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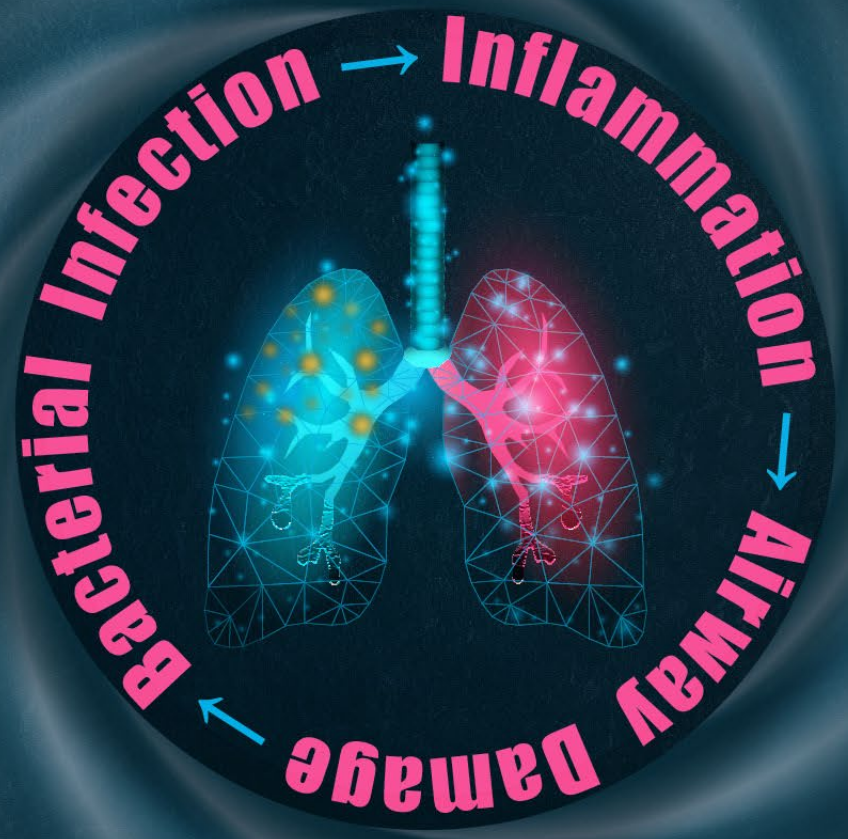
DISRUPTING THE VICIOUS VORTEX IN NCFBE:

The Evolving Role of Emerging Neutrophil Agents



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Mark L. Metersky, MD, has relevant financial relationships with Boehringer-Ingelheim, Insmed, Tactile Medical, Zambon (*Consultant*); AN2, Insmed, Renovion (*Other: Data Safety Monitoring Board*).

Timothy R. Aksamit, MD, has no relevant financial relationship(s) with ineligible companies to disclose.

Margaret Johnson, MD, has no relevant financial relationship(s) with ineligible companies to disclose.

Patient participating in this activity has no relevant financial relationship(s) with ineligible companies to disclose.

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Readily Diagnosing NCFBE: Addressing the Barriers and Implementing Clinical Practice Guidelines

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Patient Case Woody – Past Medical History

Initial Presentation

- Long history of bronchiectasis diagnosed in 1996 by open lung biopsy after multiple bouts of pneumonia

Sputum Culture

- MSSA/MAC initially
  - Never grew MAC again
- 2 years later, grew MSSA/*Pseudomonas* on multiple cultures

Airway Clearance

- Oscillatory PEP device BID

Treatment History

- Exacerbations responded well to levofloxacin
- Enrolled in inhaled mannitol trial – no benefit
- Grew *Pseudomonas* repeatedly
- Switched to inhaled tobramycin
  - Chronic sputum production completely remits
  - "Life changing"
  - Creatinine increased from 0.9 to 1.4
- Switched to inhaled aztreonam
  - Developed diffuse papular rash within several days
- Tried to enroll in liposomal ciprofloxacin trial – MSSA only so is a screen failure
- Did well on Augmentin 10 days each month for many years

MSSA: Methicillin-susceptible *Staphylococcus aureus*
MAC: *Mycobacterium avium* complex
PEP: Positive expiratory pressure
BID: Twice a day

Patient Case Woody – Recent History

Recent Presentation

- Lung function gradually declines

Airway Clearance

- Switched to high frequency chest wall oscillation vest

Sputum Culture and Treatment

- 2017 – grows *Nocardia* repeatedly with worsened symptoms. Treated and symptoms improved.
- Started chronic low-dose azithromycin (had avoided due to prior MAC isolation)
- Increased purulent sputum repeatedly growing *Achromobacter*

Patient Perspectives on Bronchiectasis

- How would you describe the feeling when you were diagnosed with bronchiectasis?
- Did you know what bronchiectasis was?
- How did bronchiectasis affect your quality of life?
- What challenges did you have with your bronchiectasis treatments, including airway clearance and antibiotics and how did you overcome them?
- Why did you decide to participate in bronchiectasis clinical trials?
- What advice do you have for healthcare professionals who provide care for patients with bronchiectasis?

Increasing Prevalence of Bronchiectasis in the United States

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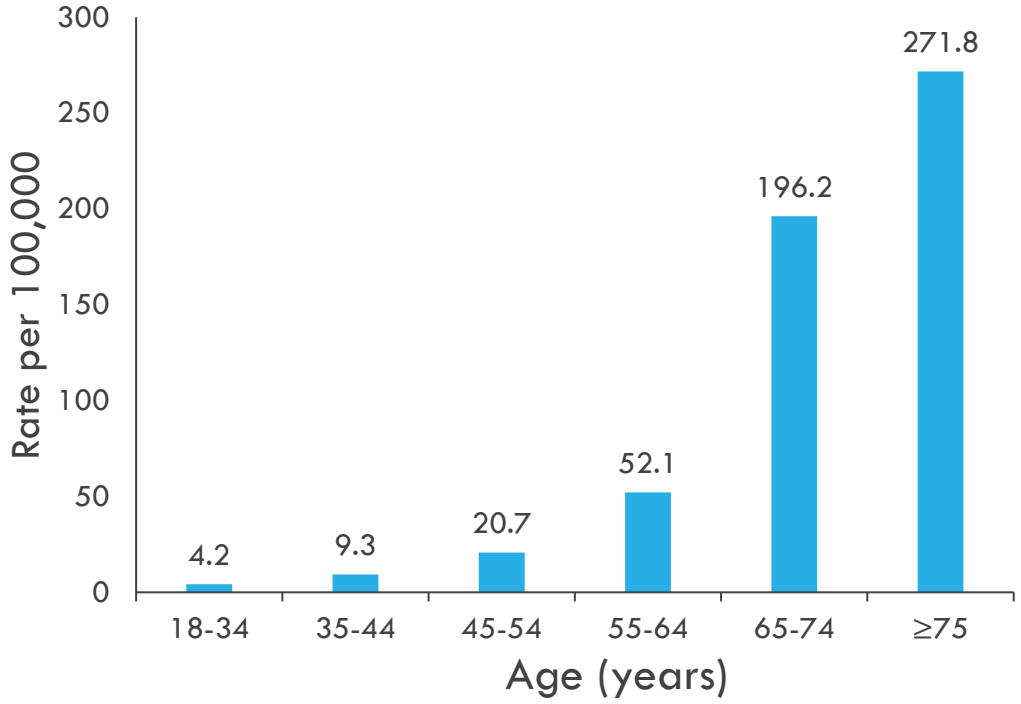
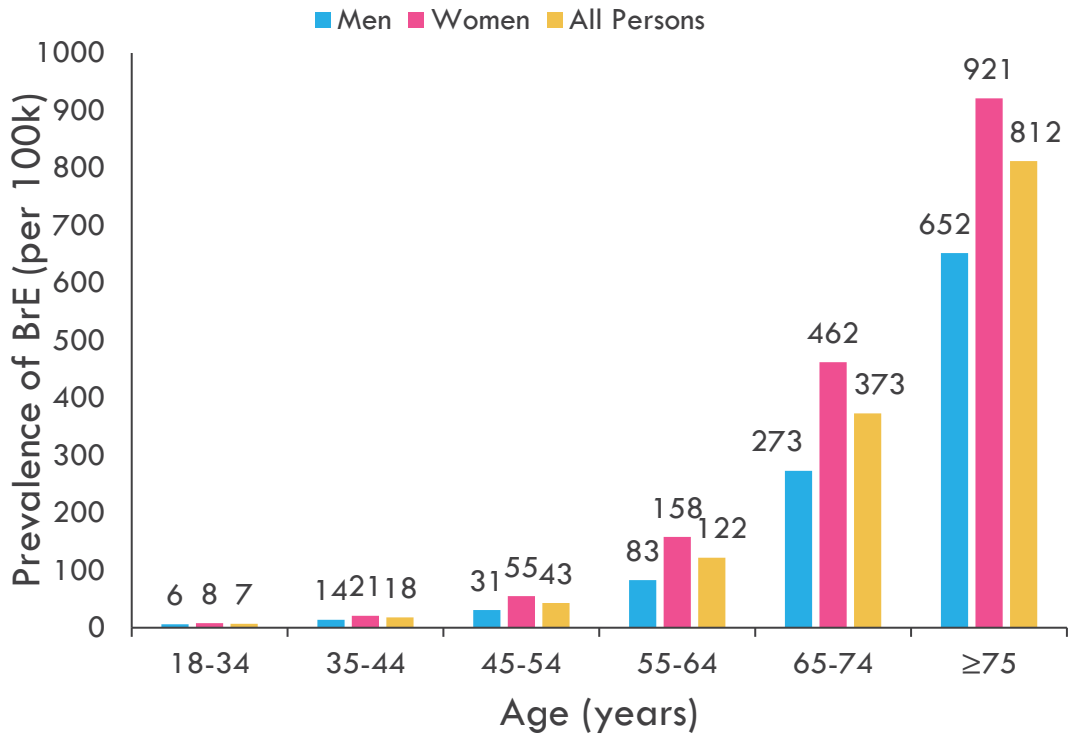
Estimated prevalence in 2001
~110,000



Estimated prevalence in 2013
~400,000



Weycker D, et al. *Clin Pulm Med*. 2005;12:205-209.
Weycker D, et al. *Chron Respir Dis*. 2017;14(4):377-384.

Increasing Prevalence of Bronchiectasis in the United States (cont'd)

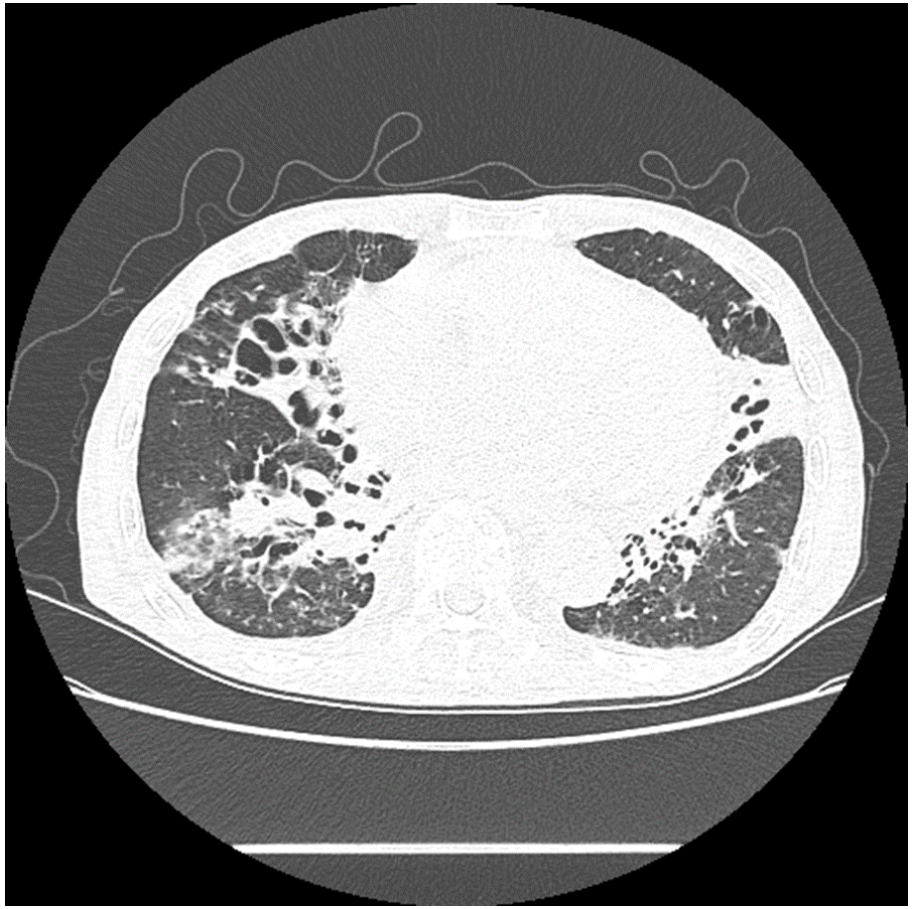
- 8.7% annual increase in bronchiectasis prevalence among Medicare population from 2000 to 2007
- 36% more common in females than males
- Minorities are under-represented in virtually all published cohorts of bronchiectasis patients in the United States[1]
  - There is no reason to suspect markedly lower rates of bronchiectasis in these populations
  - Again, speaks to underdiagnosis, especially in patients with poor access to specialized healthcare

