




**Reducing the Burden and Improving QoL
in Non-Cystic Fibrosis Bronchiectasis:
New Insights into the
Pathophysiology and
Treatment**



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**Recognizing the Burden
of Bronchiectasis**

Molly Mailes, MSN, RN, MEDSURG-BC



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Disease Burden



US Prevalence

- 340,000 to 520,000



Demographics

- Caucasians
- Females
- Never smokers
- Mean age: 64 ± 14 years
- Prior NTM disease



Severity Associated with:

- Poor nutrition/low BMI
- *P. aeruginosa* infection



Characterized by:

- Dilated bronchi
- Poor mucus clearance
- Repeated bacterial infection
- Bronchial wall injury



Patient Burden

- Reduced QoL
- Significant financial burden
- Significant morbidity
- Increased mortality with low BMI
- Osteopenia/osteoporosis

Despotes KA, et al. *Chronic Obstr Pulm Dis.* 2020;7(4):390-403; Choate R, et al. *Respir Med.* 2020;177:106285; Diehl N, Johnson MM. *South Med J.* 2016;109(12):779-783.



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Mortality Risk

- 1.15 times greater mortality versus matched controls
- Mortality greatest in elderly patients and men
- Comorbidities increasing mortality:
 - Asthma
 - COPD
 - Pneumonia
 - Lung cancer
 - Cardiovascular disease

Choi H, et al. *Sci Rep.* 2021;11(1):7126.



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Diagnosing Bronchiectasis

Margaret Johnson, MD

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Recognizing Bronchiectasis

Clinical Suspicion

- Cough
- Excessive sputum production
- Recurrent respiratory infections
- Pleuritic chest pain
- Hemoptysis
- Breathlessness
- Lethargy
- Weight loss/low BMI
- *P. aeruginosa* or NTM in the respiratory tract

At-Risk Population

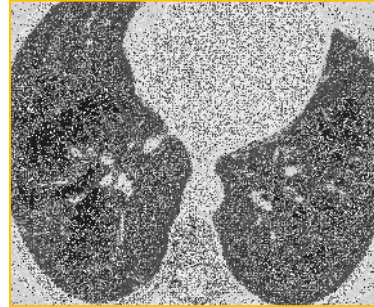
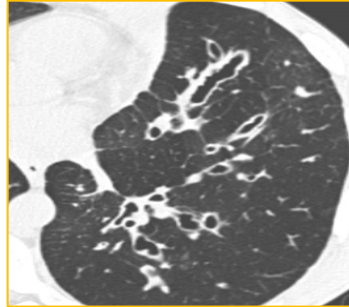
- Older age
- Female gender
- Co-existent lung disease
- Prior infections
- Autoimmune disease
- Immunodeficiency
- Chronic aspiration

Quinn TM, Hill TA. *Clin Interv Aging*. 2018;13:1649-1656; Macfarlane L, et al. *Clin Med (Lond)*. 2021;21(6):e571-e577.



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CT Signs of Bronchiectasis



- Airway dilation
- Mucus plugging
- Lack of airway tapering
- Tree-in-bud opacities

Images Courtesy of M. Johnson.

Clinical
CONSULTS

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Clinically Significant Bronchiectasis?



- CT**
- Airway diameter > blood vessel
 - Lack of airway tapering
 - Visibility of airway in periphery

- Symptoms**
(At least 2 of following)
- Cough most days of the week
 - Sputum production most days of the week
 - History of exacerbations

International Consensus Recommendations for Diagnosis

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

Clinical
CONSULTS

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Diagnostic Testing for Bronchiectasis



Labs

- CBC with differential
- History directed lab work-up:
 - RF, anti-CCP, ANCA, A1AT, HIV-1 serology
- Respiratory Cultures
 - Bacteria
 - Fungus
 - AFB
- Antibody Testing
 - Serum total IgE
 - Aspergillus fumigatus IgE
 - Serum IgG, IgA, IgM
 - Baseline antibodies against capsular polysaccharides of *S. pneumoniae*
 - Vaccinate if low and reassess titer at 4 to 8 weeks



