectasis



Normal

A = Pseudostratified columnar, ciliated epithelium

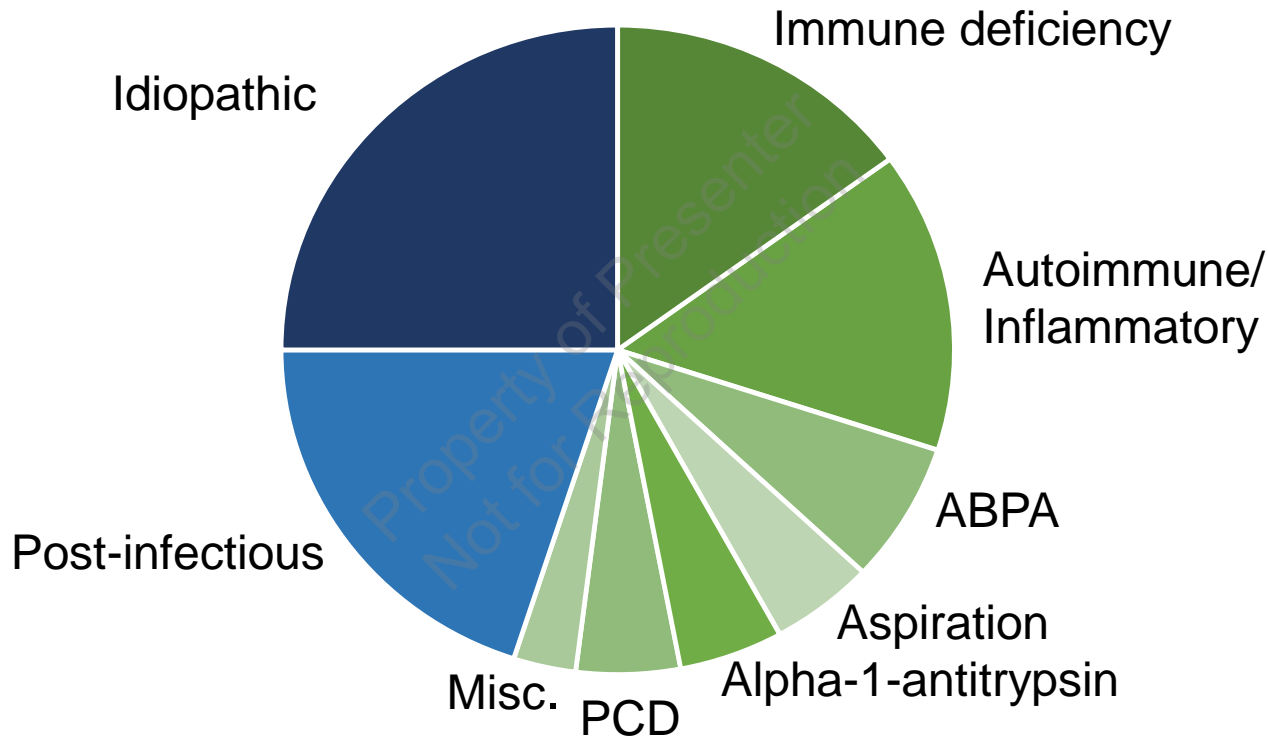
B = thickened epithelium with intraepithelial lymphocytes

C = submucosa with dense infiltrate of lymphocytes and plasma cells

D = blood vessel with reactive endothelial cells

Photos courtesy of Aliya N. Husain, MD

Etiology (or associated diseases) of Bronchiectasis



PCD: Primary Ciliary Dyskinesia

ABPA: Allergic Bronchopulmonary Aspergillosis

Pasteur et al. *Am J Respir Crit Care Med* 2000; 162: 1277

Shoemark et al. *Resp Med* 2007; 101: 1163

McShane et al. *Chest* 2012; 142: 159

Bronchiectasis: evaluation for etiology

Historical Investigation

- Family History
- Neonatal respiratory health
- Childhood symptoms
- Fertility History
- Gastrointestinal Symptoms
- Symptoms of Aspiration
- Prior Infections
- Connective Tissue symptoms
 - Dry Eyes, mouth
 - Red, hot, swollen joints
 - Rash

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Bronchiectasis: evaluation for etiology

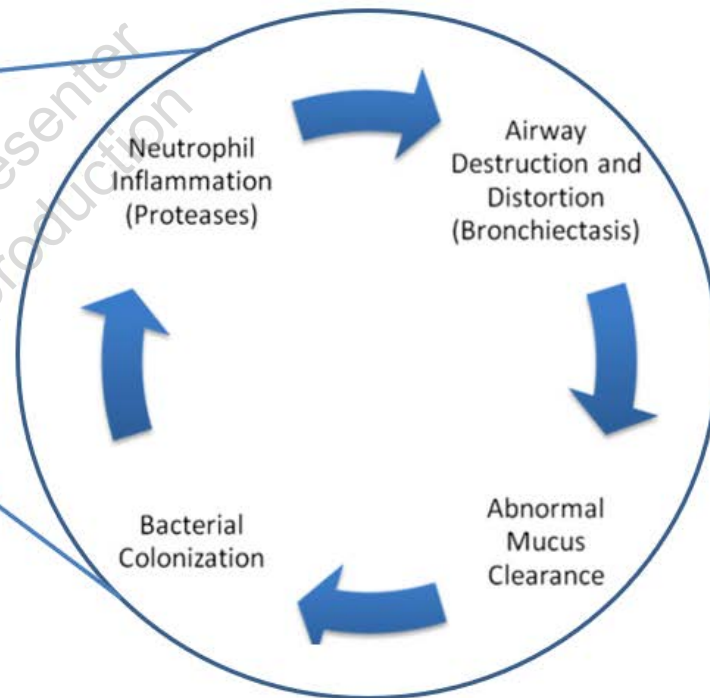
Historical Investigation

- Family History
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Laboratory Testing

- ✓ **Sputum for AFB and bacteria**
- ✓ CBC with differential
- ✓ Serum Immunoglobulins (incl. IgE)
- ✓ Specific IgE or G to Aspergillus
- ✓ Alpha 1 anti-trypsin
- Consider depending on symptoms:
 - Swallow eval / pH monitoring
 - Auto ab relevant to history
 - S. pneumo 23 serotypes
 - nasal Nitric Oxide

Pathophysiology of Bronchiectasis



McShane, et al. *Am J Respir Crit Care Med* 2013; 188:647
Cole, *Eur J Respir Dis Suppl* 1986; 147:6