Bronchiectasis Prevalence by Sex and Race/Ethnicity – 2000 to 2007[2]

1. Aksamit TR, et al. *Chest*. 2017;151(5):982-992.
2. Seitz AE, et al. *Chest*. 2012;142(2):432-9.

Delays in Diagnosis

- New patient I saw recently for “cough”
- CT ordered



Bronchiectasis Underdiagnosis/Delayed Diagnosis

- Mean time from symptom onset to diagnosis/referral
  - Ranges from 8 to 19 years[1-4]
- Underdiagnosis also indicated by marked increase in age-adjusted rates/prevalence of bronchiectasis over the last 1 to 2 decades[5]
  - In part due to "incidental finding" of bronchiectasis in patients who receive chest CT scanning
    - CT angiograms
    - Lung cancer CT screening

1. Nicotra M, et al. *Chest*.1995;108(4):955-961.
2. Shoemark A, et al. *Respir Med.* 2007;101(6):1163-1170.
3. Anwar GA, et al. *Respir Med.* 2013;107(7):1001-1007.
4. Giron RM, et al. *Chronic Resp Dis*. 2017;14(4):360-369.
5. Cai Q, et al. *Radiology*. 2022;304(2):437-447.

What leads to Underdiagnosis/Delays in Diagnosis?

- Limited awareness among non-pulmonologists
- Similarity to more common pulmonary conditions
  - COPD
  - Asthma
- Poor sensitivity of chest radiograph
- Distinguishing Characteristics
  - Onset in older adults (often distinguishes from asthma)
  - Chronic cough productive of ***purulent*** sputum
    - With COPD, sputum is usually not purulent *except* during exacerbations
  - Sputum cultures more commonly demonstrate unusual organisms, such as:
    - *Pseudomonas aeruginosa, Staphylococcus aureus*, other gram negatives, such as *Achromobacter, Stenotrophomonas*
    - Non-tuberculous mycobacteria, fungal species, especially molds
  - Chest pain or hemoptysis with exacerbations may be helpful (if present)

Clinical Suspicion of Bronchiectasis

- Suspect bronchiectasis in anyone with a chronic cough and sputum production or frequent respiratory infections
- Additional factors that should raise the index of suspicion in someone exhibiting symptoms include:
  - Daily sputum production
  - Rhinosinusitis
  - Fatigue
  - Hemoptysis
  - Difficult-to-treat asthma
  - Nonsmokers with "COPD"
  - Presence of *P. aeruginosa* or NTM in sputum

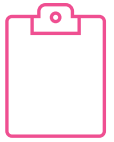
COPD: chronic obstructive pulmonary disease; NTM: nontuberculous mycobacteria

McShane PJ, et al. *Am J Respir Crit Care Med*. 2013;188(6):647-656.

Diagnostic Criteria for Bronchiectasis

CT Findings

- Defined by permanent dilatation of bronchi
- In one sense a strictly CT diagnosis
  - Airway inner diameter – artery diameter ≥1
  - Airway outer diameter – artery diameter ≥1
  - Lack of bronchial tapering
  - Visible airway within 1 cm of peripheral pleura
    - Can be false positives with atelectatic lung



Symptoms

- Proposed definition for use with **clinical trials**
- At least 2 of the following:
  - A cough most days of the week
  - Sputum production most days of the week
  - A history of exacerbations
- These symptoms do not define bronchiectasis. They define clinically significant bronchiectasis in a patient who has the CT findings.
- This definition is based on consensus, not evidence

Aliberti S, et al. *Lancet Respir Med*. 2022;10(3):298-306.

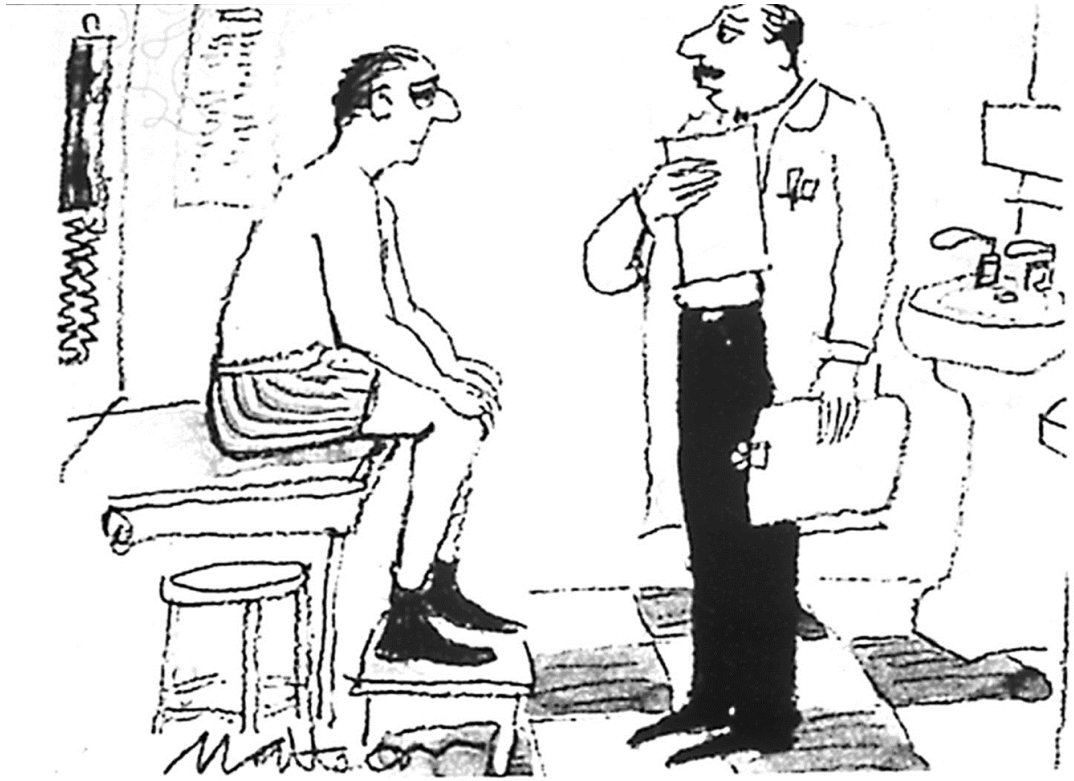
Clinical Caveats for Bronchiectasis Diagnostic Criteria

- Very reasonable for the purpose of **clinical trials**
- Should be used with caution for **clinical care,** in my opinion
- Plenty of patients present with only 1 symptom
  - A mostly dry cough without exacerbations is not unusual in early bronchiectasis
  - Would not want to ignore these patients until they progress
- Should also not be dogmatic about the presence of airway dilatation
- Persistent Bacterial Bronchitis
  - Patients who clinically have features of bronchiectasis, including chronic purulent sputum, unusual organisms but no airway dilatation
    - Often have underlying factors that lead to bronchiectasis, eg, immunosuppression
    - Likely is "pre-bronchiectasis"

Metersky ML, Mangardich A. *J Thorac Dis.* 2016;8(9):E974-E978.

Initial Diagnostic Evaluation of Bronchiectasis

- Approximately 40% of cases remain idiopathic despite extensive evaluation



"We have a lot more tests to go through before we can say for certain we don't know."

Etiologies of Bronchiectasis

Specific causes that often result in change in therapy

- Allergic bronchopulmonary aspergillosis
- Nontuberculous mycobacterial infection (eg, *Mycobacterium avium*)
- Immunodeficiency (eg, common variable immunodeficiency)
- Alpha-1-antitrypsin deficiency
- Gastroesophageal reflux
- Cystic fibrosis

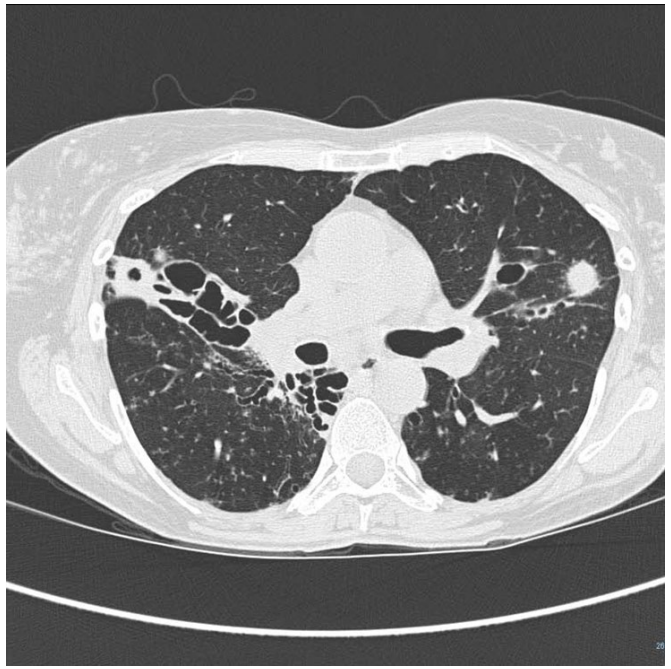
Other common causes

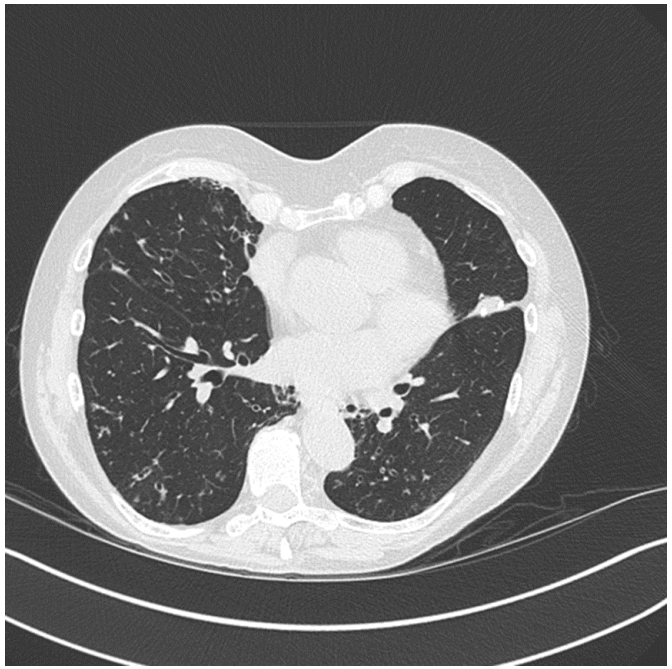
- Post-infectious (eg, severe pneumonia, pertussis, measles)
- COPD related
- Asthma
- Prior tuberculosis
- Autoimmune disease (eg, Sjogren's, ulcerative colitis)
- Primary ciliary dyskinesia
- Many other rarer conditions

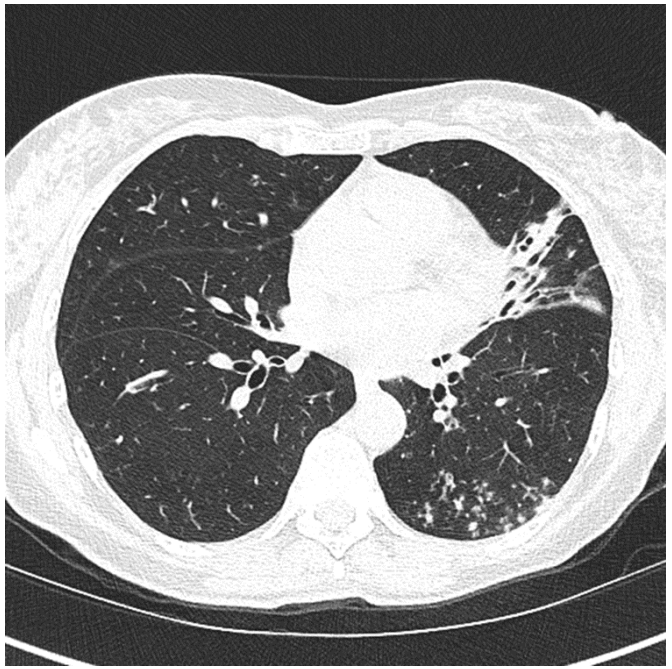
Approximately 20% will have an underlying diagnosis or condition identification of which may lead to a change in therapy

Metersky ML. *Clin Chest Med*. 2012;33(2):219-231.