Additional Testing (Selected)

- Cystic fibrosis
- Primary ciliary dyskinesia
- Reflux and aspiration
- Bronchoscopy to rule out endobronchial lesion or foreign body



Idiopathic Cases

- About 40% of bronchiectasis cases are idiopathic

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



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Bronchiectasis Pathophysiology and Emerging Therapies

Mark Metersky, MD

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Current Treatment Options

- Airway clearance devices and chest physical therapy
- Hypertonic saline
- Bronchodilators
- Anti-inflammatory treatment
 - Chronic low-dose macrolide therapy
 - Inhaled corticosteroids
- Antimicrobial therapy (oral, inhaled)
- Surgery and transplant (limited role)



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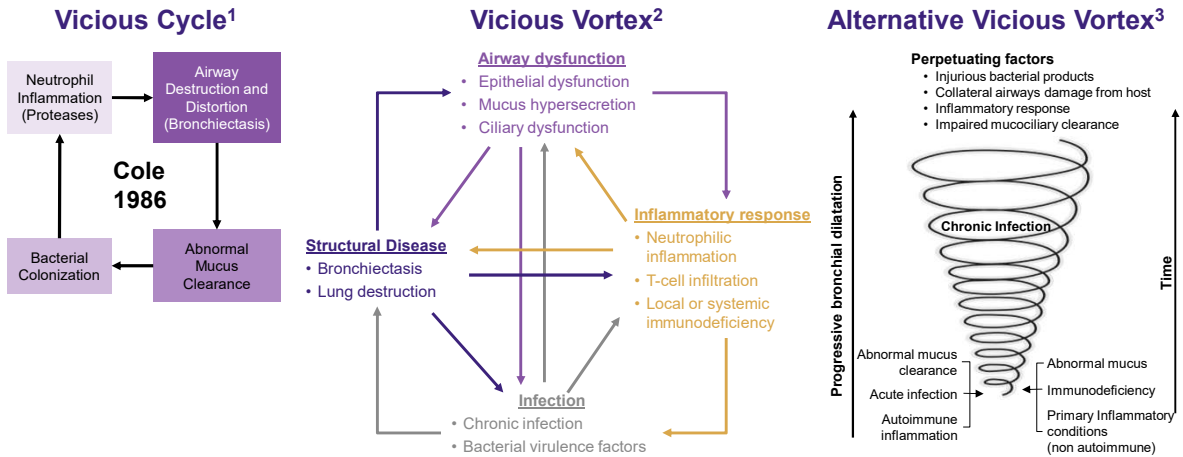
Role of the Nurse or Respiratory Therapist

- Educate on airway clearance therapy
 - What it is
 - Why it is important and consequences of mucus accumulation
 - Proper use and cleaning of mucus-clearing devices
 - Integrating treatment into their daily regimen
- Discuss fears and misconceptions



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Bronchiectasis: Pathogenesis



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.



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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

DPP-1, dipeptidyl peptidase 1
 Usansky H, et al. *Clin Pharmacol Drug Dev.* 2022;11(7):832-842..

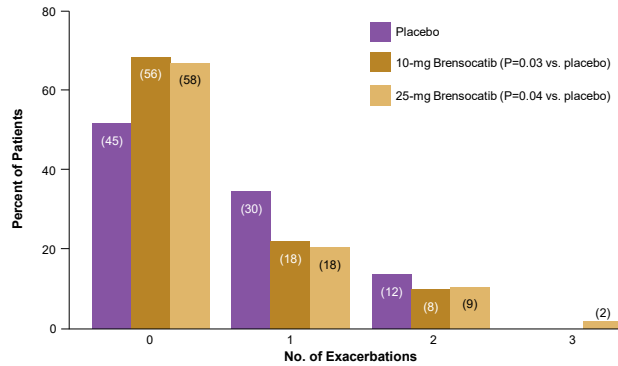
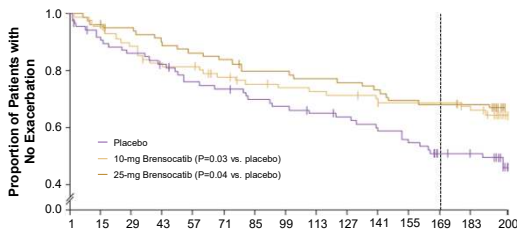