Treatment of Bronchiectasis

1) Nebulized Agents

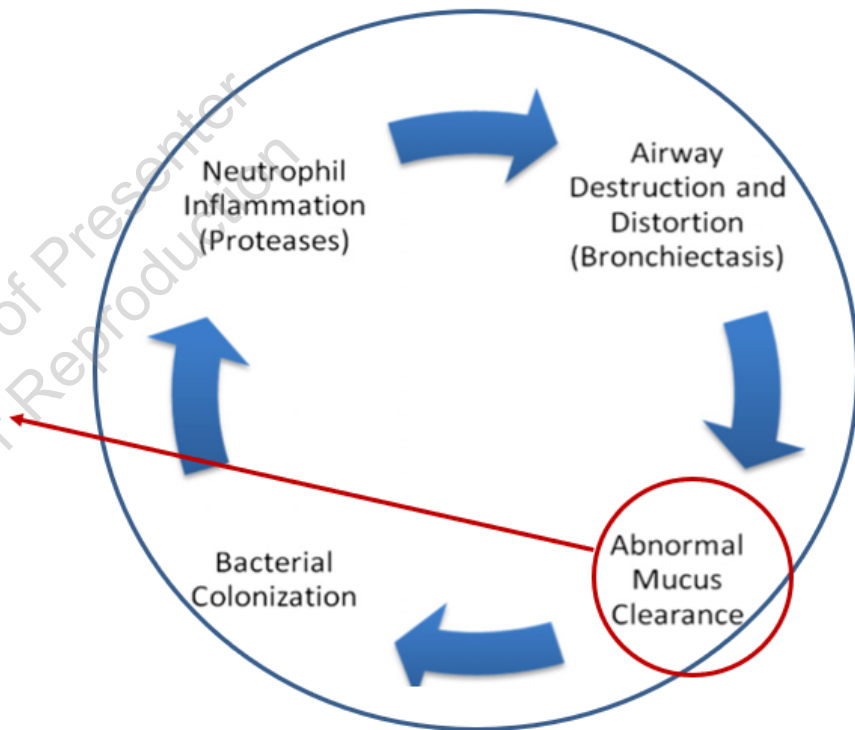
- 7% Hypertonic Saline

2) Breathing Techniques

- Active Cycle of Breathing

- Postural Positioning

3) Chest Physiotherapy:



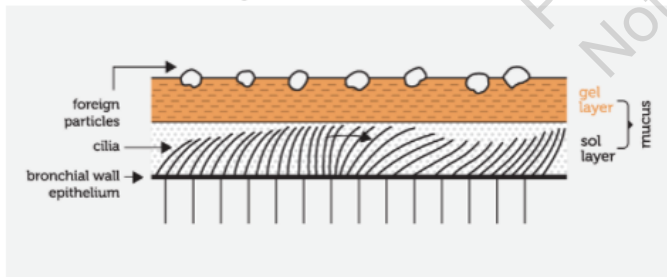
McShane, et al. *Am J Respir Crit Care Med* 2013; 188:647

Cole, *Eur J Respir Dis Suppl* 1986; 147:6

Sputum is not the same as mucus

Mucus

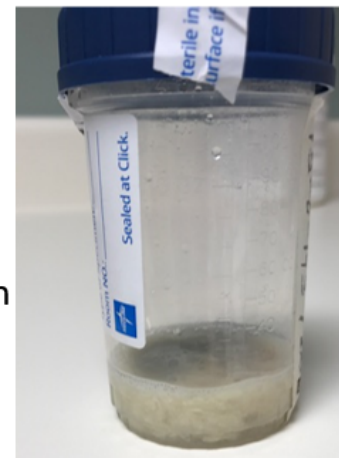
- Mucin Glycoproteins
- Antimicrobial and anti-inflammatory properties
- Cleared by cilia



Bronchiectasis Toolbox: www.bronchiectasis.com.au

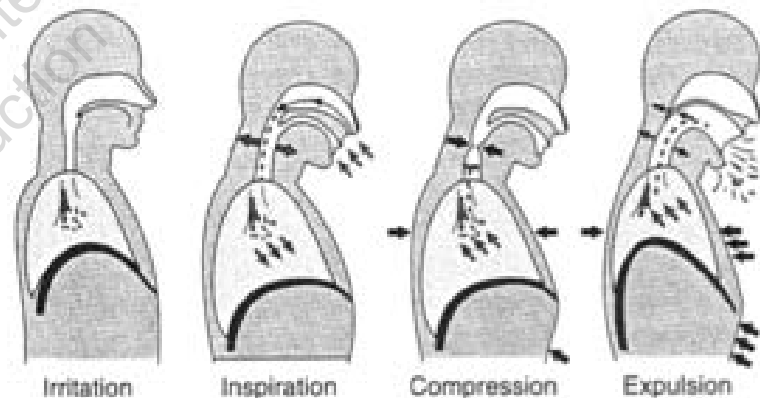
Sputum

- Large polymers that include:
 - DNA
 - Filamentous actin
 - Proteoglycans
 - Bacteria
 - Inflammatory cells
 - Impairs cilia motion



Normal Cough

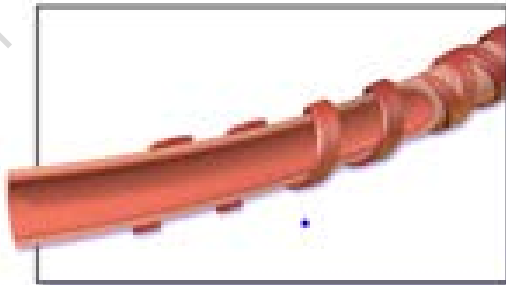
- Clears secretions to the 7th or 8th generation
- Deep inspiration → closure of the glottis:
 - Up to **300 mmHg intra-thoracic pressure** → dynamic airway compression & shear force detaching mucus from the airway wall
 - High explosive, turbulent expiratory flow rate (~500 L/min)



Coughing is not effective in bronchiectasis

- Bronchial wall instability and “floppy” airways close prematurely
 - ***Expiratory flow is reduced, thereby limiting the effectiveness of the cough***

Normal Airway



Airway with Bronchiectasis



Airway Clearance Techniques

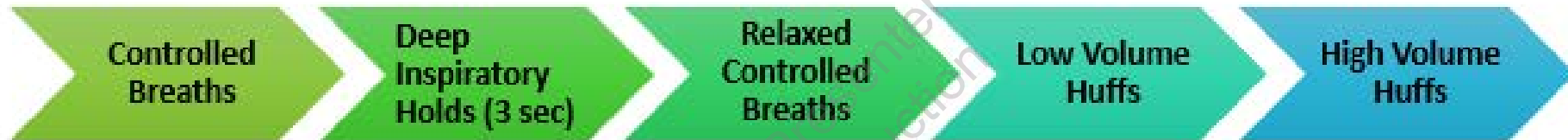
- ✓ Allow air to move behind obstruction and ventilate distal regions
- ✓ Modulate expiratory airflow in a way to propel secretions proximally up the airways

Modes of Airway Clearance

to be CUSTOMIZED to patient preference and success

<u>Breathing Techniques</u>	<u>Devices</u>	<u>Nebulized Solutions</u>	<u>Assistance</u>
Active Cycle of Breathing	Positive Expiratory Pressure (PEP) Mask	Hypertonic saline (7%, 3%)	Percussion
Autogenic Drainage	Positive Expiratory Pressure (PEP) with Oscillation	Albuterol	
Huff	High Frequency Chest Wall Oscillation (HFCWO) "Vest"	<u>Acetylcysteine</u>	
Postural Positioning			

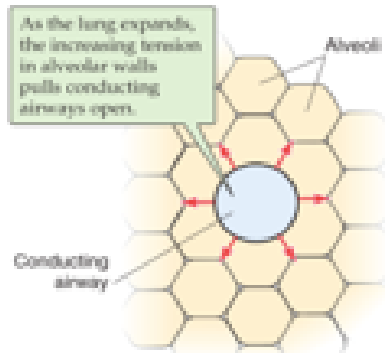
Active Cycle of Breathing Technique



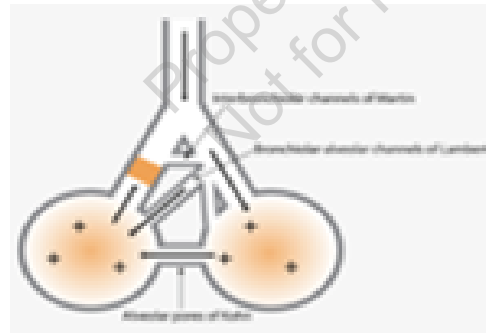
Active Cycle of Breathing Technique



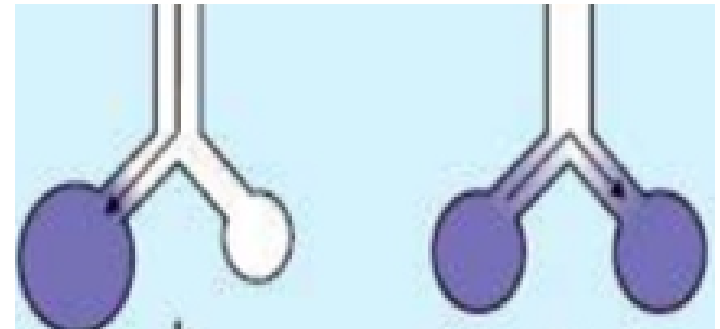
Thoracic Expansion and Breath Hold improves ventilation