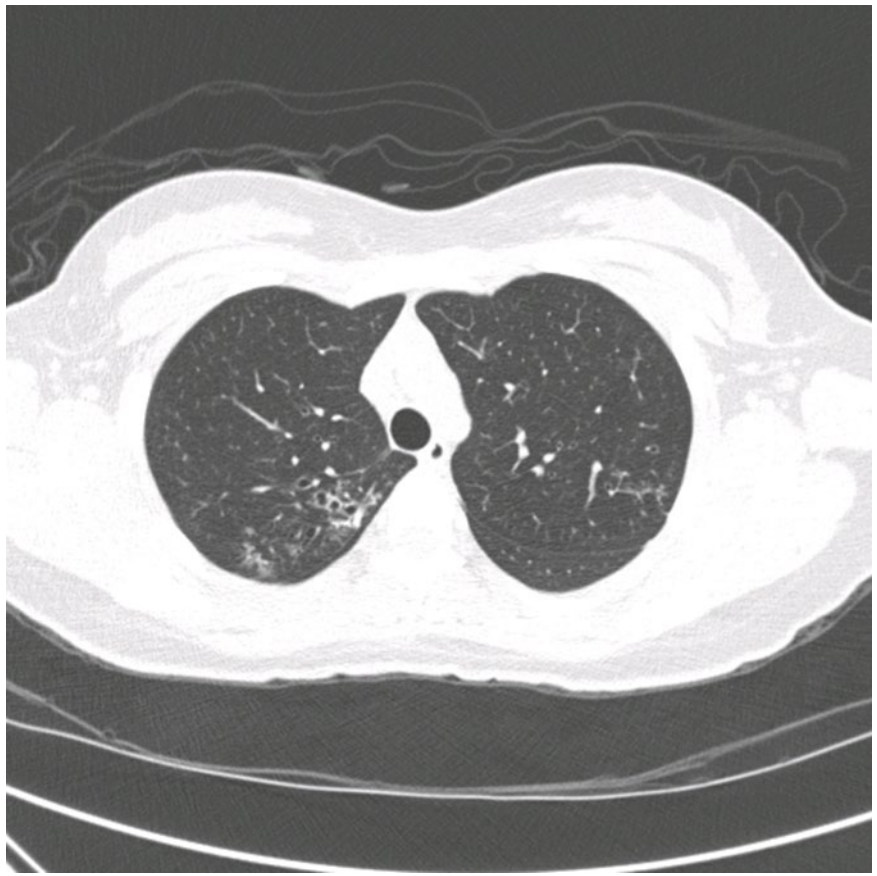
Initial Evaluation of Patients with Bronchiectasis-Imaging Clues

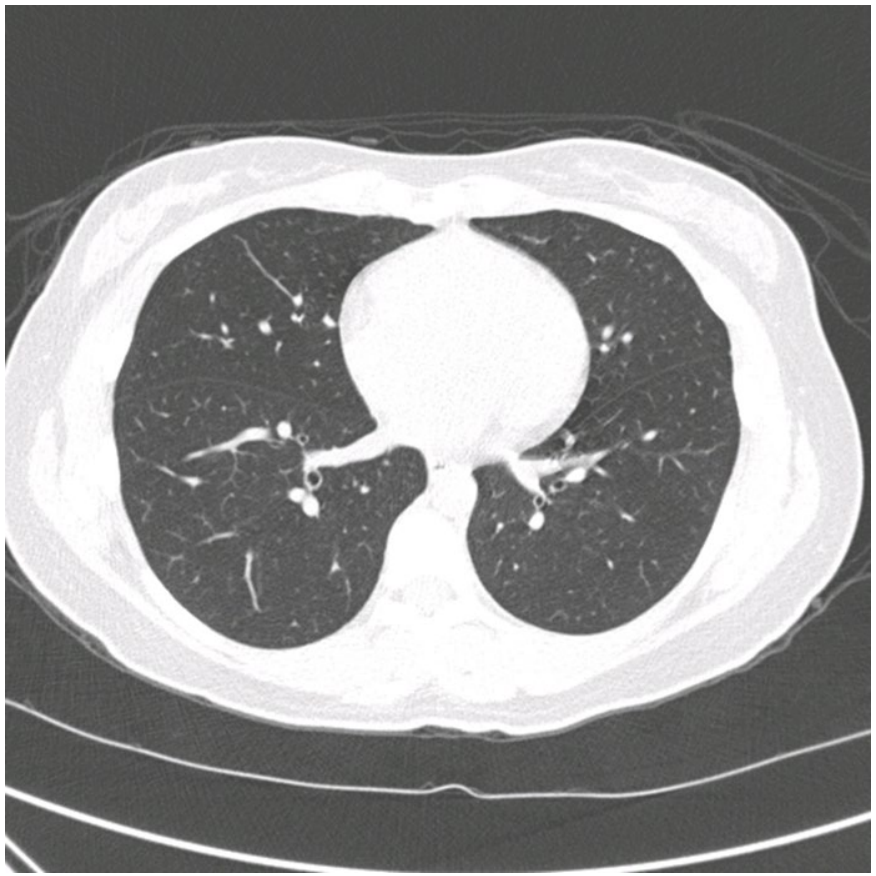






Initial Evaluation of Patients with Bronchiectasis-Imaging Clues (cont'd)





Recommended Initial Testing for Bronchiectasis Patients

Recommended for all patients[1]	Recommended for most patients without a specific diagnosis[1]
• Pulmonary function testing with bronchodilator responsiveness ±ABG • Chest radiograph • High-resolution CT of the chest • Sputum for bacterial, mycobacterial, and fungal culture • CBC with differential • Quantitative immunoglobulin levels (IgG, IgA, IgM) • IgE level	• Alpha-1-antitrypsin level • Testing for cystic fibrosis (eg, mutation screen, sweat chloride)

These opinions differ from those in European Respiratory Society and British Thoracic Society Guidelines [2, 3]

- Prevalence of underlying causes, such as ABPA, NTM different in Europe
- Replacement therapy for AAT deficiency not available, so limited need to test for it

1. Metersky ML. *Clin Chest Med*. 2012;33(2):219-231.
2. Hill AT, et al. *Thorax*. 2019;74(Suppl 1):1-69.
3. Polverino E, et al. *Euro Resp J*. 2017;50(3):1700629.

Additional Initial Testing

Recommended for selected patients without a diagnosis after above testing

- Aspergillus-specific IgG, IgE, aspergillus skin testing
- Bronchoscopy to rule out endobronchial obstruction (if focal disease)
- Bronchoscopy for mycobacterial cultures (if suggestive CT imaging)
- More extensive testing for immunodeficiency
- Nasal nitric oxide or other testing for primary ciliary dyskinesia
- Esophageal pH monitoring or swallow evaluation
- Serologies for autoimmune disease

Metersky ML. *Clin Chest Med*. 2012;33(2):219-231.

Current Management Strategies for NCFBE

Timothy R. Aksamit, MD
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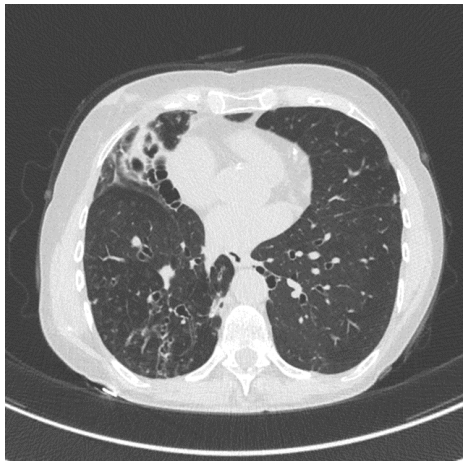
Professor, Medicine
Mayo Clinic
Rochester, MN

NCFBE: The Vicious Vortex

- Bronchiectasis
  - Abnormal, usually permanent dilation of the bronchial tubes
  - Impaired mucociliary clearance
  - Retention of secretions, mucus plugging
  - Recurrent infection, inflammation, and further airway damage



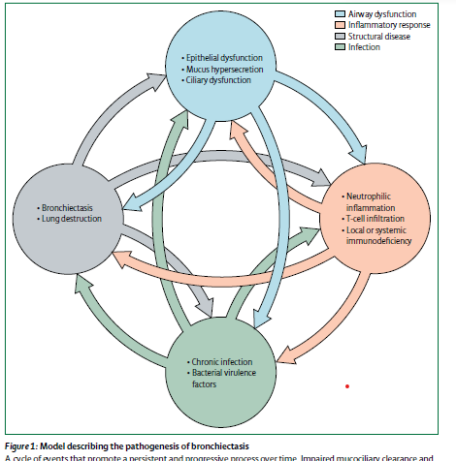
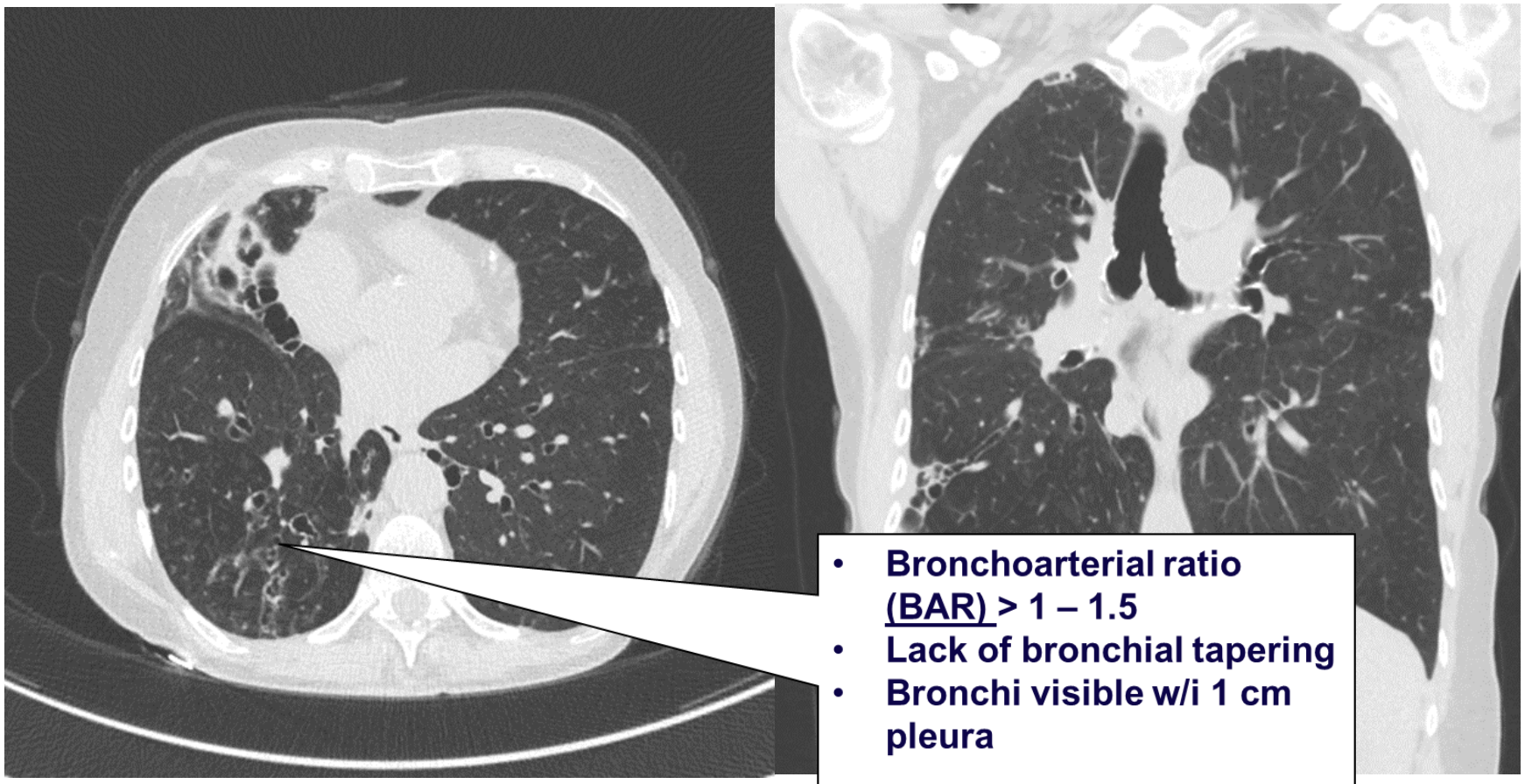


Figure 1: **Model describing the pathogenesis of bronchiectasis**

Flume PA, et al. *Lancet.* 2018;392(10150):880-890.
Cole PJ. *Eur J Resp Dis Suppl*. 1986;147:6-15.
King PT. *Int J Chron Pulmon Dis.* 2009;4:411-419.