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Brensocatic: Phase 2 WILLOW

Mechanism of Action

- Selective reversible DPP-1 inhibitor
- Oral small molecule
- Blocks NSP activation



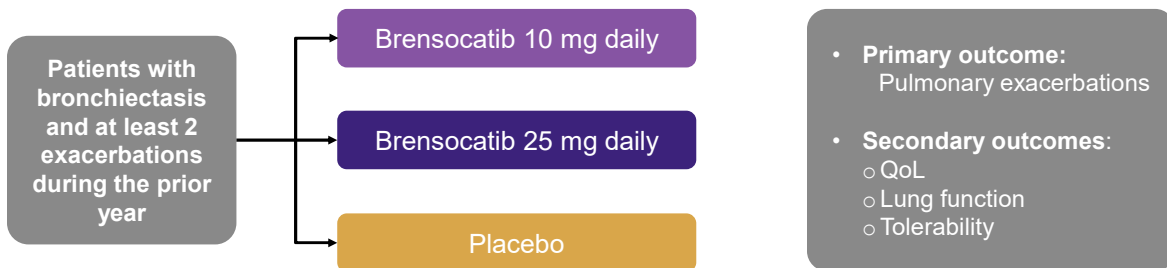
Click here to view the clinicaltrials.gov study record for this study: <https://tinyurl.com/4w4a8wa4>

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



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Brensocatic: Phase 3 ASPEN¹



Click here to view the clinicaltrials.gov study record for this study: <https://tinyurl.com/yeyv45va>

Eligible patients completing the ASPEN study were invited to participate in the expanded access trial:² <https://tinyurl.com/2d67tana>

1. ClinicalTrials.gov: NCT04594369.
2. ClinicalTrials.gov: NCT05344508.



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Role of Eosinophils



Inflammatory Response^{1,2}

Up to a **third** of patients with bronchiectasis have a predominant eosinophilic rather than neutrophilic inflammatory response



IL-5 Receptor (IL-5R)

Expressed on the surface of eosinophils



Is there a role for anti-IL5 or anti-eosinophilic therapy?

Anti-IL5 monoclonal antibodies directly bind the alpha subunit of the IL-5R leading to apoptosis of eosinophils

1. Rademacher J, et al. *Eur Respir J*. 2020;55(1):1901333.
2. Guan WJ, et al. *J Allergy Clin Immunol Pract*. 2022;S2213-2198(22)01129-1.
3. ClinicalTrials.gov: NCT05006573. For study record, click here: <https://tinyurl.com/yaef7dbv6>.



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Other Agents in Development

Phase 1

- Neutrophil elastase inhibitor BI 1323495¹
- Neutrophil elastase inhibitor CHF 6333² (Inhaled)
- Nebulized human plasma-derived polyvalent immunoglobulin G (IgG): CSL787³

Phase 2

- DPP-1 inhibitor HSK31858⁴
- Ascorbic acid/glutathione/bicarbonate inhalation⁵

For these and other ongoing clinical trials for NCFBE, please see: <https://tinyurl.com/ye9f3w43>

1. ClinicalTrials.gov: NCT04656275.
2. ClinicalTrials.gov: NCT04010799.
3. ClinicalTrials.gov: NCT04643587.
4. ClinicalTrials.gov: NCT05601778.
5. ClinicalTrials.gov: NCT05495243.



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