### **Respiratory Institute**





# BRONCHIECTASIS Evaluation, Clinical Course, Update

Evaluation, Clinical Course, Inflammation and Treatment

OCTOBER 16, 2022 | NASHVILLE, TN



# Thank You!

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### Faculty

- Charles Daley, MD discloses that he is on an advisory board for AN2, Hyfe, Insmed, Paratek, Matinas and Spero; an investigator for AN2, Insmed and Paratek.
- Jeffrey Hoag, MD does not have any relevant financial relationships to disclose.
- Steven Lommatzsch, MD does not have any relevant financial relationships to disclose.
- Sarah Taimur, MD does not have any relevant financial relationships to disclose.

### **Planners and Reviewers**

- Meghan Brenner does not have any relevant financial relationships to disclose.
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### Faculty Introductions



#### Charles L. Daley, MD

Chief, Division of Mycobacterial & Respiratory Infections Professor Department of Medicine National Jewish Health Denver, CO



#### Steven E. Lommatzsch, MD

Associate Professor of Medicine Director of the Non-CF Bronchiectasis Program Division of Pulmonary, Critical Care Department of Medicine National Jewish Health Denver, CO



#### Jeffrey B. Hoag, MD

Associate Professor of Medicine Section Chief, Jefferson Northeast Division of Pulmonary, Allergy and Critical Care Medicine

The Jane and Leonard Korman Respiratory Institute –

Jefferson Health and National Jewish Health Sidney Kimmel Medical College, Thomas Jefferson University Philadelphia, PA



#### Sarah Taimur, MD

Associate Professor of Medicine Division of Infectious Diseases The Mount Sinai – National Jewish Health Respiratory Institute Icahn School of Medicine at Mount Sinai New York, NY



# Learning Objectives

### Upon completion of this activity, participants should be able to:

- Review bronchiectasis burden, etiologies, and best practice evaluation strategies.
- Describe the clinical course and progression of bronchiectasis.
- Describe the role of neutrophilic inflammation in patients with bronchiectasis.
- Identify current and emerging treatments for patients with bronchiectasis.



### Welcome, Overview and Epidemiology

#### Steven E. Lommatzsch, MD

Associate Professor of Medicine Director of the Non-CF Bronchiectasis Program Division of Pulmonary, Critical Care & Sleep Medicine Department of Medicine National Jewish Health Denver, CO





- This program consist of four sections with a unifying clinical case scenario throughout the entire presentation.
- The program will have several video animations that help to visualize important points.
- At the end, there will be time for questions to afford the audience to participate and obtain clarification on any information presented.



## Epidemiology and Burden of Disease

- Estimated that 350,000 to 500,000 adults in the US have the condition
  - However, higher estimated prevalence are continually seen with ongoing publications into this field: Henkle et al. CHEST 2018. showed a prevalence of 701 per 100,000 patients
- The condition is twice as common in women than men
- The disease increases in prevalence with increasing age
- The mean frequency of exacerbations in cohorts of patients from specialist clinics is between 1 and 3 per year
- Mean annual hospitalization rates per patient, reported in six studies, ranged from 0.3–1.3
- A US study suggested treatment for bronchiectasis resulted in additional expenditures of \$630 million annually
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# **Our Case Introduction**

- Chief Complaint: "I can't get rid of this cough"
- 52-year-old male with history of asthma during his childhood that presented for further evaluation of a chronic cough that has plagued him the past 30 years. He recalls getting repeated sinus infections and recurrent bouts of bronchitis intermittently throughout his life.







# Our Patient's History

- PAST MEDICAL HISTORY:
  - Asthma
  - Chronic Sinusitis requiring surgery
  - No other surgeries

- FAMILY HISTORY:
  - Diabetes
  - Hypertension
  - COPD
  - Myocardial infarction

- SOCIAL HISTORY:
  - Non-smoker
  - Married; no children
  - Lawyer
  - No hot tub at home
  - No pets





### **Evaluation and Diagnosis**

### Sarah Taimur, MD

Associate Professor of Medicine Division of Infectious Diseases The Mount Sinai – National Jewish Health Respiratory Institute Icahn School of Medicine at Mount Sinai New York, NY





### Outline

### Overview

- Bronchiectasis definition
- Etiologies
- Clinical presentation
- Evaluation



# **Bronchiectasis Definition**

- Bronchial widening leading to a dilated airway larger than its associated blood vessel, which causes tortuosity of the bronchi and a propensity for infection
  - Chronic, irreversible, abnormal dilatation (Greek ektasis) of the bronchi
    - Bronchoarterial ratio >1 to 1.5 (internal airway lumen/adjacent pulmonary artery)
    - · Thickened walls from inflammation
- How about pediatric patients?
  - 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 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)
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# **Bronchiectasis Definition**