Interdependence

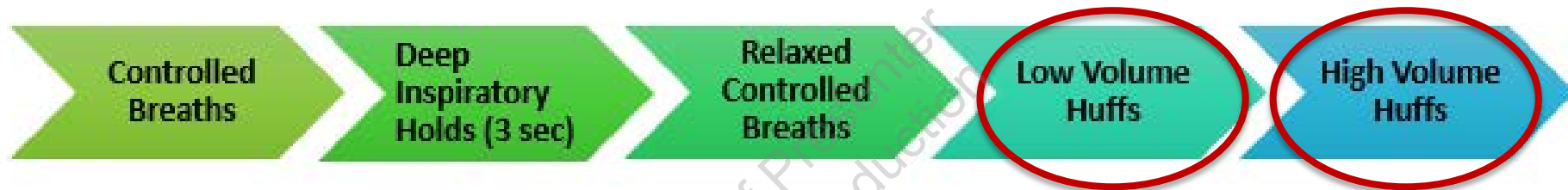


Collateral Ventilation



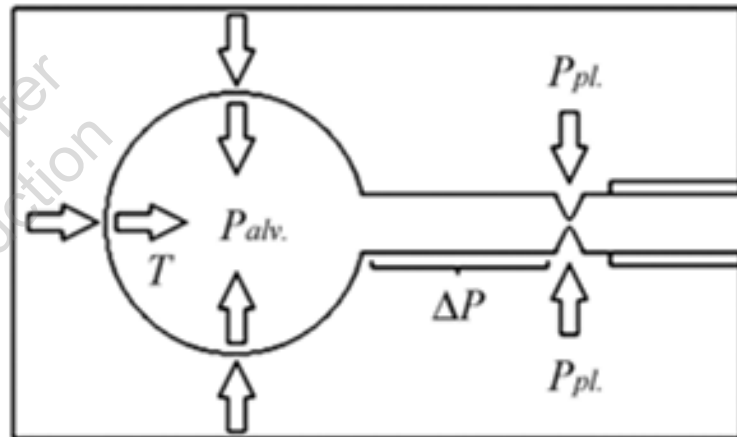
Pendelluft Flow

Active Cycle of Breathing Technique



Huff

- Accelerates expiratory airflow creating high linear velocities which:
 - **Increases airway surface liquid**
 - **Shears mucus from the airway wall***
- At low lung volumes, Equal Pressure Point (EPP) shifts to the periphery



At EPP dynamic compression of the airways creates increase of linear velocity of expiratory airflow which helps to propel secretions proximally

* Depends on mucus depth and viscoelastic properties

www.bronchiectasis.com.au



Bronchiectasis
Toolbox

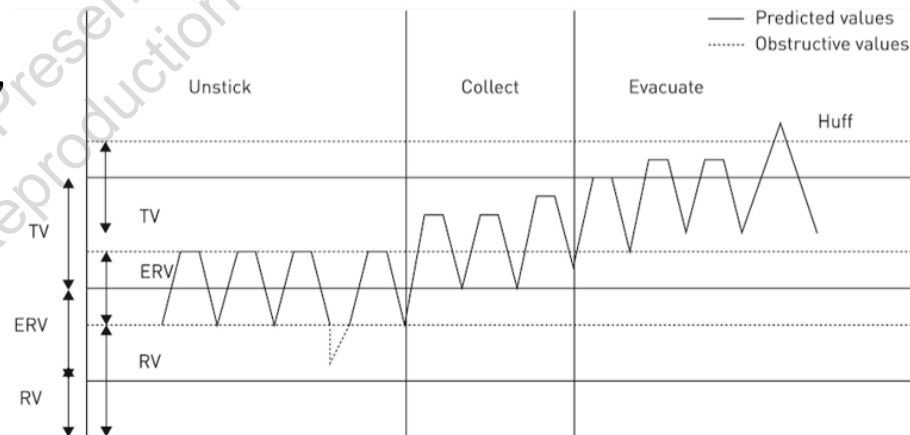
www.bronchiectasis.com.au



Bronchiectasis
Toolbox

Autogenic Drainage

- Uses controlled breathing in 3 stages
- Different lung volumes to loosen, mobilize, and move secretions to the central airways
- Performed with an open glottis
- Typically performed in seated position



Bronchiectasis Toolbox: www.bronchiectasis.com.au

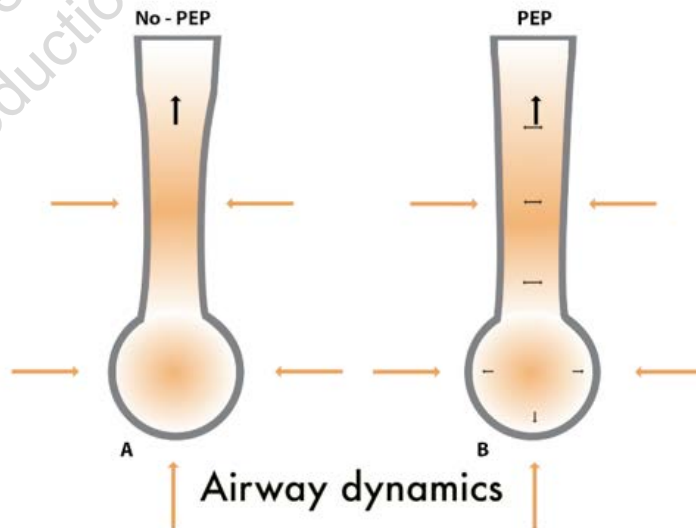
- ✓ *Ventilates obstructed regions of the lung*
- ✓ *Avoids dynamic compression of the airways by modulation of expiratory airflow*

Oscillating with positive expiratory pressure

Oscillation

- Improves mucus rheological properties:
 - Reduces mucus rigidity (sum of viscosity and elasticity)
 - Reduces spinnability (thread forming capacity of mucus)
 - Improves cough clearance index (higher index = easier to clear)

Positive Expiratory Pressure



High frequency chest wall oscillation (HFCWO)



High-frequency chest wall oscillation

Benefits

- Alters rheological properties of mucus
- Creates an expiratory flow bias that shears mucus from the airway walls
- Enhances ciliary beat frequency
- Creates peak expiratory flow rate sufficient to overcome mucus adhesion

High-frequency chest wall oscillation

Benefits

- Alters rheological properties of mucus
- Creates an expiratory flow bias that shears mucus from the airway walls
- Enhances ciliary beat frequency
- Creates peak expiratory flow rate sufficient to overcome mucus adhesion

Concerns

- Provides no means of ventilating behind obstructive airways
- Does not provide PEP
 - End expiratory volume has been reported to decrease by 10-15% during compression