NCFBE: Fundamental Variation in Severity

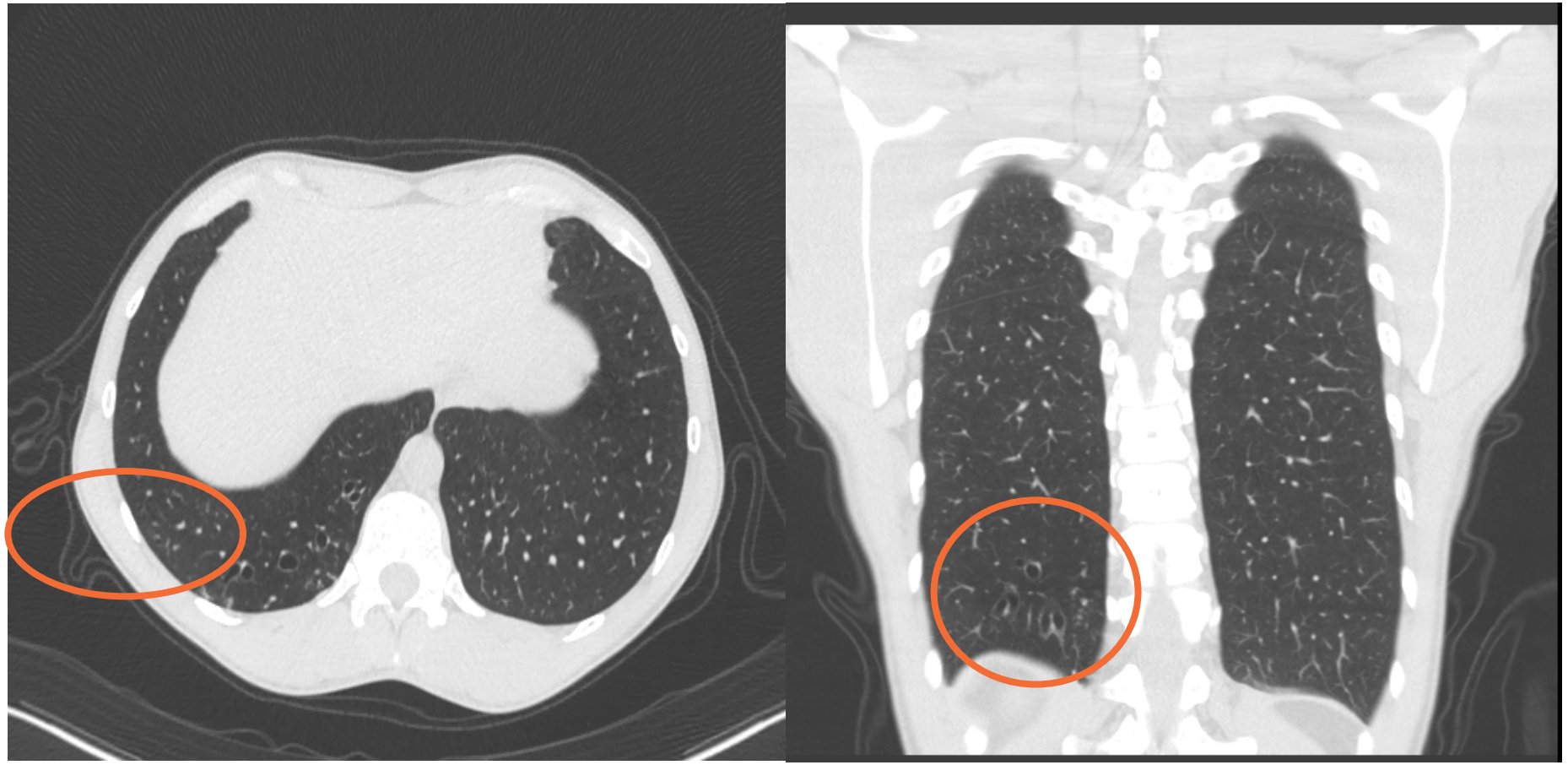


- **Bronchoarterial ratio (BAR) > 1 – 1.5**
- **Lack of bronchial tapering**
- **Bronchi visible w/i 1 cm pleura**

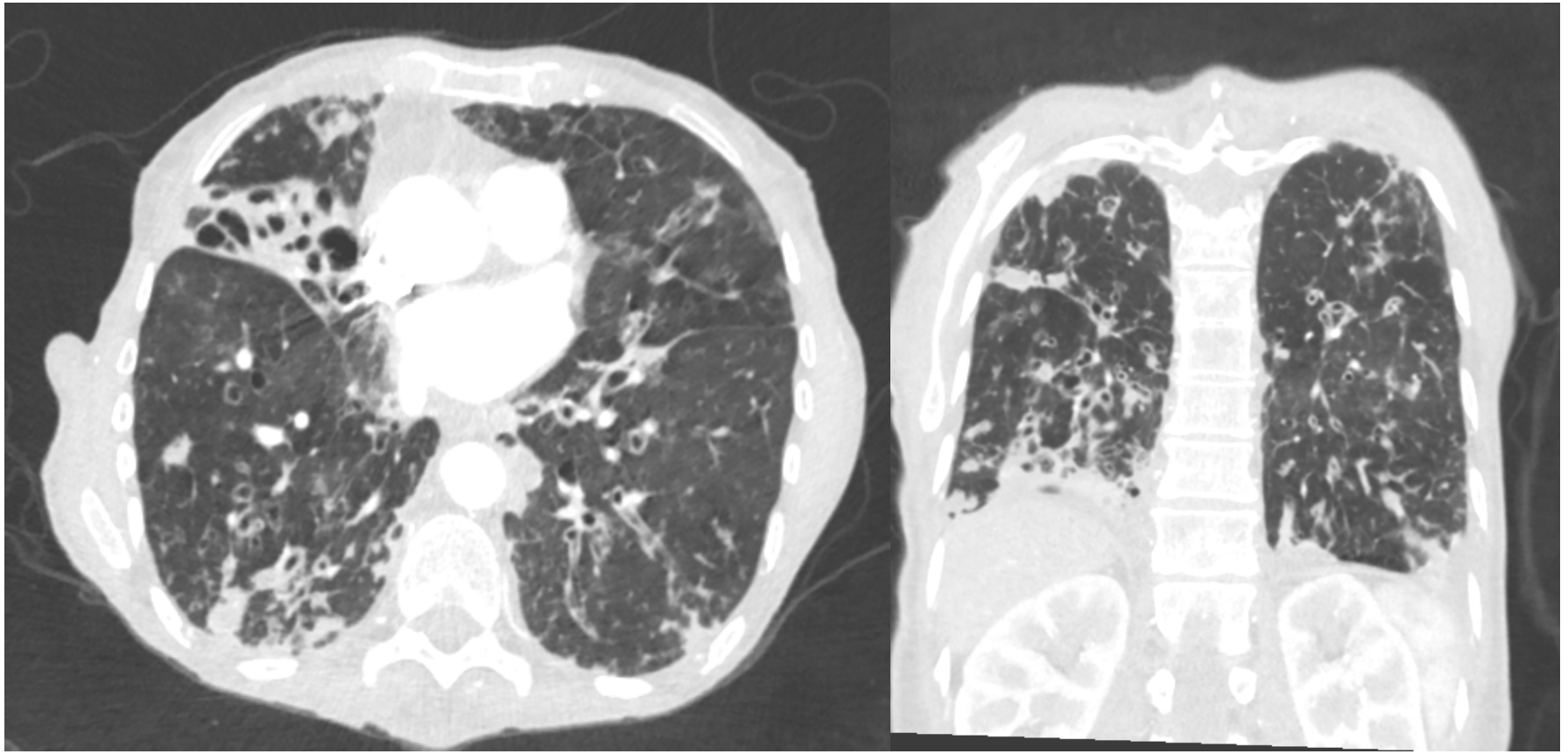
- **Bronchial wall thickening**
- **Mucous plugging**

Aliberti S, et al. *Lancet Respir Med*. 2022;10(3):298-306.

NCFBE: Fundamental Variation in Severity (cont'd)



NCFBE: Fundamental Variation in Severity (cont'd)



Overall Tenets of Bronchiectasis Treatment

Educate patient (pay now or pay later)

- Infection and inflammation superimposed on abnormal anatomy (airway clearance)
- Manageable

Understand impact of disease on the patient

- Symptoms
- Exacerbation frequency
- QoL – Quality of Life

Understand extent, complexity, and heterogeneity of disease

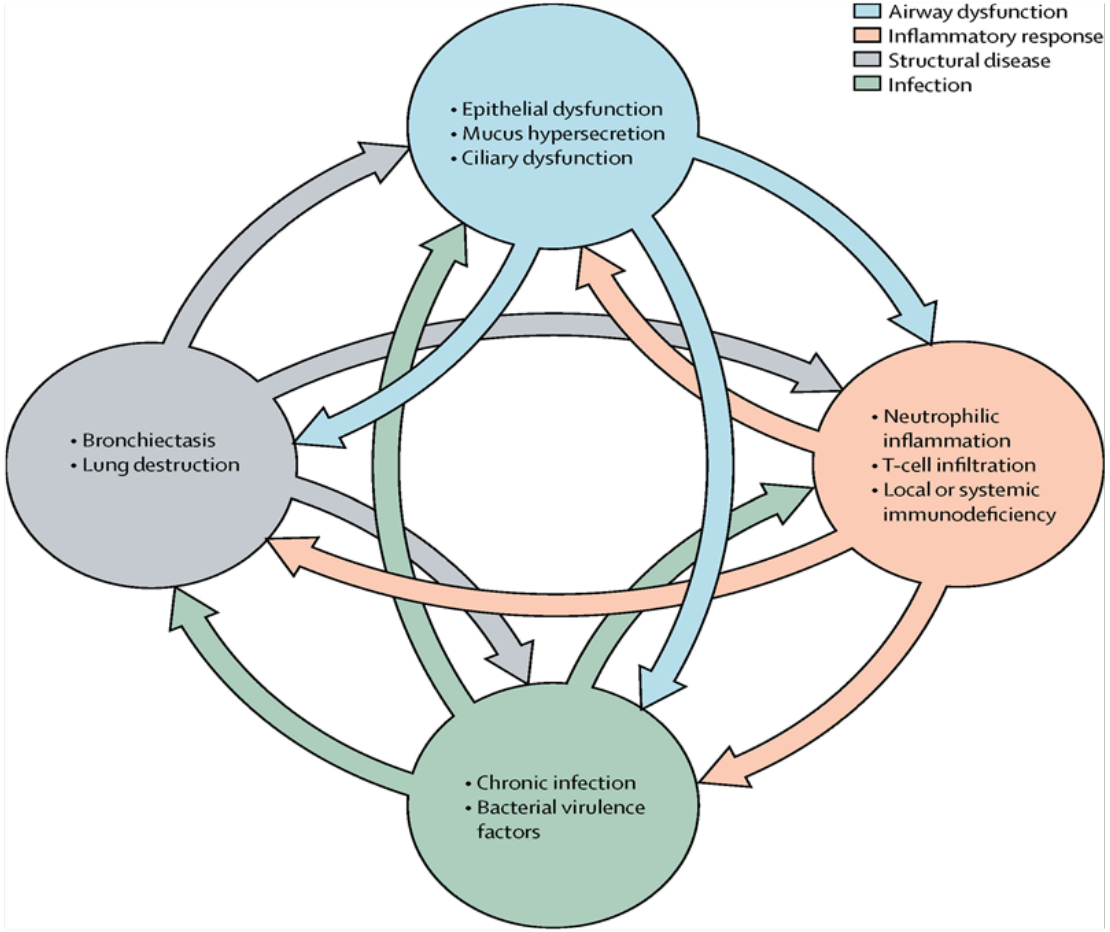
- CT findings
- PFTs
- '*Biomarkers*'
- Vortex

