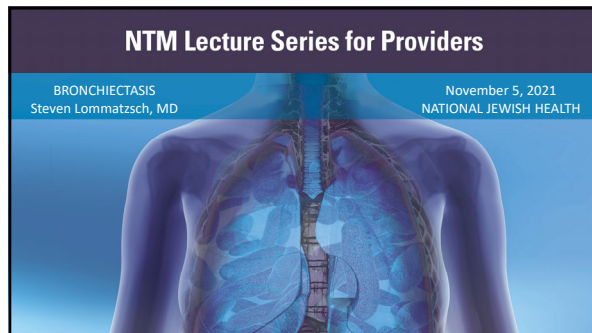
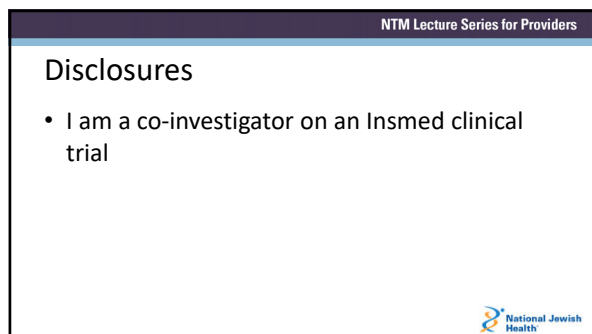
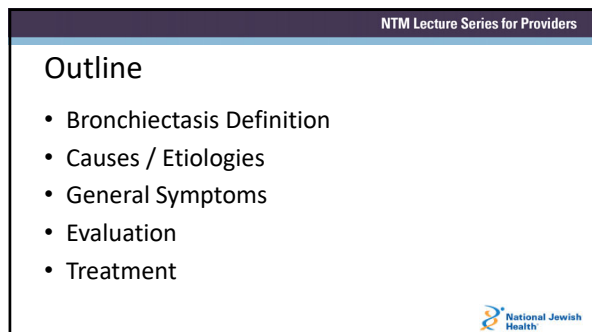


Bronchiectasis







Bronchiectasis

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Bronchiectasis Definition

- Abnormal dilatation (Greek ektasis) of the bronchi
 - Broncho-arterial ratio > 1 to 1.5 when comparing the internal airway lumen/adjacent pulmonary artery
 - Thickened walls from inflammation
 - Chronic and irreversible
- Estimated 350,000 – 500,000 adults in the US
- More common in women and increases with age

Weycker, D. et al. Chron Respir Dis. 2017;14(4):377-384

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Bronchiectasis Definition

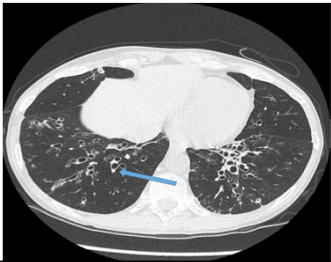
- How about the pediatric patient?
 - Broncho-arterial ratio of the inner airway diameter as compared to the outer vessel diameter (BAR) should be > 0.80
 - As age increases, so does the airway diameter
 - Children typically have 0.49-0.58 as normal BAR; and the upper limit of normal is the mean plus twice the standard deviation (0.76)
 - More viewed as a clinical syndrome
 - Persistent episodes ($>3/\text{yr}$) of chronic (>4 weeks) wet cough

Chang, A. et al. Bronchiectasis in children: diagnosis and treatment. Lancet 2018; 392: 866-79

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Bronchiectasis Appearance



<https://bronchiectasis.com.au/wp-content/uploads/2012/08/00475.png>

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[illegible]

Bronchiectasis

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General Symptoms


- Chronic cough (98%)
- Chronic sputum production (78%)
- Shortness of breath (62%)
- Fatigue (43%)
- Hemoptysis (27%)
- Wheezing (20%)



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Evaluation


<ul style="list-style-type: none">• History and Physical• HRCT of chest• PFTs• CBC and diff, IgG, IgA, and IgM• Rheumatoid factor/CCP, SSA, SSB• IgE (initial per BTS)• Aspergillus precipitins (initial per BTS)• IgG subclasses• A1AT level/genotype• Sinus CT	<ul style="list-style-type: none">• Sputum bacterial, mycobacterial and fungal cultures• Bronchoscopy with endobronchial biopsy and BAL• Testing for PCD and CF (CF is first line per BTS if under 40yo)• Antibody titers to pneumococcal vaccination (initial work-up per BTS)• Aspiration and GERD evaluation
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Treatment Outline