Nebulized Hypertonic Saline

- **Nicolson et al. *Resp Med* 2012; 106: 661-667**
- Blinded, prospective, randomized, 12-month study
- 6% hypertonic saline vs. 0.9% saline Q 12hrs.
- QOL improved in both groups
- **Sputum bacterial load decreased:**
 - 55% of hypertonic saline group had positive cultures at the *start* of the study
 - 15% of hypertonic saline group had positive cultures at the *end* the study

Nebulized Hypertonic Saline

- **Nicolson et al. *Resp Med* 2012; 106: 661-667**

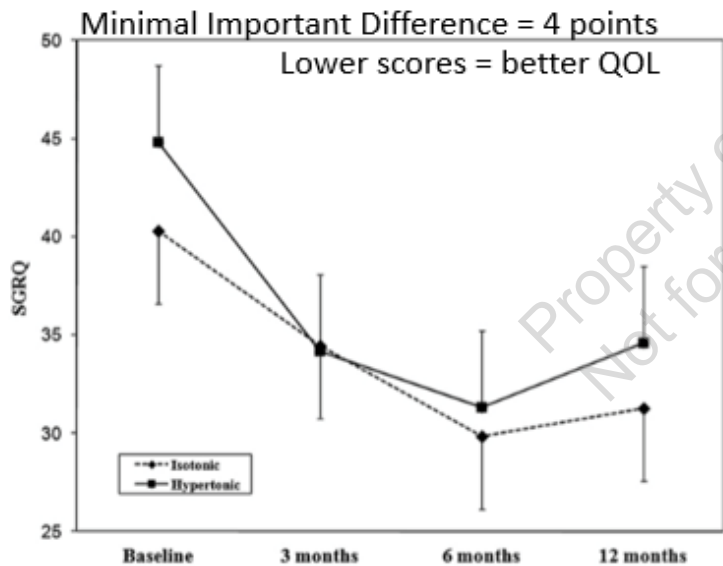


Figure 2 SGRQ Totals. No significant difference between groups at any time point.

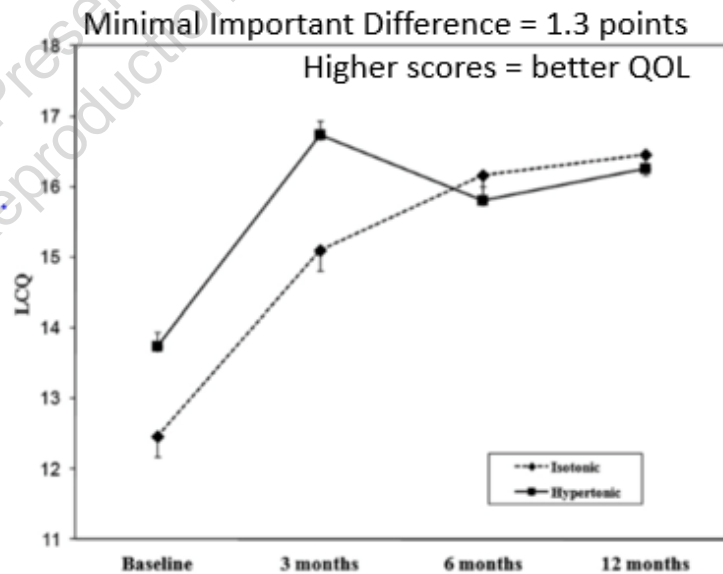
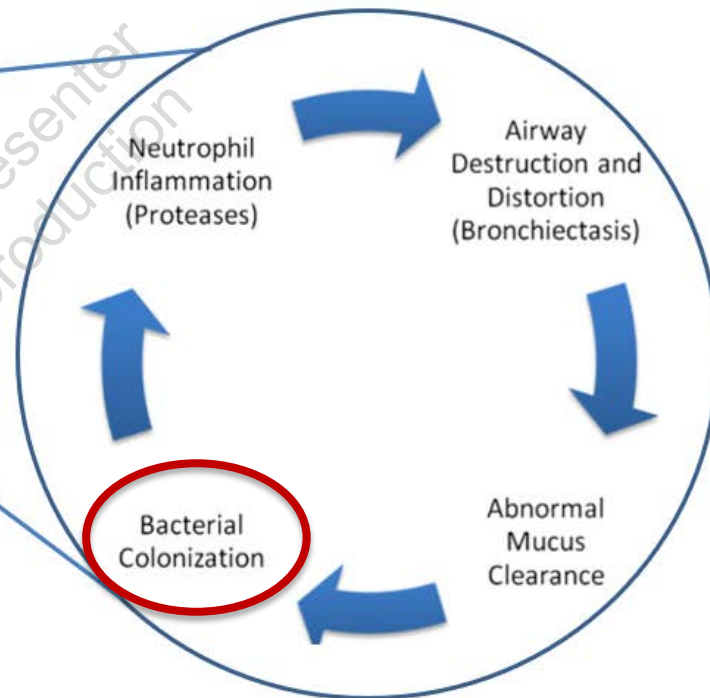


Figure 3 LCQ Totals. No significant difference between groups at any time point.

Pathophysiology of Bronchiectasis



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Nebulized Antibiotics



Mias using the nebulizer (credit: Denver Zoo)

Nebulized Antibiotics

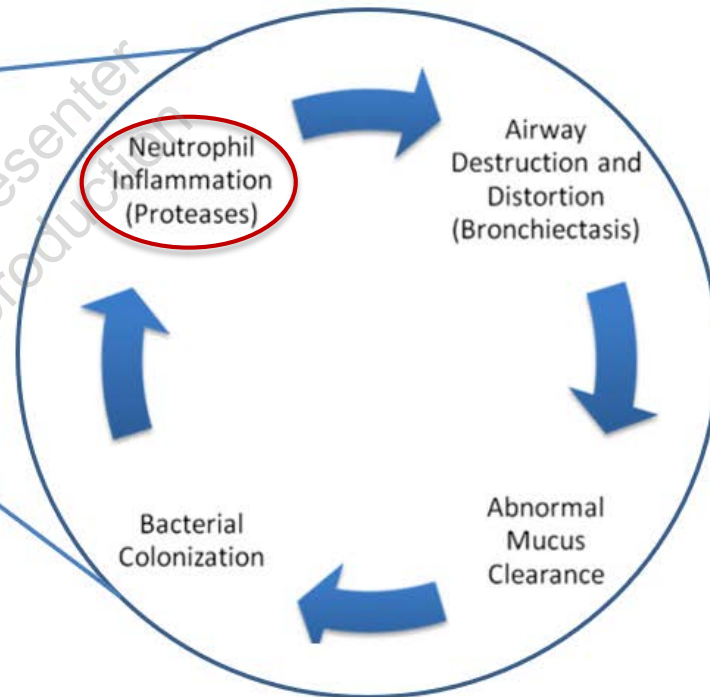
- Tobramycin
 - Colisitin
 - Gentamicin*
 - Aztreonam
 - Ciprofloxacin
- ✓ Reduce bacterial load
 - ✓ Variable improvement in Quality of Life
 - ✓ **Have not *consistently* reduced exacerbations**
 - ✓ **NOT FDA approved!!**

* The only inhaled antibiotic shown to reduce exacerbations in study

Nebulized Antibiotics

- Strongest guideline recommendation:
 - **Chronic infection with *P. aeruginosa***
 - **At least 3 exacerbations per year**

Pathophysiology of Bronchiectasis



McShane, et al. *Am J Respir Crit Care Med* 2013; 188:647
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Reducing Exacerbation Frequency