Target organisms

- Role of laboratory support
- Sputum cultures
  - Exacerbation
  - Surveillance

Treatment Strategy

- Airway clearance
  - Mechanical and exercise
  - Pharmacologic
- Anti-inflammatory therapies
  - Macrolides
  - *Investigational (neutrophilic and eosinophilic)*

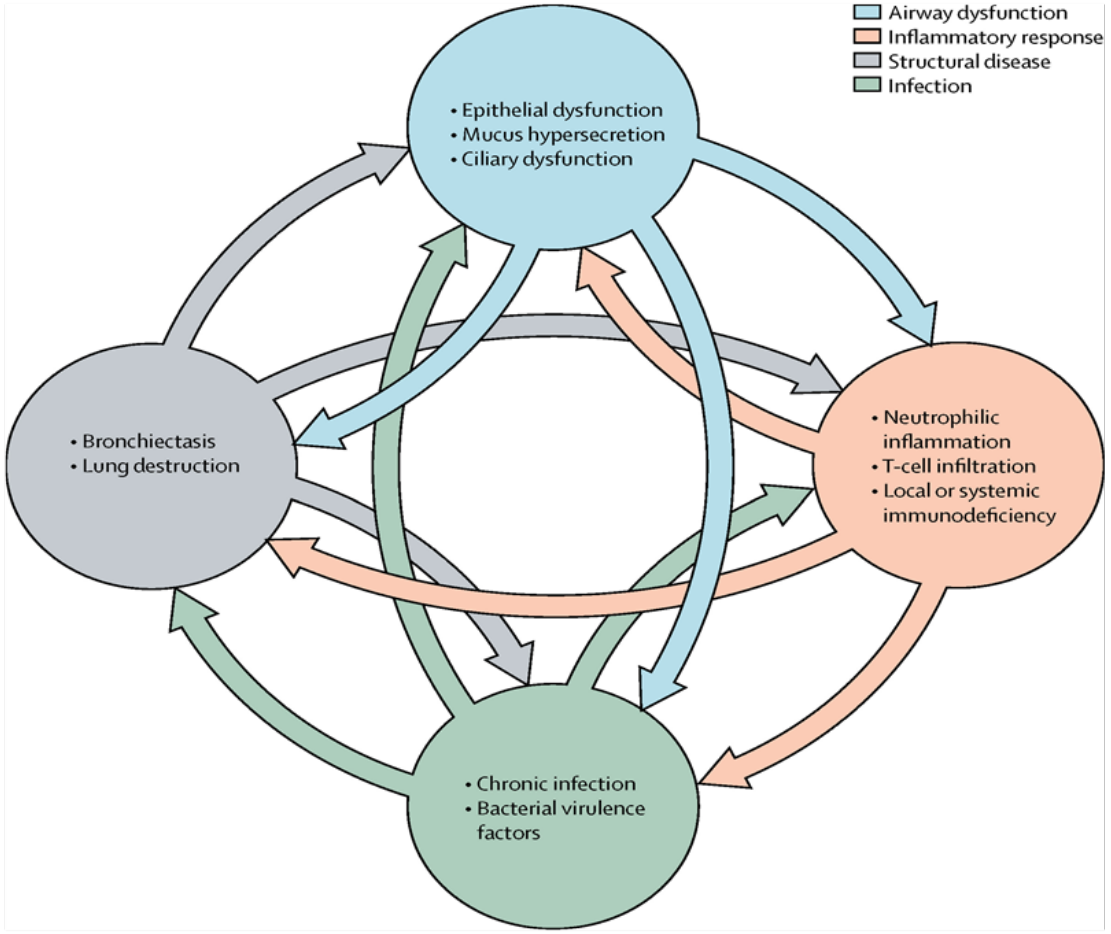


Vortex

Flume PA, et al. *Lancet.* 2018;392(10150):880-890.

Treatment Strategy (cont'd)

- Antibiotics
  - Inhaled
- Treat exacerbations
  - Targeted to organisms
- Co-morbidities / Underlying disease
  - Rhinosinusitis, GERD
  - Asthma, COPD, IBD, ABPA
- Surgery and transplant (limited role)



Vortex

Flume PA, et al. *Lancet.* 2018;392(10150):880-890.

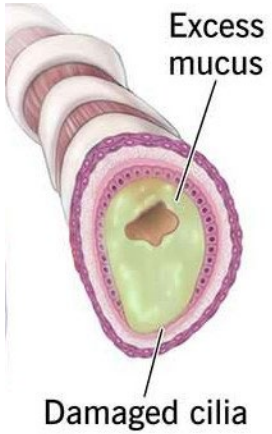
Goals of Airway Clearance

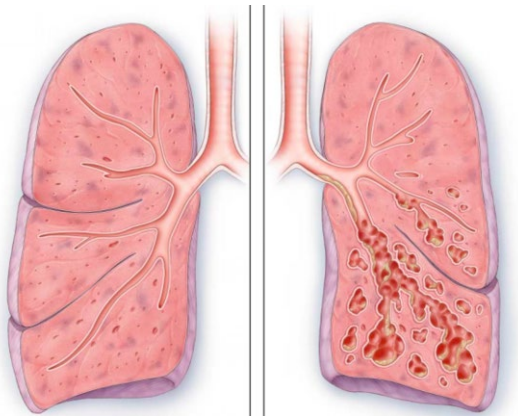
Short term

- Sputum clearance
  - Reduce cough
  - Reduce dyspnea

Longer term

- Reduce further airway damage
  - Interrupting the vicious cycle (infection / inflammation)
- Reduce exacerbations
- Improve quality of life





O'Neill K, et al. *Respirology*. 2019;24(3):227-237.

Airway Clearance Techniques

Techniques

- Active cycle of breathing
- Autogenic drainage
- ELTGOL
  - Slow expiration with the glottis open in lateral decubitus position
- Manual chest percussion
- Huffing

Optimizing Airway Clearance

- No one technique has been found to be more effective than another[1-3]
- ***BEST*** – Whatever the patient will do/time constraints/cost
- Respiratory therapy consultation
- ***Individualize*** airway clearance techniques for each patient[4]

1. Lee AL, et al. *Cochrane Database Syst Rev.* 2013;(5):CD008351.
2. Lee AL, et al. *Cochrane Database Syst Rev.* 2015;(11):CD008351.
3. Lee AL, et al. *Cochrane Database Syst Rev.* 2017;(9):CD011699.
4. McIlwaine M, et al. *Eur Respir Rev.* 2017;26:160086.

Airway Clearance Devices

Oscillatory Positive Expiratory Pressure (OPEP)

High Frequency Chest Wall Oscillation (HFCWO)

COMBINATION

Airway Clearance Pharmacologic Agents

Mucoactive Agents

- Hypertonic saline, 3% versus 7%
  - May improve QoL outcomes and sputum clearance[1]
- Other
  - Guaifenesin, N-acetyl cysteine
- Inhaled Mannitol
  - Increased time to first exacerbation, but did not decrease exacerbation rate[2]
- Recombinant Human DNase
  - Increased exacerbation frequency[3]
  - Should not be used routinely

1. Kellet F, Robert NM. *Respir Med.* 2011;105(12):1831-1835.
2. Bilton D, et al. *Thorax.* 2014;69(12):1073-1079.
3. O'Donnell AE, et al. *Chest.* 1998;113(5):1329-1334.

Pulmonary Rehabilitation and Exercise

- Pulmonary rehabilitation
  - 108 patients with NCFBE, 3-week program[1]
  - Significant improvement
    - 6-min walk distance
    - Dyspnea score
    - QoL index
- Exercise training
  - 85 patients with NCFBE, random assignment[2]
  - 8-week program
  - Significant improvement
    - Including less frequent exacerbations

1. Zanini A, et al. *Respiration.* 2015;89(6):525-533.
2. Lee AL, et al. *Respir Res.* 2014;15(1):44.\

Anti-inflammatory Therapies

Macrolides have been shown to:

- Modify mucus production
- Inhibit production of biofilms
- Suppress inflammatory mediators
- Moderate leukocyte recruitment and function

Azithromycin[1,2] and erythromycin[3] have been shown to:

- Reduce exacerbation frequency
- Reduce the number of patients with at least 1 exacerbation

Candidates for long-term macrolide therapy

- Long-term macrolide treatment is recommended in adults who have ≥3 exacerbations per year

Problems with chronic macrolide use[4]

- Development of macrolide-resistant bacterial strains, particularly NTM
  - **NTM infection** should be ruled out prior to starting chronic macrolide therapy
  - **Resistance** is more likely with chronic macrolide therapy
  - Cardiac, ototoxicity risk potential

1. Wong C, et al. *Lancet.* 2012;380(9842):660-667.
2. Altenburg J, et al. *JAMA.* 2013;309(12):1251-1259.
3. Serisier DJ, et al. *JAMA.* 2013;309(12):1260-1267.
4. Chalmers JD, et al. *Lancet Respir Med.* 2019;7(10):845-854.

Bronchiectasis: Key Pathogens

Organism	EMBRACE (macrolide arm)[1]	BAT (macrolide arm)[2]	BLESS (macrolide arm)[3]	US NCFB Registry[4]
Pseudomonas aeruginosa	13%	14%	39%	37%
Haemophilus influenzae	27%	30%	20%	10%
Staphylococcus aureus	3%	9%	NR	11%
Moraxella catarrhalis	4%	NR	NR	1%
Normal flora	52%	47%	44%	7%
NTM	Excluded	0%	Excluded	33%

1. Wong C, et al. *Lancet.* 2012;380(9842):660-667.
2. Altenburg J, et al. *JAMA*. 2013;309(12):1251-1259.
3. Serisier DJ, et al. *JAMA*. 2013;309(12):1260-1267.
4. Aksamit T, et al.*Chest*. 2017;151(5):982-992.

Inhaled Antibiotic Patient Selection

- Maintenance inhaled antibiotics
  - Three or more exacerbations per year
  - Evidence is mainly for *pseudomonas* infection
  - Other considerations/questions
    - Very symptomatic patient, daily symptoms
    - Suboptimal airway clearance
    - Adherence
    - Cost/insurance coverage
- ***Individualize*** to the patient

Hill AT, et al. *Thorax*. 2019;74(Suppl 1):1-69.

Current Data on Inhaled Antibiotics

Gentamycin[1-2]	Increased time to exacerbation, reduced exacerbation rate, improved QoL
Colistin[3]	Increased time to exacerbation in patients with *P. aeruginosa* and 1 or more exacerbations/year
Aztreonam[4]	• Baseline bronchitic symptoms suggest response • More frequent exacerbators may respond positively
Tobramycin[5]	Continuous and cyclic regimens reduce *P. aeruginosa* density
Amikacin[6]	Increased bacterial eradication rate in patients with *P. aeruginosa* versus controls
Ciprofloxacin[7]	• Reduced frequency of exacerbations • Significantly prolonged time to first exacerbation • Decreased *P. aeruginosa* in lungs

1. Murray MP, et al. *Am J Respir Crit Care Med.* 2011;183:491-499.
2. Chalmers JD, et al. *Am J Respir Crit Care Med.* 2012;186:657-665.
3. Haworth CS. *Eur Respir J.* 2021;58:RCT4267.
4. Crichton ML, et al. *Eur Respir J.* 2020;56(1):2000608.
5. Loebinger MR, et al. *Eur Respir J.* 2021;57(1):2001451.
6. Ailiyaer Y, et al. *Respiration*. 2018:95:327-333.
7. Wang, et al. *Int Med J*. 2021;51(9):1505-1512.

Macrolides or "Antibiotics"

Macrolides

- First step
  - If patient can tolerate
  - If no contraindication
  - Azithromycin 500 mg TIW
- Rule out contraindications
  - NTM co-infection
  - Cardiac issues
  - Hearing
  - Drug-drug interactions

Inhaled Antibiotics

- If macrolides do not help
  - Target the organism
- If macrolides are contraindicated
  - Aminoglycoside
  - Colistin
  - Aztreonam
  - Pipeline

Surgery

Surgery for Bronchiectasis

- Localized disease
- Remove worst area of disease
- Bronchiectasis/NTM infection
- Fail to improve despite long-term, comprehensive management
- Cannot tolerate therapy

Thoracoscopic Surgery

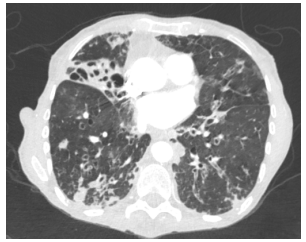
- While challenging, is associated with 0% mortality and a <9% overall complication rate

Lung Transplantation

- Diffuse, bilateral disease
- Indicated where survival is expected at 50% at 2 years without transplant
- Outcomes in line (or worse) with other diseases

Mitchell JD. *Thorac Surg Clin.* 2019;29(1):77-83.
McShane PJ, et al. *Am J Respir Crit Care Med*. 2013;188(6):647-656.
Hill AT, et al. *Thorax*. 2019;74(Suppl 1):1-69.