 Chronic and Irreversible bronchial dilatation; bronchoarterial ratio >1 to 1.5 - internal airway lumen/adjacent pulmonary artery







### Representative CT images for Bronchiectasis Types

### Saccular/cystic

### Cylindrical/tubular

### Varicose







# **Bronchiectasis Etiologies**

- <u>Congenital:</u>
  - Tracheobronchomegaly
  - Cartilage deficiency
  - Pulmonary sequestration
  - Yellow nail syndrome
  - Young's syndrome
  - Alpha-1 antitrypsin Def
  - Primary ciliary dyskinesia
  - Cystic Fibrosis
  - Other:
    - ABPA

- Immunodeficiency:
  - Hypogammaglobulinemia
  - CLL
  - Chemo
  - Immunosuppression
- Post infectious:
  - Bacteria
  - Mycobacterium
  - Aspergillus
  - Viruses

### Rheumatologic:

- RA
- SLE
- Sjögren's syndrome
- Relapsing polychondritis
- IBD
- Aspiration/Inhalation:
- Chlorine
- Overdoses
- Foreign bodies Respiratory Institute





# **Bronchiectasis Etiologies**

- Most common etiologies excluding idiopathic
  - Post-infectious (26%)
  - COPD related (11%)
  - Connective tissue disease related (8%)
- Barriers to early diagnosis
  - Cough is common symptom to many pulmonary disorders
  - Early bronchiectasis is not always seen on chest X-ray
  - Lack of ordering CT scan, sputum cultures, and other testing
  - Misdiagnoses

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Aliberti et al. Eur resp J 2016; 47:1113-1122



### Distribution of Etiologies Across Clinical Phenotypes

	Cluster 1: "Pseudomonas"	Cluster 2: "Other chronic infection"	Cluster 3: "Daily sputum"	Cluster 4: "Dry bronchiectasis"	Overall p-value
Patients	179 (100)	273 (100)	373 (100)	307 (100)	
Idiopathic	46 (26)	86 (33)	131 (36)	110 (36)	0.09
Post-infective	63 (36)	54 (21)	96 (26)	77 (25)	0.004
COPD	21 (12)	29 (11)	50 (14)	20 (6.6)	0.03
Connective tissue disease	10 (5.6)	26 (9.8)	26 (7.1)	27 (8.9)	0.377
Immunodeficiency	11 (6.2)	17 (6.4)	14 (3.8)	14 (4.6)	0.436
ABPA	10 (5.6)	20 (7.6)	12 (3.3)	12 (3.9)	0.083
Asthma	2 (1.1)	10 (3.8)	8 (2.2)	15 (4.9)	0.071
Inflammatory bowel disease	3 (1.7)	6 (2.3)	12 (3.3)	3 (1)	0.233
Ciliary dysfunction	7 (4)	6 (2.3)	5 (1.4)	2 (0.7)	0.055
Aspiration	2 (1.1)	6 (1.9)	3 (0.8)	3 (1)	0.419
α <sub>1</sub> -antitrypsin deficiency	0 (0)	1 (0.4)	3 (0.8)	6 (2)	0.091
Congenital	0 (0)	2 (0.8)	3 (0.8)	0 (0)	0.284
Other	2 (1.1)	1 (0.4)	2 (0.5)	15 (4.9)	<0.001

Data are presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; ABPA; allergic bronchopulmonary aspergillosis.

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Aliberti et al. Eur resp J 2016; 47:1113-1122



### Sputum markers of inflammation among clusters of bronchiectasis



#### **Bronchiectasis clusters**

- 1: Pseudomonas
- 2: Other chronic infection
- 3: Daily sputum
- 4: Dry bronchiectasis

Vational Jewish

FIGURE 1 Sputum markers of inflammation among different clusters in the validation cohort: a) neutrophil elastase, b) myeloperoxidase (MPO), c) chemokine CXCL8 (interleukin (IL)-8)], d) tumour necrosis factor (TNF)- $\alpha$  and e) IL-1 $\beta$ . Bars indicate mean±sp. Cluster 1: "Pseudomonas"; cluster 2: "Other chronic infection"; cluster 3: "Daily sputum"; cluster 4: "Dry bronchiectasis".