Macrolides

	EMBRACE¹ <i>Lancet</i> 2012; 380:660	BAT² <i>JAMA</i> 2013; 309:1251	BLESS³ <i>JAMA</i> 2013; 309:1260
Number	141	83	117
Treatment	<u>Azithromycin</u> 500mg PO vs placebo Mon/Wed/Fri	Azithromycin 250mg PO vs placebo Daily	<u>Erythromycin ethylsuccinate</u> 400mg PO vs placebo Twice daily
Trial Length	6 months (treatment); 1-year total follow up	1 year	1 year
Location	New Zealand	Netherlands	Australia
Exacerbations in prior 12 months	≥1 exacerbation needing antibiotic treatment	≥3 exacerbations needing antibiotic treatment	≥2 exacerbations needing antibiotic treatment

Recommendations for chronic macrolide use in bronchiectasis

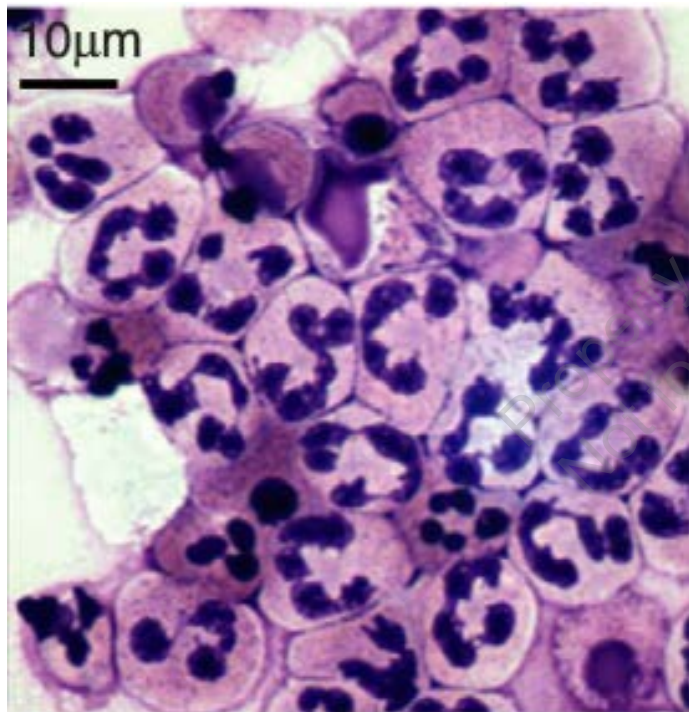
<p>Adults with bronchiectasis and chronic <i>Pseudomonas</i> infection for whom <u>inhaled antibiotics are contraindicated, not tolerated or not feasible</u></p>	<p>Adults with bronchiectasis and chronic <i>Pseudomonas</i> infection in addition to inhaled antibiotics Who <u>have high exacerbation frequency</u> despite taking an inhaled antibiotic</p>	<p>Adults with bronchiectasis NOT infected with <i>Pseudomonas</i> who have frequent exacerbations</p>
<p>Conditional recommendation, low quality of evidence</p>		<p>Conditional recommendation, moderate quality of evidence</p>

Recommendations for chronic macrolide use in bronchiectasis

<p>Adults with bronchiectasis and chronic infection for <u>antibiotics contraindicated</u> or <u>not tolerated</u></p>	<p>Adults with bronchiectasis and chronic <i>Pseudomonas</i> infection to</p>	<p>Adults with bronchiectasis NOT infected with <i>Pseudomonas</i> <u>who have frequent exacerbations</u></p>
<p>Conditional recommendation, low quality of evidence</p>	<p>antibiotic</p>	<p>recommendation, moderate quality evidence</p>

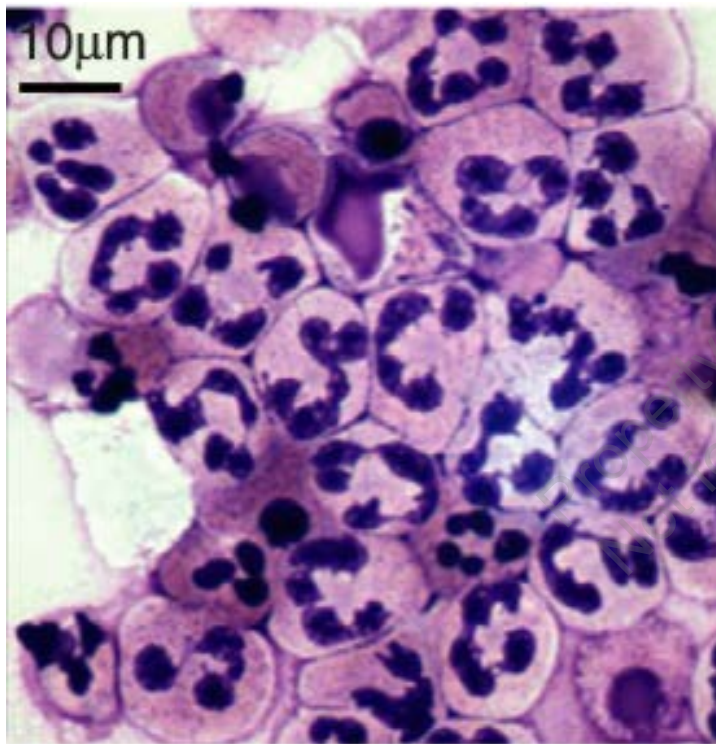
Rule out NTM infection PRIOR to initiating macrolide therapy!!

Bronchiectasis conundrum:
many neutrophils but *Pseudomonas* persists



Sputum on LJ Slant growing *P aeruginosa*

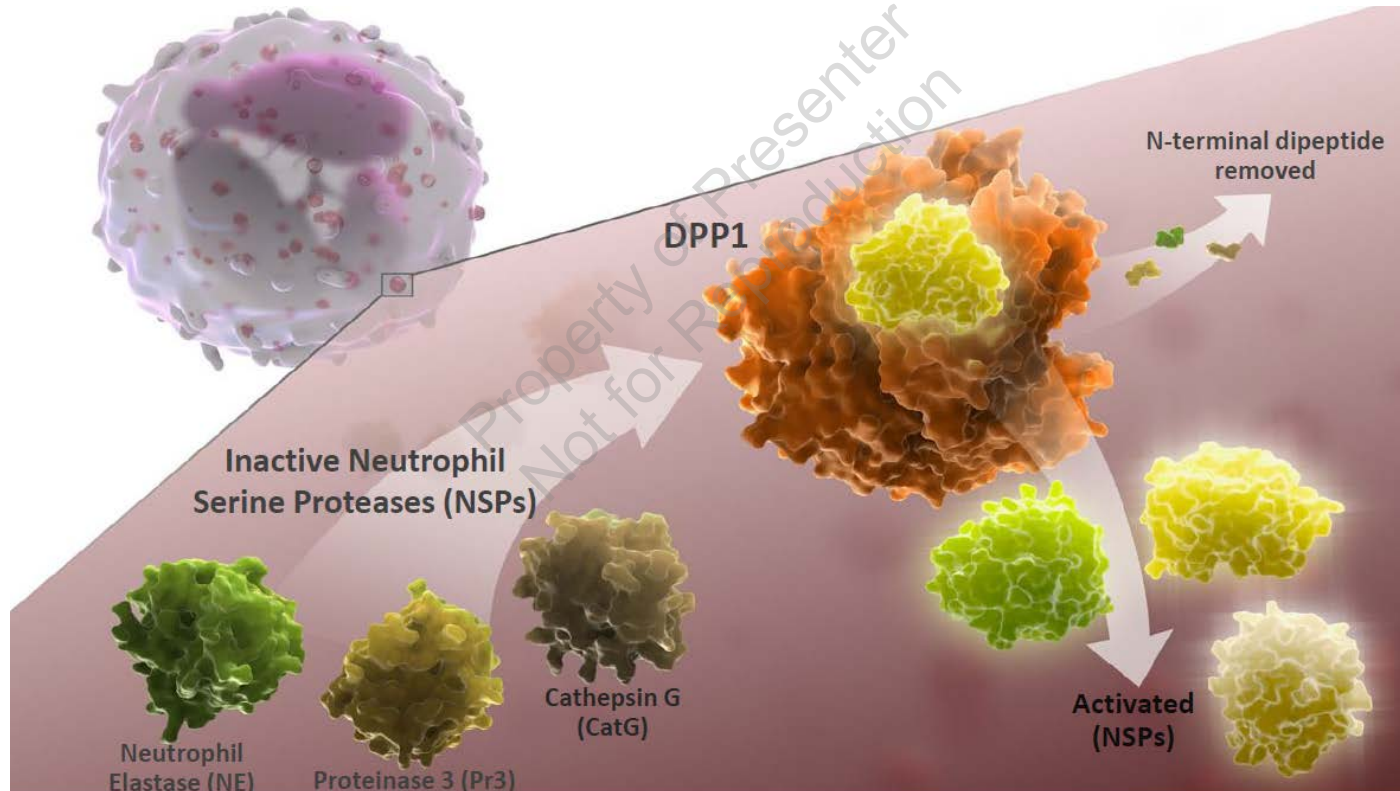
Neutrophils are impaired compared to normal hosts