Management Summary



Step-wise and *individualized* approach

- First-line therapy – EDUCATION
  - Airway clearance and aerobic activity, mucoactive agents
- Anti-inflammatories for frequent exacerbator
  - Macrolide – azithromycin 500 mg TIW
    - Multiple cautions
- Inhaled antibiotics
  - Chronic pseudomonas infection
  - Best data is for aminoglycosides and colistin
- Treatment of exacerbations
  - Targeted microbiology
  - Surveillance / exacerbation

Therapies that should not be routinely used

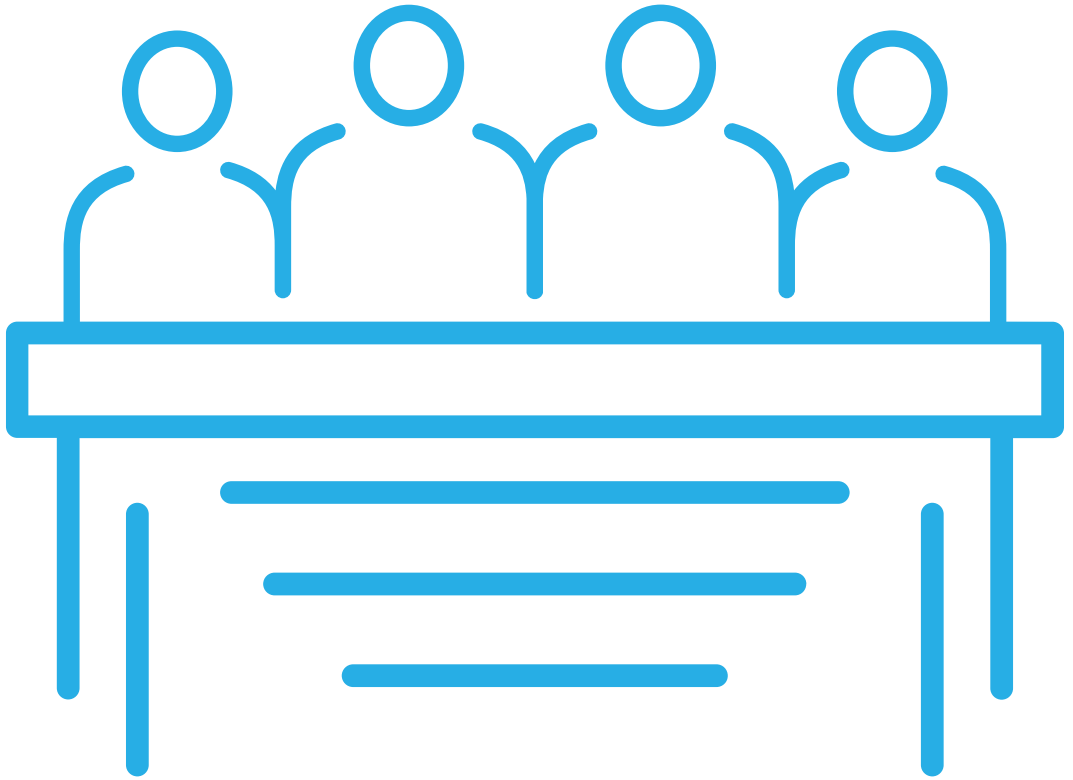
- Routine inhaled corticosteroids
- Routine oral steroids
- Routine oral antibiotics
- Macrolide monotherapy when NTM infection is present or has not been ruled out

Comorbidities and underlying disease

Hill AT, et al. *Thorax.* 2019;74(Suppl 1):1-69.
Polverino E, et al. *Eur Respir J.* 2017;50(3):1700629.
Hill AT, et al. *Chest.* 2018;153(4):986-993.

Panel Discussion

- Do pathogens impact prognosis in NCFBE?
- Does eradication of potential pathogens improve outcomes in stable NCFBE?

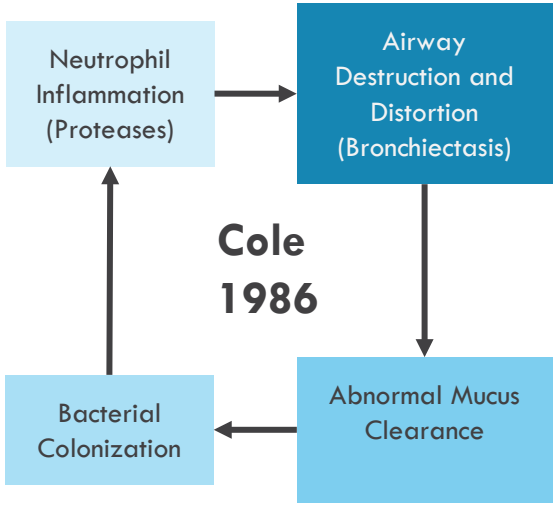


Targeting the Pathophysiology of NCFBE: The Role of Emerging Therapies

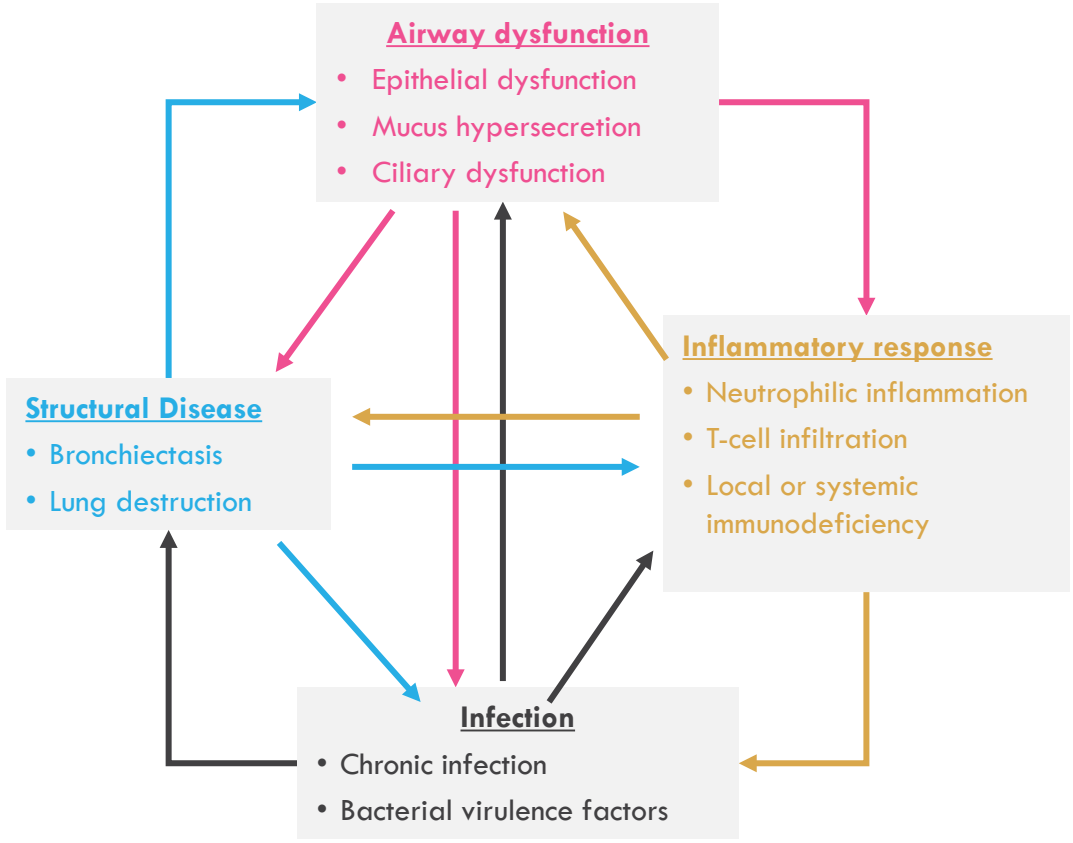
Margaret M. Johnson, MD
Professor, Medicine
Dean of Education
Mayo Clinic College of Medicine and Science
Jacksonville, FL

Bronchiectasis: Pathogenesis

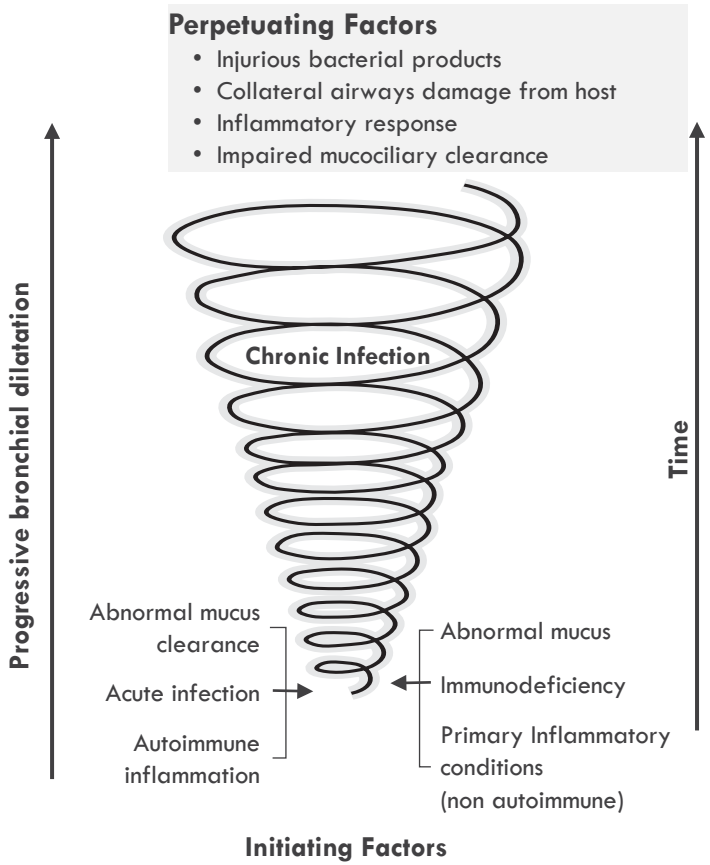
Vicious Cycle[1]



Vicious Vortex[2]



Alternative Vicious Vortex[3]



1. McShane PJ, et al. *Am J Respir Crit Care Med.* 2013;188(6):647-656.
2. Flume PA, et al. *Lancet.* 2018;392(10150):880-890.
3. Metersky M, Barker AF. *Clin Chest Med.* 2022;43(1):35-46.