- Airway clearance
- Chronic macrolide therapy
- Inhaled antibiotics



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Treatment


- Always first try and identify cause and treat
 - Treat underlying disease
 - Infection: TB, NTM, etc.
 - Immunodeficiency states: CVID
 - Aspiration: oropharyngeal, GERD
 - Allergic Bronchopulmonary Aspergillosis (ABPA)
 - Rheumatologic/inflammatory disease: RA, Sjogren's, IBD
 - Alpha-1 Antitrypsin deficiency



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Treatment Goals

- Goals of Chronic Maintenance Regimen
 - Reduce symptoms and improve quality of patient life
 - Prevent exacerbations
 - Slow or stop disease progression and lung function decline




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3 Cornerstones of Treatment

1. Airway clearance
2. Airway clearance
3. Airway clearance

Amazingly this cornerstone is often forgotten and overlooked!




Bronchiectasis

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Treatment: Airway Clearance

- Recommended
 - Use one to two times per day
 - Short acting Beta-agonist prior to treatments
 - Mechanical Airway Clearance
 - Hypertonic Saline Nebulization
 - Aerobic Exercise is a great form of airway clearance
- Not Recommended
 - Dornase alpha nebulization ^(1, 2)
 - Routine use of anticholinergics – unless there is another indication

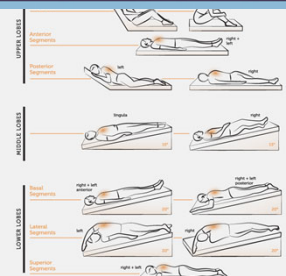
(1) O'Donnell AE, et al. Treatment of Idiopathic Bronchiectasis with Aerosolized Recombinant Human DNase. CHEST. 1998;113(5): 1329-1334.



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Treatment: Airwa

- Mechanical Clearance
 - Postural drainage
 - Manual percussion
 - Flutter valve devices ⁽³⁾
 - Vest-type mobilization devi
- Hypertonic saline
 - Normal saline ⁽⁵⁾
 - 3%, 7%, and 10% ⁽⁶⁾




(6) Nicolson, CHH, et al. The Long Term Effect of Inhaled Hypertonic Saline

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Treatment: Reducing Inflammation

- Chronic Macrolide Therapy
 - Benefits:
 - Proven to decrease exacerbations → PIVOTAL TRIALS
 - EMBRACE ⁽²⁾
 - SAAT ⁽³⁾
 - BLESS ⁽⁴⁾
 - Proven to reduce sputum production
 - Proven to improve FEV1 and attenuate its decline
 - Risks:
 - Associated with increased risk of bacterial resistance - NTM
 - Prolonged QTc
 - Hearing decrements




Bronchiectasis

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Treatment: Reducing Inflammation

- Chronic Macrolide Effects
 - Reduction of biofilms
 - Decreasing neutrophil activation/migration
 - Promotion of gastric emptying




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Treatment: Reducing Inflammation


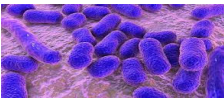
- Recommended
 - Chronic macrolide therapy in those with frequent exacerbations ⁽¹⁰⁾
- Not Recommended
 - Routine daily use of systemic steroids; unless there is another indication ⁽¹¹⁾
 - Routine use of inhaled steroids; unless there is another indication ⁽¹²⁾
 - Ibuprofen; no established role in non-CF bronchiectasis
 - Chronic daily statins ⁽¹³⁾



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Treatment: Inhaled Antibiotics

- Inhaled antibiotic therapy: Meta-analysis ⁽¹⁴⁾
 - Proven to eradicate bacteria from sputum
 - Proven to reduce sputum bacterial load
 - Proven to help reduce risk of acute exacerbations




<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3815121/> <http://www.medicalnewstoday.com/articles/323215.php>

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Treatment: Inhaled Antibiotics