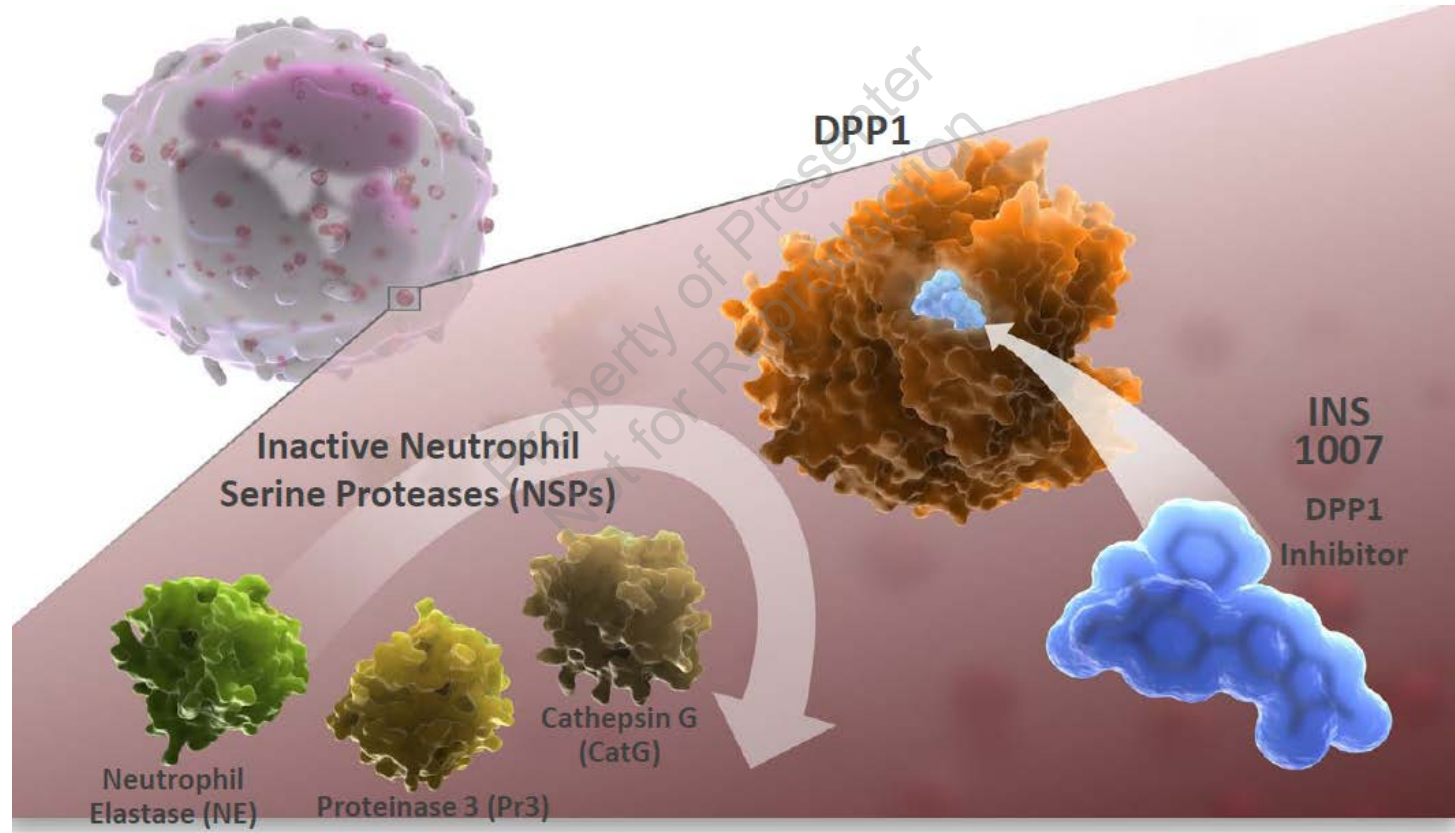
Blood neutrophils from bronchiectasis patients have:

- ✓ Increased activation & degranulation, even in the stable state and irrespective of disease severity
- ✓ Impaired phagocytosis
- ✓ Delayed apoptosis