Role of Neutrophils

Sputum Neutrophils are Associated with:

- Decline in pulmonary function
- Bacterial colonization
- Severe disease
- Inflammatory morbidity

Neutrophil Elastase is an NSP Associated with:

- Extracellular matrix degradation
- Mucus gland hyperplasia
- Increased mucus production
- Reduced ciliary beating rate
- Direct epithelial damage

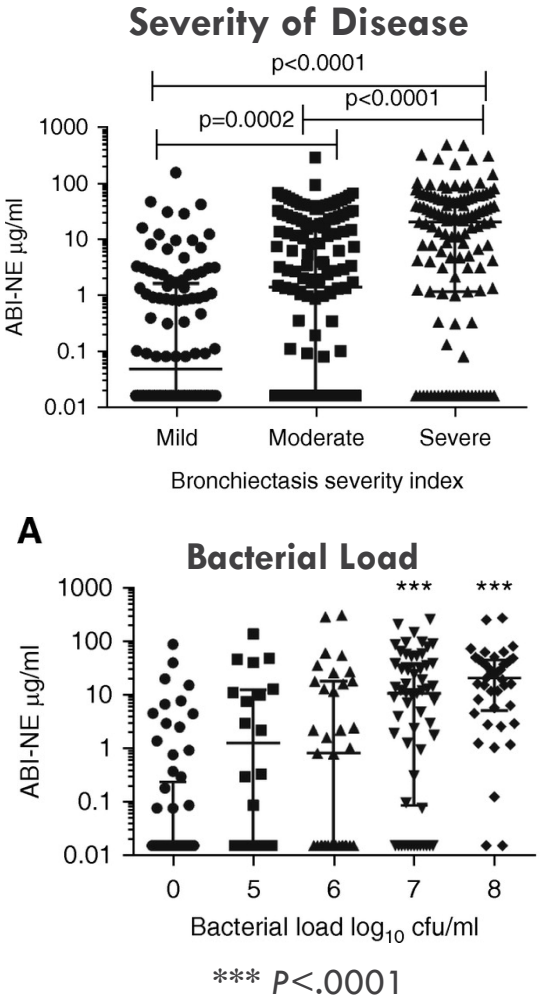
Inhibiting DPP-1

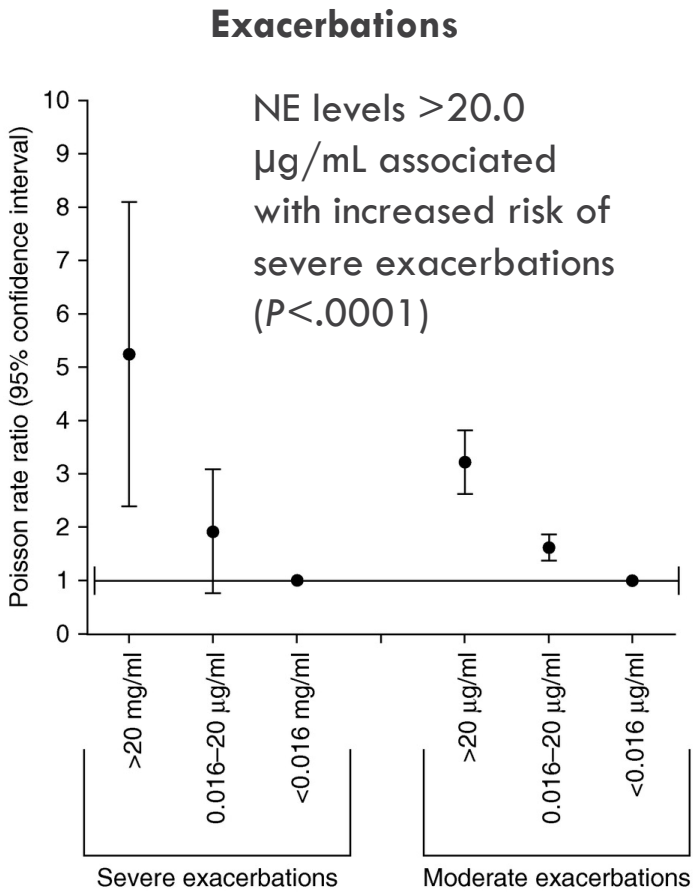
- DPP-1 activates neutrophil elastase in the bone marrow during neutrophil maturation
- Direct neutrophil elastase inhibition failed to improve NCFBE in Phase 2 studies
- DPP-1 is currently an investigational target

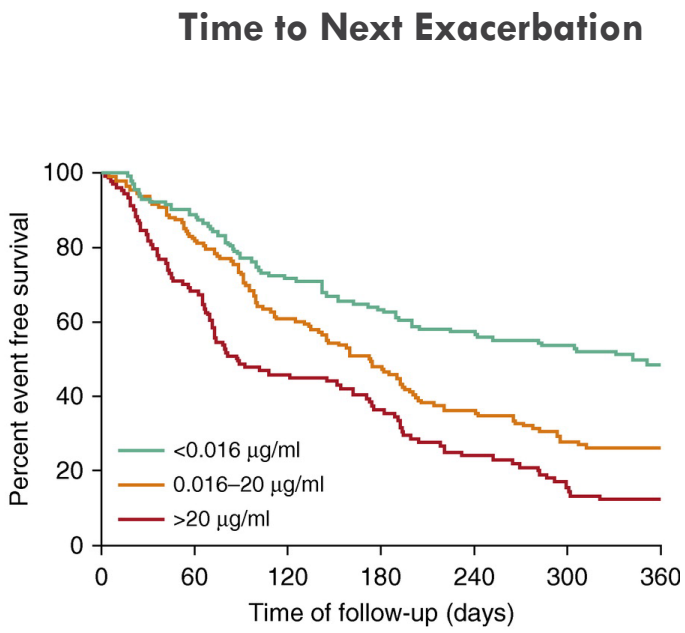
NSP, neutrophil serine protease; DPP-1, dipeptidyl peptidase 1

Usansky H, et al. *Clin Pharmacol Drug Dev.* 2022;11(7):832-842.

Neutrophil Elastase Parallels Disease Severity and Outcomes





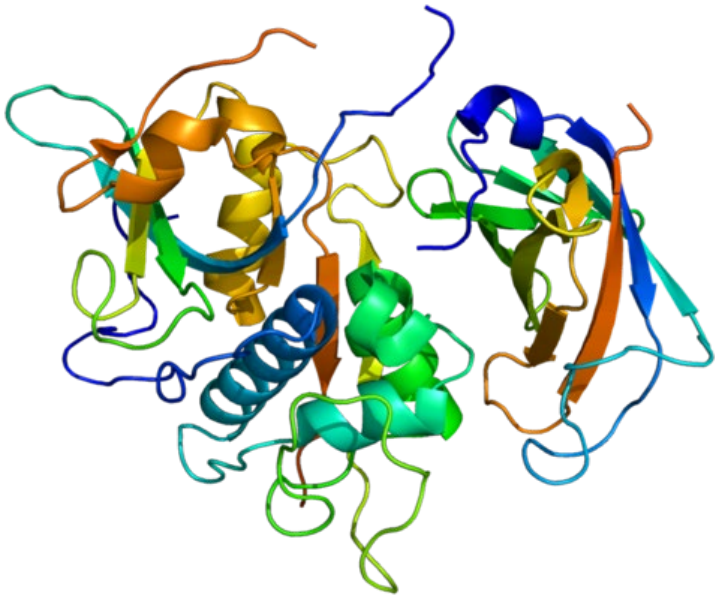


Elevated NE associated with shorter time to next exacerbation (*P*<.0001)

Chalmers JD, et al. *Am J Respir Crit Care Med.* 2017;195(10):1384-1393.

Targeting Activation of Neutrophil Serine Proteases (NSPs)

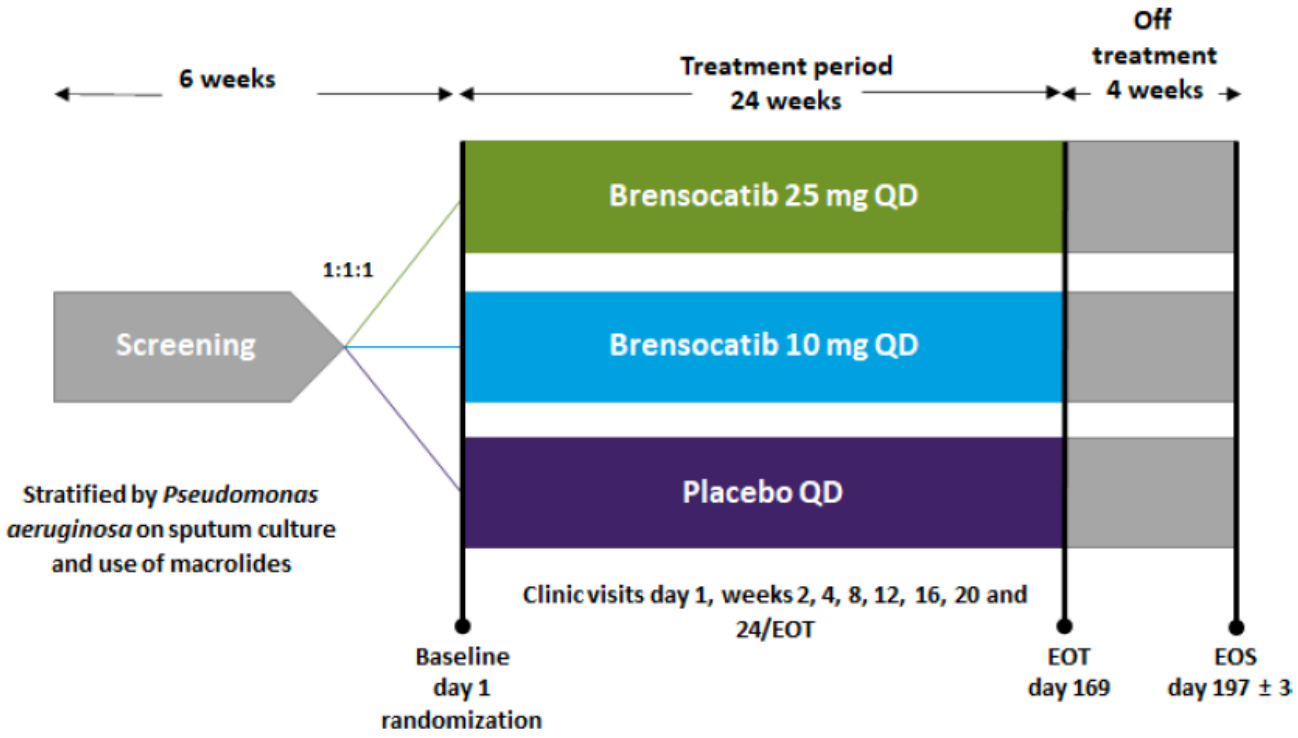
- DPP-1 is a lysosomal cysteine protease that cleaves NE, cathepsin G, and proteinase 3, activating these NSPs through maturation
- The activated NSPs are packaged in the neutrophil granules and the mature neutrophils are released into the systemic circulation
- Can inhibition of DPP-1 prevent activation of NSPs and exert clinical benefit?



DPP-1, dipeptidyl peptidase 1; NE, neutrophil elastase

Chalmers JD, Chotirmall SH. *Lancet Respir Med.* 2018;6(9):715-726.

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



N=256

Brensocatib is an oral reversible inhibitor of DPP-1

Primary Endpoint:

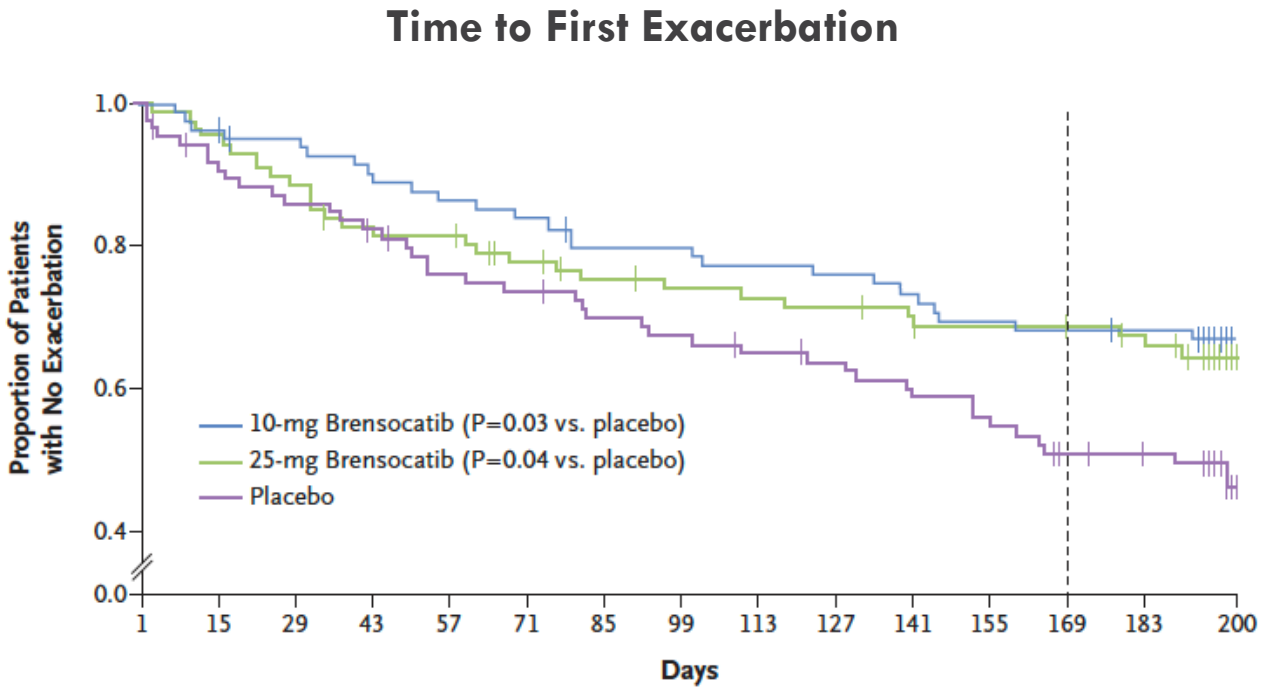
- Time to first bronchiectasis exacerbation

Secondary Endpoints:

- Rate of exacerbations
- Change in QOL-B respiratory symptoms domain
- Change in post-bronchodilator ppFEV1
- Change in sputum neutrophil elastase activity

Chalmers JD, et al. *N Engl J Med*. 2020;383(22):2127-2137.