- Eradication antibiotic therapy for Pseudomonas
 - Pseudomonas is associated with patients having more daily symptoms, exacerbations and FEV1 decline ^(15, 16)
 - The ERS guidelines suggest eradication attempt of a new Pseudomonas isolation
 - There are different regimens
 - Inhaled antibiotic after IV antibiotic course
 - Inhaled antibiotic with oral antibiotic



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Treatment: Inhaled Antibiotics


- Inhaled antibiotic therapy agents
 - **Tobramycin**: decrease sputum Pseudomonas ⁽¹⁷⁾, decreased exacerbations ⁽¹⁸⁾, improved symptoms ⁽¹⁹⁾
 - **Gentamycin**: reduced sputum bacteria, reduced exacerbations ⁽²⁰⁾
 - **Colistin**: reduced sputum bacteria, improved symptoms, and longer time to median time to exacerbation ⁽²¹⁾
 - **Aztreonam**: one study with small change in symptom score ⁽²²⁾
 - **Amikacin**: now FDA approved for nontuberculous mycobacterial infections ^(23, 24)
 - **Ciprofloxacin**: not available in the US



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Treatment: Inhaled Antibiotics

- If Pseudomonas is *present*, the ERS recommends antibiotic therapy for patients experiencing ≥ 3 exacerbations per year
 - If Pseudomonas aeruginosa (PSA) is present, then start chronic INHALED antibiotic.
 - If Pseudomonas is present and patient is intolerant or can not take inhaled antibiotic, then chronic ORAL macrolide recommended.
 - If Pseudomonas is present and patient is on inhaled antibiotic but still having exacerbations, then ADD a chronic ORAL macrolide.



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Future Treatments

- Developing ways to increase compliance with current therapies
- Neutrophil elastase (NE) inhibitor therapy**
- CXCR2 antagonism therapy to decrease neutrophils
- New inhaled antibiotic therapy
- Novel antimicrobials based on the peptide protegrin

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Phase 2 Trial of DPP-1 Inhibitor

- Patients with bronchiectasis have frequent exacerbations that are thought to be due to neutrophilic inflammation
- Activity and quantity of neutrophil serine proteases (NSPs), including neutrophil elastase, are increased in the sputum of patients with bronchiectasis at baseline and increase further during exacerbations
- NSPs are activated during neutrophil maturation in the bone marrow by dipeptidyl peptidase 1 (DPP-1)
- Brensocatib (INS1007) is an oral reversible inhibitor of DPP-1

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

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Brensocatib in Bronchiectasis

Study met its primary endpoint / outcome

Brensocatib prolonged time to first exacerbation c/w placebo:

10 mg ($p = 0.03$)

25 mg ($p = 0.04$)

Risk of exacerbation was approximately 40% lower than with placebo

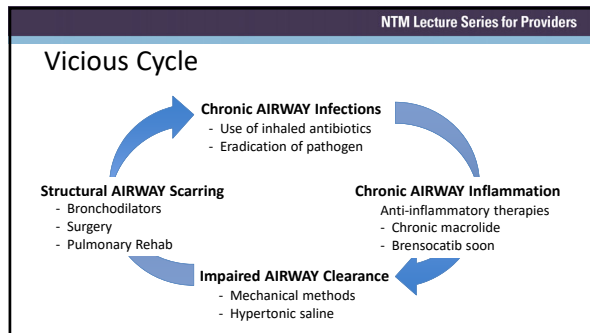
Brensocatib is currently being evaluated in a Phase 3 randomized, placebo-controlled study (ASPEN)

Cumulative No. of Events/No. at Risk	0/82	3/79	4/76	9/72	11/69	13/66	16/62	18/60	19/59	21/57	24/54	25/52	26/4
10-mg Brensocatib	0/82	4/76	16/71	16/70	19/64	21/60	22/58	23/57	24/56	26/52	26/52	28/49	29/10
Placebo	0/82	9/76	12/72	15/69	19/64	21/60	22/58	23/57	24/56	26/52	26/52	28/49	29/10

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

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Bronchiectasis



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Take Home Points


- Airway clearance is a must!
- Get sputum cultures at regular intervals.
- Chronic macrolide therapy for those experiencing recurrent exacerbations with or without chronic *Pseudomonas aeruginosa* (PSA).
- Inhaled antibiotics for:
 - Patients with PSA and recurrent exacerbations



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Thank You

- Any questions?



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