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Aliberti et al. Eur resp J 2016; 47:1113-1122





- The patient has been treated for GERD, chronic rhinosinusitis, and asthma with continued cough that is progressing in frequency and sputum production.
- A chest X-ray is completed and demonstrates bronchial wall thickening with a nodule in the right lower lobe. A CT chest scan is obtained and demonstrates bronchiectasis with mucus plugging and lower lobe predominance. There are several nodules, and the recommendation is to repeat a scan in six months.
- Spirometry is done and reveals an FEV1 of 67% of predicted with an obstructive pattern.





### Evaluation

- 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

- 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





# **Diagnostic Clues on Imaging**

### **Upper lobe predominant**

- CF
- Sarcoidosis
- Pneumoconiosis/silicosis
- Tuberculosis









### **Diagnostic Clues on Imaging**

### Central

- ABPA
- NTM









# **Diagnostic Clues on Imaging**

### Lower lobe predominant

- PCD
- Hereditary Immunodeficiency
- AAT deficiency
- Chronic aspiration
- IPF/NSIP







# Management and Treatment Options

### Jeffrey Hoag, MD

Associate Professor of Medicine Section Chief, Jefferson Northeast Division of Pulmonary, Allergy and Critical Care Medicine The Jane and Leonard Korman Respiratory Institute – Jefferson Health and National Jewish Health Sidney Kimmel Medical College, Thomas Jefferson University Philadelphia, PA



# **Cornerstones of Management and Treatment**

- Providing Education and Setting Expectations
- Cause specific therapies
- Airway Clearance
- Antibiotics, Eradications, Pseudomonas & Chronic Macrolide Therapy
- Monitoring and follow-up



# Providing Education and Setting Expectations

- Clearly defining and discussing goals of chronic maintenance therapies
  - Improve quality of life and reduce symptoms
  - Prevent exacerbations
  - Slow / prevent disease progression and lung function decline





# Treating Underlying Cause(s)

- Allergic Bronchopulmonary Aspergillosis (ABPA)
- Alpha-1 Antitrypsin Deficiency
- Aspiration / GERD
- Cystic Fibrosis
- Immunodeficiency (CVID)
- Infection: (TB, NTM, etc.)
- Rheumatologic/Autoimmune/Inflammatory Diseases: RA, Sjogren's, IBD, etc.





### Airway Clearance

- Goals:
  - Get Mucus out
  - Decrease symptoms (cough / shortness of breath)
  - Decrease exacerbations and inflammation
- Methods:
  - Pharmacologic
  - Mechanical
  - Activity
- Sequencing: SABA -> Mucolytics/Adjuncts -> Airway Clearance -> Antibiotics (if appropriate)

### Cannot stress enough the importance of airway clearance as the cornerstone of treatment for bronchiectasis





### Mechanical Mechanisms

- Manual Chest Physiotherapy
- Active Cycle Breathing, Autogenic drainage, Huff Coughing
- Postural Drainage
- Positive expiratory pressure devices
- Oscillating devices, High-frequency chest wall oscillation, Flutter, Acapella devices
- Inspiratory muscle training

- At least daily...
- May need to ramp up intensity during exacerbations
- Choice of therapy based on patient characteristics and support
- Best to teach multiple modalities for varying situations
- Involvement of Respiratory Therapists is paramount





- Hypertonic saline (0.9%, 3%, 7%, 10%)
  - HR-QOL, 6MWT improvement, decrease healthcare utilization
- Bronchodilator therapy SABA before saline / airway clearance
- Not recommended in absence of other processes:
  - Dornase alpha (Pulmozyme; in absence of CF)
  - Inhaled or oral corticosteroids
  - Statins
  - Long-acting bronchodilators (in absence of COPD/Asthma)



### Activity Related Airway Clearance

- Aerobic training
- Strength training
- Pulmonary Rehabilitation
- Singing?





# **Our Patient's Treatment**



- His autoimmune, immunodeficiency, aspiration evaluation are unremarkable. His sweat test returns at 25 mmol/L from the right arm and 15 mmol/L from the left arm.
- Sputum cultures are obtained with each visit with a goal of 2-4 per year as surveillance.
- What should be considered for further evaluation?
  - The patient gets a nasal NO done that is very low at 25 nl/min
  - The patient gets a nasal scrape biopsy showing abnormal cilia structure
  - The patient's PCD genetic panel comes back positive for two genes with mutations



### **Our Patient's Sputum Culture**

- The patient's sputum culture does not reveal any Acid Fast Bacilli (AFB) or mycobacterium on culture. He does isolate Pseudomonas aeruginosa.
- The patient feels at his baseline in cough and mucus at the time of his culture, but he has had three courses of oral antibiotics in the past year for respiratory symptoms.