Inhibition of DPP-1 with Brensocatib Prolonged Time to First Exacerbation



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

Brensocatib prolonged time to first exacerbation that come with placebo:

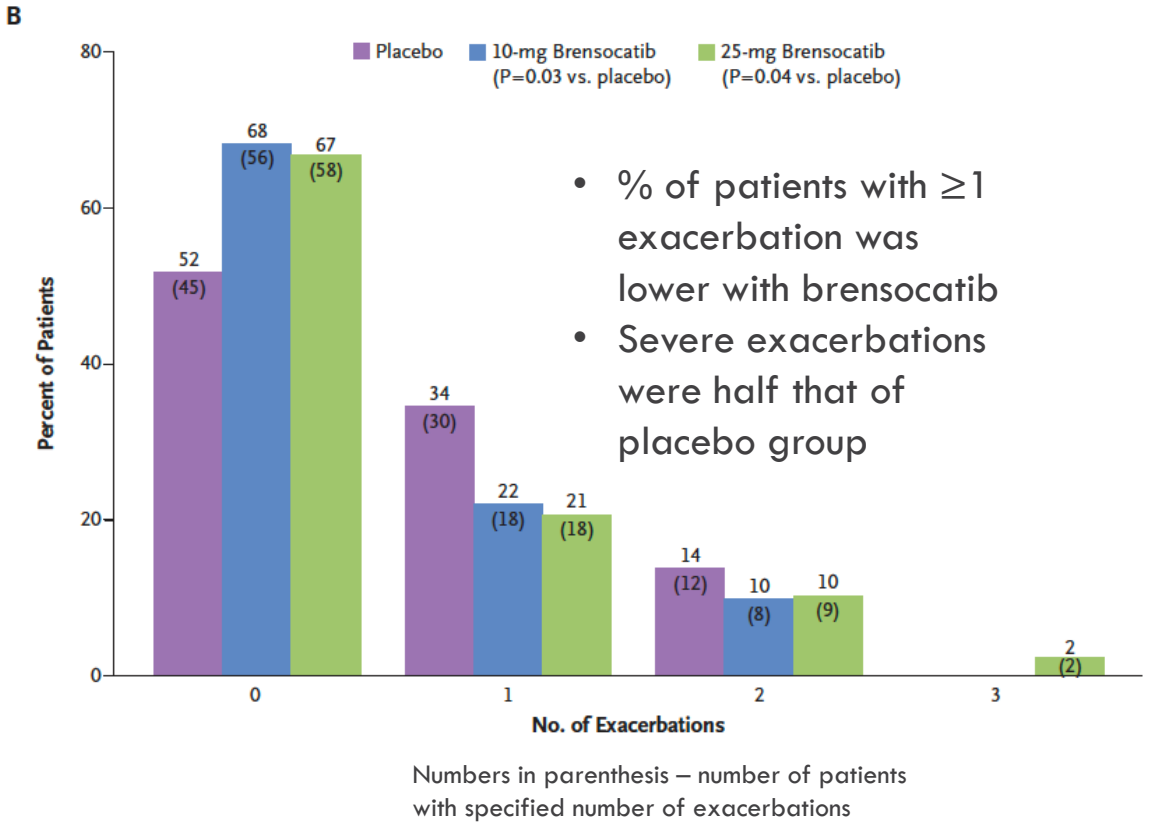
10 mg (*P*=.03)

25 mg (*P*=.04)

Chalmers JD, et al. *N Engl J Med.* 2020;383(22):2127-2137.

Brensocatib Reduced Number of Exacerbations and Sputum NE Concentration

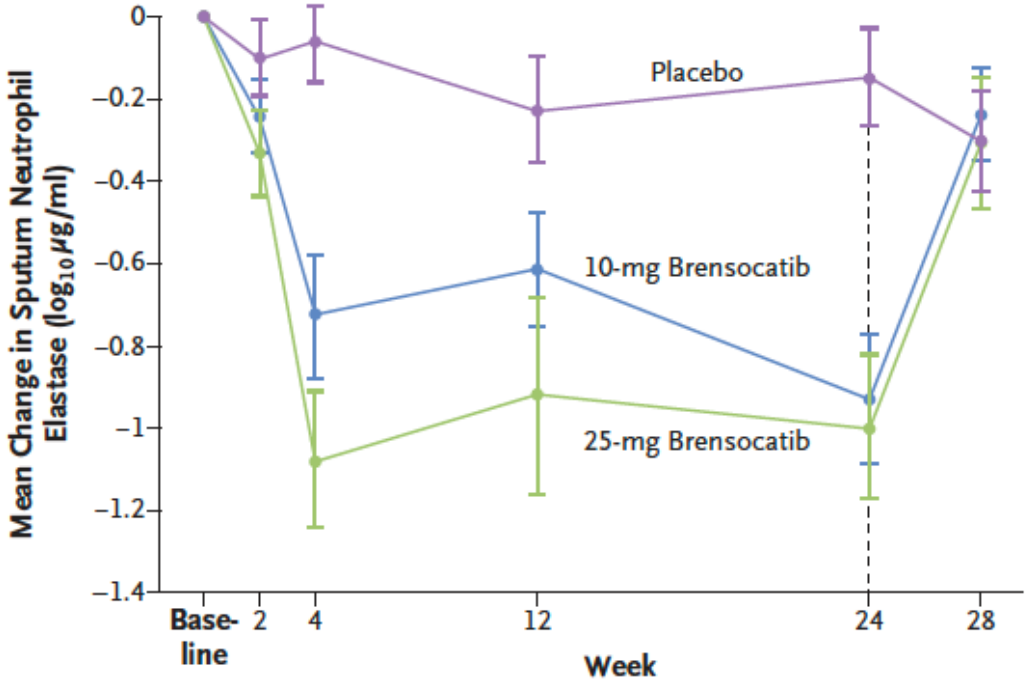
Number of Exacerbations



- % of patients with ≥1 exacerbation was lower with brensocatib
- Severe exacerbations were half that of placebo group

Numbers in parenthesis – number of patients with specified number of exacerbations

Mean Change in Sputum Neutrophil Elastase Concentration



NE, neutrophil elastase

Chalmers JD, et al. *N Engl J Med.* 2020;383(22):2127-2137.

Brensocatib: Phase 3 Study

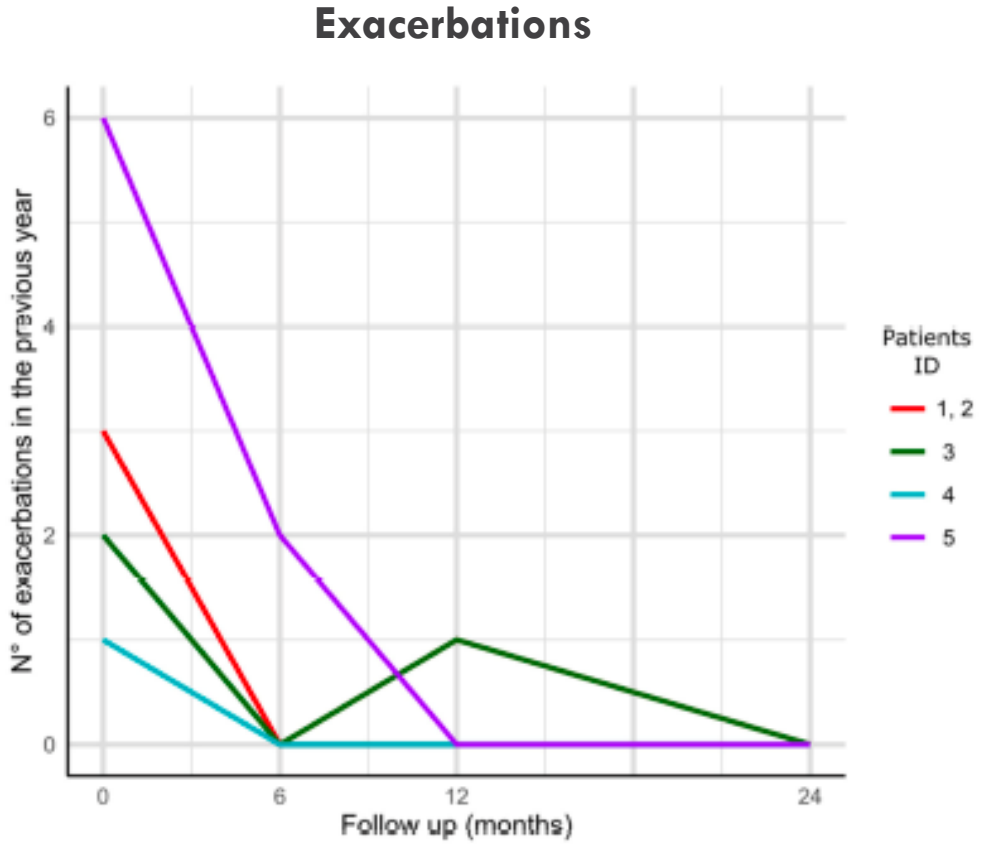
ASPEN – Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects With Non-Cystic Fibrosis Bronchiectasis

- More than 1,700 adult NCFBE patients enrolled; adolescent enrollment ongoing
- Primary outcome
  - Rate of adjudicated pulmonary exacerbations
- Select secondary outcomes
  - Time to first adjudicated exacerbation
  - Percentage free from exacerbation
  - Postbronchodilator FEV1
  - Rate of severe adjudicated pulmonary exacerbations
  - QoL
- Results expected Q2 2024

ClinicalTrials.gov NCT04594369

T2-High Endotype (Eosinophilic Inflammation)

- Up to one-third of patients with bronchiectasis have predominant eosinophilic inflammation
- Reduced exacerbation rate demonstrated in 5 patients with severe eosinophilic asthma and co-morbid bronchiectasis after use of anti-IL5 (mepolizumab) or anti-IL5ra (benralizumab)



Fitzgerald JM, et al. *Lancet.* 2016;388(10056):2128-2141.
Ortega HG, et al. *N Engl J Med.* 2014;371(13):1198-1207.

Benralizumab: Ongoing Phase 3 Study

- Benralizumab is a humanized recombinant monoclonal antibody that binds to the alpha chain of IL-5R, thus blocking signal transduction
- FDA approved benralizumab for treatment of severe eosinophilic asthma and an eosinophilic phenotype
- 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

ClinicalTrials.gov NCT05006573

Other Therapies Under Investigation for NCFBE

- Human derived immunoglobulin
- Monoclonal antibody (mepolizumab)
- Oral DPP-1 inhibitor (BI1291583)
- Nebulized NE inhibitor (CHF 6333)
- Phosphodiesterase inhibitor (roflumilast)
- Nebulized ascorbic acid and reduced glutathione
- CFTR potentiator (QBW 251)
- Transplantation of autologous bronchial basal cells
- Mesenchymal stem cells

DPP-1, dipeptidyl peptidase-1; NE, neutrophil elastase; CFTR, cystic fibrosis transmembrane conductance regulator
www.clinicaltrials.gov

Summary

- Neutrophilic predominant airway inflammation is characteristic in most people with bronchiectasis
- Airway neutrophils are associated with high levels of neutrophil serine proteases (NSPs) including neutrophil elastase which induce tissue damage and remodeling
- DPP-1 is required for the activation of NSPs in the bone marrow
- Brensocatib is an oral reversible DPP-1 that prolongs the time to first exacerbation and decreases frequency of exacerbations that come with placebo (Phase 2)
- Eosinophilic inflammation occurs in one-third of people with bronchiectasis
  - Benralizumab is being evaluated in a Phase 3 trial
- Robust pipeline of directed therapies for bronchiectasis with many in different phases of investigation

Panel Discussion

- Some of the drugs in clinical trials are targeting specific endotypes. For example, those with neutrophilic versus eosinophilic inflammation. Do you currently treat these patients differently?
- Any concerns about the safety of these new agents?