Activation of serine proteases



Activation of serine proteases

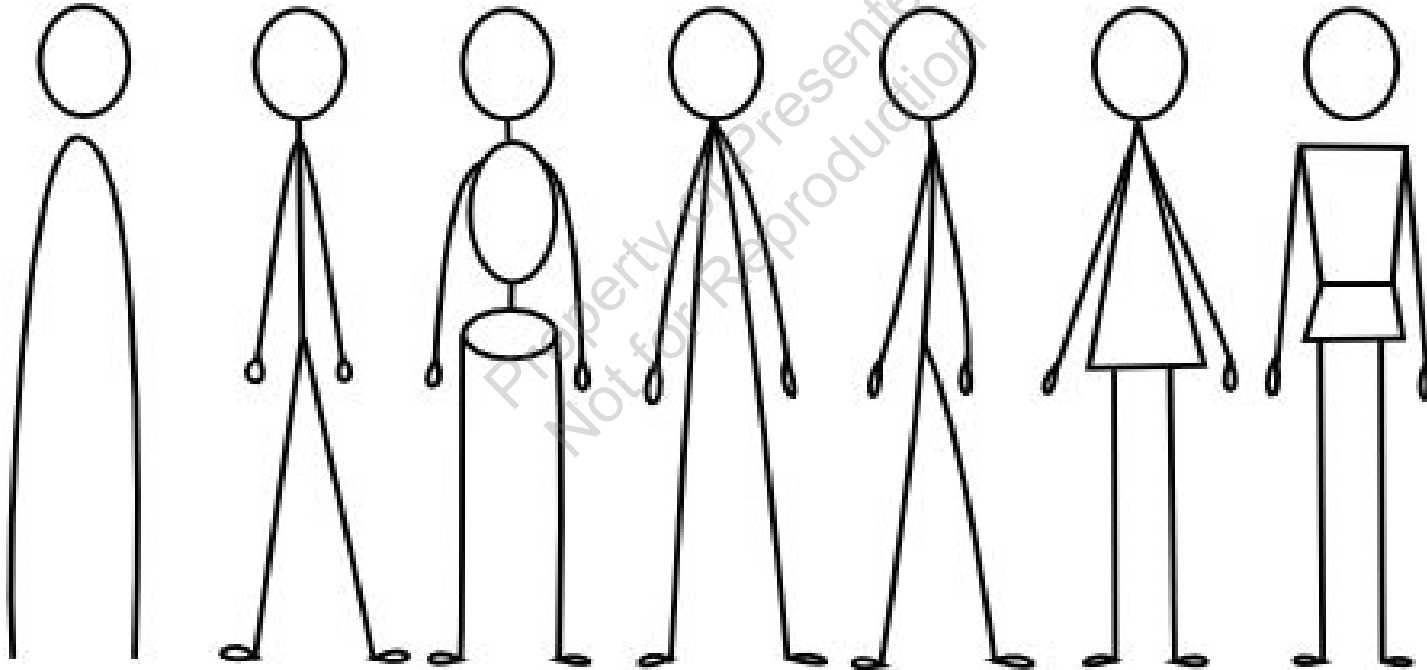


The Willow Study

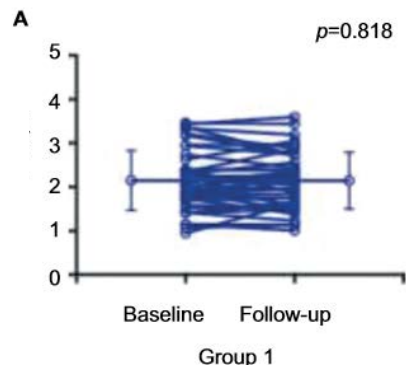
Assessment of INS 1007 in Subjects with Bronchiectasis

- Phase 2, Randomized, double-blind, placebo controlled, multi-center Study
 - **Once daily oral tablet, administered for 24 weeks**
 - **Primary outcome: time to first pulmonary exacerbation**
 - **Secondary outcomes: exacerbation frequency; QOL; FEV1; sputum Neutrophil Elastase**
- Initial data expected early 2020
- <https://clinicaltrials.gov/ct2/show/NCT03218917>

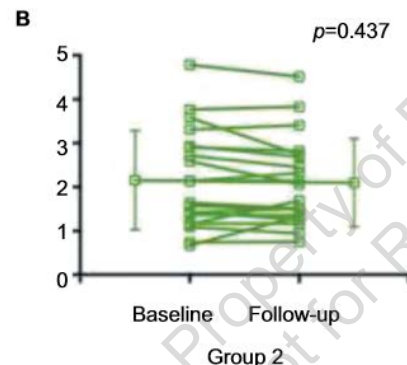
Bronchiectasis Phenotypes



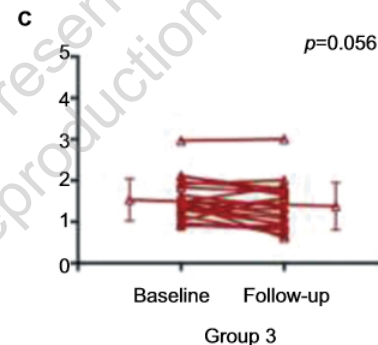
Concomitant NTM and *Pseudomonas aeruginosa* Decrease in FVC



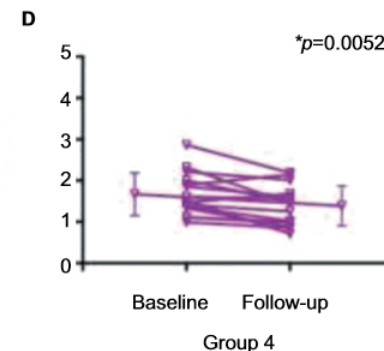
Negative for NTM
& *Pseudomonas*



NTM only

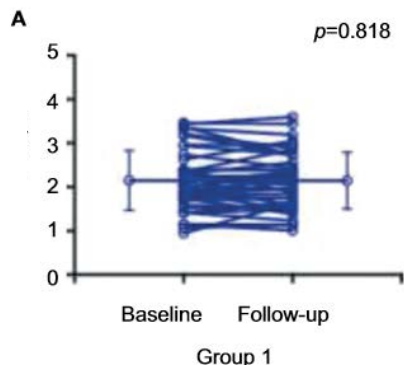


Pseudomonas
only

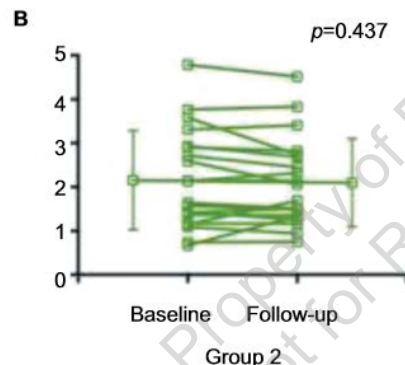


Both NTM &
Pseudomonas

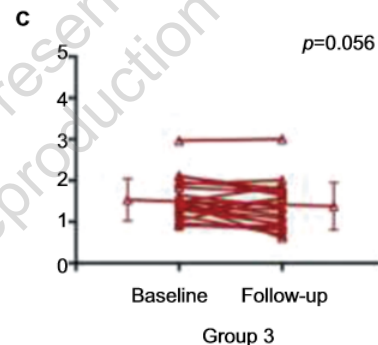
Concomitant NTM and *Pseudomonas aeruginosa* Decrease in FVC