# Pseudomonas aeruginosa

• Pseudomonas is associated with...

More symptoms More exacerbations More rapid FEV1 decline More imaging progression of disease More hospitalizations Worsening of QOL

 Registries have shown Pseudomonas may be present in up to 1/3 of patients with bronchiectasis





# **Pseudomonas Eradication**

• ERS Guideline Recommendation:

### Eradication should be attempted for new Pseudomonas isolation

- Multiple strategies, none proven better than others
  - Most are 3 months protocols
  - Start with 2 intensive weeks of therapy:
    - IV antibiotics (beta lactam +/- aminoglycoside) or
    - Oral fluoroquinolone + IV antibiotics or
    - Oral fluoroquinolone
  - Followed by or concomitant with inhaled antibiotics to complete 3 months
    - Colistin Gentamycin Tobramycin







# Inhaled Antibiotics

- Proven to eradicate bacteria from sputum
- Proven to reduce sputum bacterial load
- Proven to help reduce risk of acute exacerbation
  - Aminoglycosides
    - Tobramycin: decreases Pseudomonas density and exacerbations, improves symptoms
    - Gentamycin: decrease sputum bacteria density and exacerbations
    - Amikacin approved for NTM infections
  - Colistin decrease sputum bacteria, improve symptoms, increase time to next exacerbation
  - Aztreonam improves symptom scores
  - Fluoroquinolones (Cipro / Levo)





# Macrolide Therapy as Anti-inflammatory

- Macrolides as anti-inflammatory
- Pros:
  - Decrease exacerbations
  - Reduces Sputum Production
  - Improve FEV1/Slow decline
  - Improve Quality of Life
- Cons:
  - Risk of bacterial resistance
    - NTM
  - Prolonged QTc
  - GI side effects
  - Hearing impairment

• Long-term Use of Antibiotics ERS Guideline Recommendation:

...should be attempted for patient with ≥3 exacerbations per year...

- Inhaled antibiotics (Pa)
- Macrolide
- Inhaled antibiotics and Macrolide
- Other oral antibiotics





# Monitoring and Follow-up

- Regular visits with symptom assessments
- Spirometry clinic based / home spirometry
- Sputum cultures (NTM, Gm + or bacteria, etc.)
- Imaging / CT imaging (radiographic progression)
- Re-education and goals discussions



### Exacerbation Management and Emerging Treatments

### **Charles Daley, MD**

Chief, Division of Mycobacterial & Respiratory Infections

Professor

Department of Medicine

National Jewish Health

Denver, CO





- The patient calls with increased cough, mucus production, and fatigue above his baseline for the past 3 days. He has no fever, but notices mild blood tinged sputum the past day.
- The patient reported repeated similar episodes prior to establishing care with you, and his Primary Care Provider usually prescribed amoxicillin that seemed to help.







# **Exacerbations of Bronchiectasis**

- Definitions of an exacerbation vary: Generally speaking, an exacerbation is a significant worsening of symptoms over several days which may include:
  - Increase in frequency of cough
  - Increase in sputum volume, viscosity and/or purulence
  - Shortness of breath
- Frequency and severity of exacerbations vary by study:
  - 1-3 exacerbations/year, 20-50% hospitalized/year, 25% frequent exacerbators
- More severe exacerbations are associated with lower quality of life, daily symptoms, lung function decline and increased mortality
- Exacerbations due to *Pseudomonas aeruginosa* are associated with worse quality of life, greater loss of lung function, bronchial and systemic inflammation and mortality

Polverino E, et al. Eur Respir J 2017;50:1700629 De La Rosa-Carrillo D, et al. Int J Tuberc Lung Dis 2020;26:581-583 Oscullo G, et al. Int J Tuberc Lung Dis 2022;26:605-611







### Treatment of Exacerbations

- European Bronchiectasis Guideline: We suggest acute exacerbations of bronchiectasis should be treated with 14 days of antibiotics (conditional recommendation, very low quality of evidence)
- Evidence base for the optimum duration of therapy is lacking
- Two studies have reported significant improvement in 24-hr sputum volume, bacterial clearance, C-reactive protein, incremental walk distance and SGRQ after receiving 14 days of IV antibiotics
- Target the organism isolated previously while waiting for new culture and susceptibility results