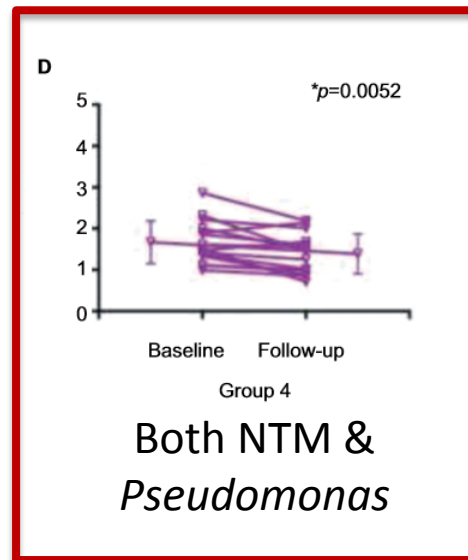
Negative for NTM
& *Pseudomonas*



NTM only

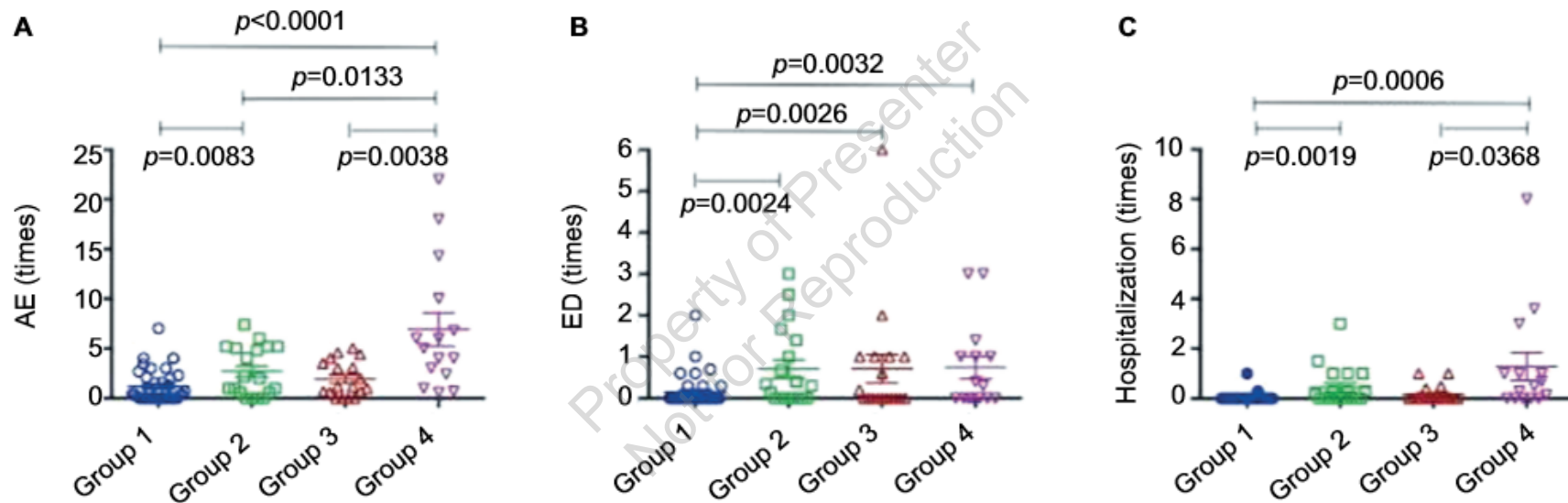


Pseudomonas
only



Both NTM &
Pseudomonas

Concomitant NTM and *Pseudomonas aeruginosa*



Group 1 no NTM / no *Pseudomonas*

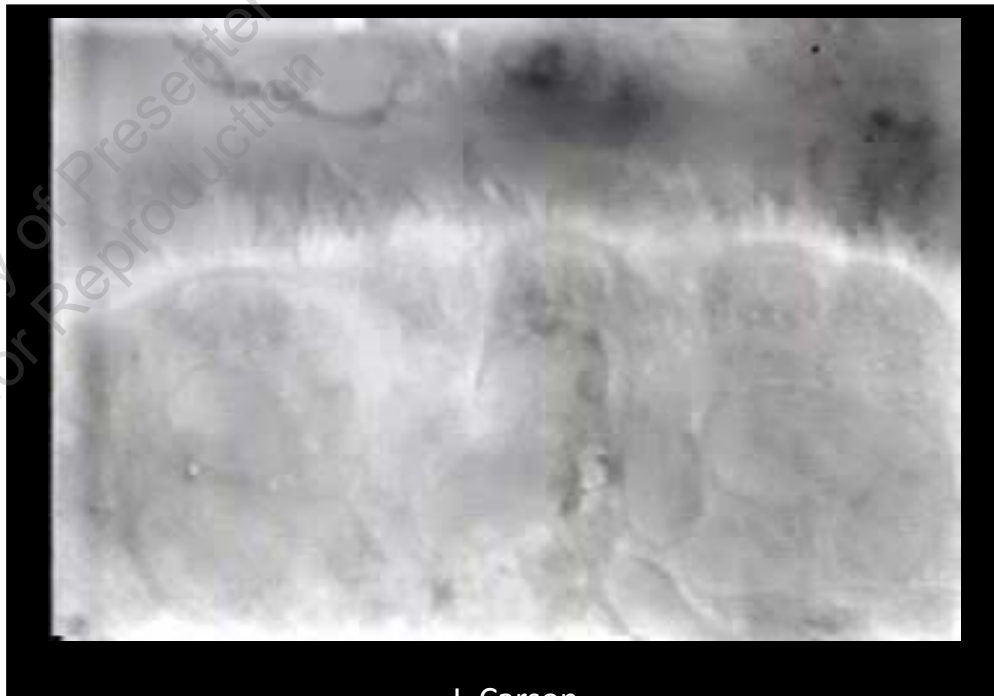
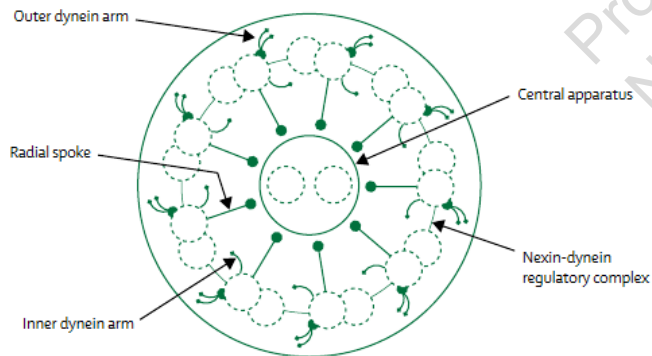
Group 2 NTM only

Group 3 *Pseudomonas* only

Group 4 NTM & *Pseudomonas*

Normal Cilia

- In healthy lungs, cilia beat at a mean frequency of 11-13 Hz
- Propelling mucus up the airways at 4-5 mm/min⁻¹



Cilia motion of a patient with absent inner dynein arms



Clinical features of primary ciliary dyskinesia

Features	Comments	Sensitivity	Specificity
Unexplained Neonatal Respiratory Distress	Term gestation Supplemental oxygen > 1 d No meconium aspiration	57%	89%
Chronic Cough	Year round Wet cough Began < 6months of age	62%	74%
Chronic Nasal Congestion	Year round Began < 6 months of age	74%	60%
Situs inversus totalis		46%	92%

Diagnostic evaluation for PCD

Features
Unexplained Neonatal Respiratory Distress
Chronic Cough
Chronic Nasal Congestion
Situs inversus totalis

Pathophysiologic / Diagnostic Criteria

- ✓ **Low nasal nitric oxide (<77 nL/min)**
- ✓ Ultrastructural abnormalities of cilia on electron microscopy
- ✓ Homozygosity of disease-causing variant on genetic testing

Diagnostic evaluation for PCD

Features
Unexplained Neonatal Respiratory Distress
Chronic Cough
Chronic Nasal Congestion
Situs inversus totalis

Pathophysiologic / Diagnostic Criteria

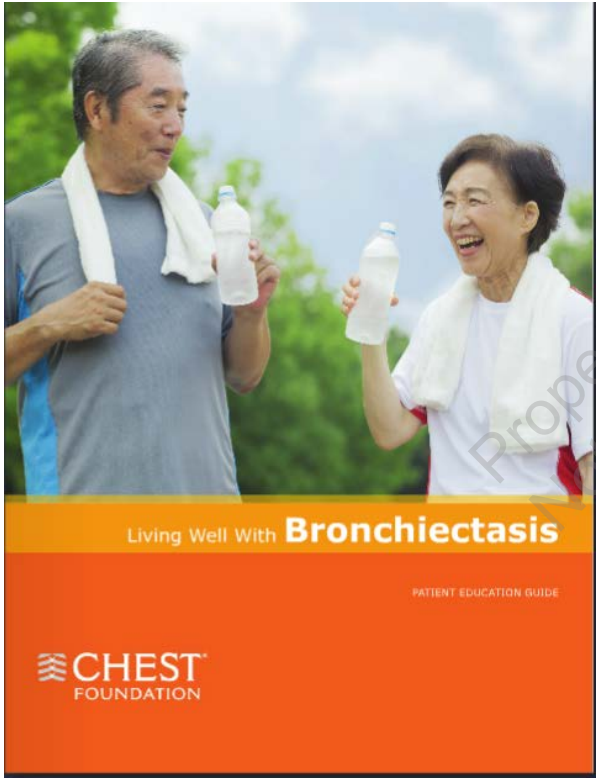
- ✓ **Low nasal nitric oxide (<77 nL/min)**
- ✓ Ultrastructural abnormalities of cilia on electron microscopy
- ✓ Homozygosity of disease-causing variant on genetic testing



Bronchiectasis in Irish Wolfhounds



Patient Resources



Thank you

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