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Polverino E, et al. Eur Respir J 2017;50:1700629



### **Prevention of Bronchiectasis Exacerbations**



#### **Respiratory Institute**



Polverino E, et al. Eur Respir J 2017;50:1700629



# Macrolides – Individual Patient Meta-Analysis

- Three randomized studies (BATT, BESS, EMBRACE)
- N = 341 patients with NCFB
- Results:
  - Reduced frequency of exacerbations
    - Including in all subgroup analyses *including* those with *P. aeruginosa* and those with 1-2 exacerbations/year
  - Delayed time to first exacerbation
  - Improved quality of life (SGRQ)
  - 4-85% developed antimicrobial resistance

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Chalmers JD, et al. Lancet 2019;7:845-54

### Interrupting The Vicious Vortex The Role of Neutrophilic Inflammation



Flume PA, et al. Lancet 2018;392:880-890 Chalmers JD, et al. *Am J Respir Crit Care Med* 2017;195:1384-1393. Stockley R, et al. Respir Med 2013;107:524-533 Watz H, et al. Pulm Pharmacol Ther 2019;56:86-93

- Patients with bronchiectasis have frequent exacerbations that are usually associated with neutrophilic inflammation
- Neutrophils are the dominant inflammatory cell in the airway of most people with bronchiectasis
  - Raised levels of neutrophil serine proteases (NSPs) including neutrophil elastase (NE)
  - NSPs are activated during neutrophil maturation in the bone marrow by dipeptidyl peptidase 1 (DPP-1)
- NE levels are associated with disease severity, bacterial load, and clinical outcomes (exacerbations)
- Two studies using neutrophil elastase inhibitors were unsuccessful but small sample size, low doses, and included some without neutrophilic inflammation





### WILLOW Study - Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis



Primary Endpoint:

 Time to first bronchiectasis exacerbation

### Secondary Endpoints:

- Rate of exacerbations
- Change in QOL-B Respiratory Symptoms domain
- Change in postbronchodilator ppFEV1
- Change in sputum neutrophil elastase activity

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



# WILLOW Study – Primary and Secondary Outcomes



# T2-High Endotype (Eosinophilic Inflammation)

- 20-30% of patients with bronchiectasis have blood eos ≥ 300 cells/µl
- Anti-IL5 (mepolizumab) or anti-IL5ra (benralizumab) drugs associated with good treatment outcomes in severe eosinophilic asthmatic patients with co-morbid bronchiectasis
- Five patients with severe eosinophilic asthma who received either of the above two agents had a significant decrease in exacerbations up to 2 years of follow-up

Fitzgerald JM, et al. Lancet 2016;388:2128-2141 Ortega HG, et al. N Engl J Med 2014;371:1198-1207 Oriano M, et al. Biomed 2021;9:772 Shoemark A, et al. Am J Resp Crit Care Med 2022205:894-902



Jefferson

Health



### Phase 3 Studies

**MAHALE** - A Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, 52 Week, Phase III Study With an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab in Patients With Non-Cystic Fibrosis Bronchiectasis - **CLOSING** 

**ASPEN** - Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects With Non-Cystic Fibrosis Bronchiectasis - **ENROLLING** 





Clinicaltrials.gov



## **Emerging Therapies – Clinical Trials**

Drug		Phase	Status
CSL787	Nebulized, plasma derived immunogloulin	1	Recruiting
ARINA-1	Inhaled ascorbic acid, glutathione	2a	Recruiting
roflumilast	phophodiesterase-4 inhibitor	2	Recruiting
icenticaftor	CFTR potentiator	2	Recruiting
BI 1291583	cathespsin C inhibitor	2	Recruiting
mepolizumab	Anti-IL5	-	Recruiting
S-1226	Inhaled CO2 enriched air + Perflubron	2	Recruiting
BCG	TB vaccine	2	Recruiting
hypertonic saline, carbocysteine	mucolytic	3	Recruiting
AZD5069	CXCR2 antagonist	2	Completed





# SUMMARY

- Non-CF bronchiectasis is more common than identified
- Definition is irreversible damage to the airway leading to abnormal dilation (bronchoarterial ratio >1-1.5)
- Obtain CT scan, Spirometry and Sputum cultures; and base additional testing on clinical scenario and location of disease
- Treatment hinges on AIRWAY CLEARANCE
- Consider ways to decrease exacerbation rate with interventions like chronic macrolide or suppressive inhaled antibiotic
- New therapies are being studied and will hopefully soon be available, so phenotype patients to target cause and pathophysiology

