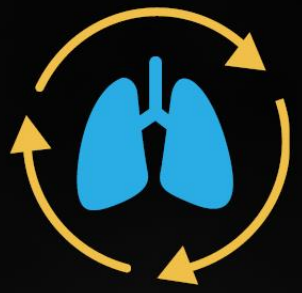
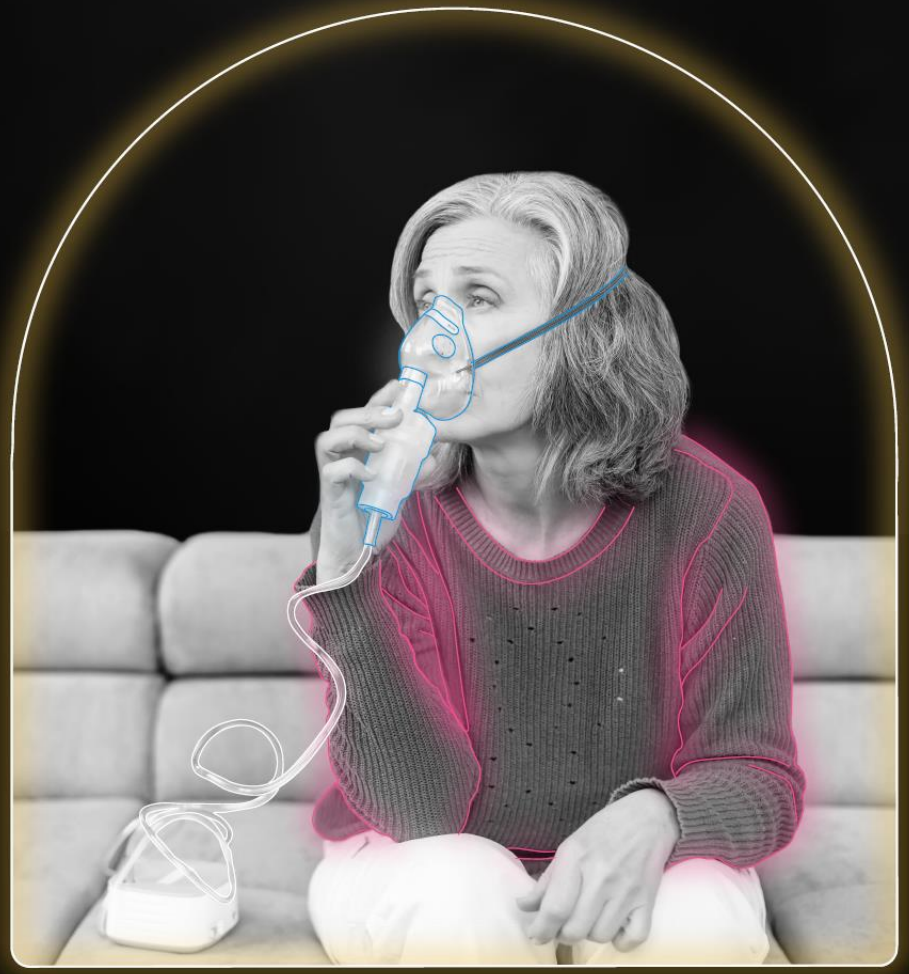
CLINICAL FORUM

Halting the Vicious Vortex

Case-based Discussions in Non-Cystic Fibrosis Bronchiectasis





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Burden of NCFBE

Characterized by:

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

Patient Burden

- Reduced QoL
- Significant financial burden
- Significant morbidity

Risk Factors

- Older age
- Female gender
- Co-existent lung disease
- Prior infections
- Autoimmune disease
- Immunodeficiency
- Chronic aspiration
- Reflux
- ABPA
- Genetic conditions
- Prior NTM-LD

ABPA: Allergic bronchopulmonary aspergillosis
NCFBE, non-cystic fibrosis bronchiectasis
NTM-LD: Nontuberculous mycobacterial lung disease

Choi H, et al. *Sci Rep.* 2021;11(1):7126.
Diehl N, Johnson MM. *South Med J*. 2016;109(12):779-783.
Macfarlane L, et al. *Clin Med* (Lond). 2021;21(6):e571-e57

Epidemiology

US Prevalence

- 340,000 to 520,000

Demographics

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

Mortality

- 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

Severity Associated with:

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

COPD:: Chronic obstructive pulmonary disease

Despotes KA, et al. *Chronic Obstr Pulm Dis.* 2020;7(4):390-403.
Choate R, et al. *Respir Med.* 2020;177:106285.

Audience Question

What do you find most challenging when managing NCFBE in patients?

A. Obtaining an accurate diagnosis
B. Providing adequate patient education
C. Preventing exacerbations
D. Treatment selection
E. Coordinating care with the interprofessional healthcare team

Case 1

AI generated image. Credit: thispersondoesnotexist.com/

“Grace”

87-year-old female

PMH

- Smoker
- Mild COPD
- GERD

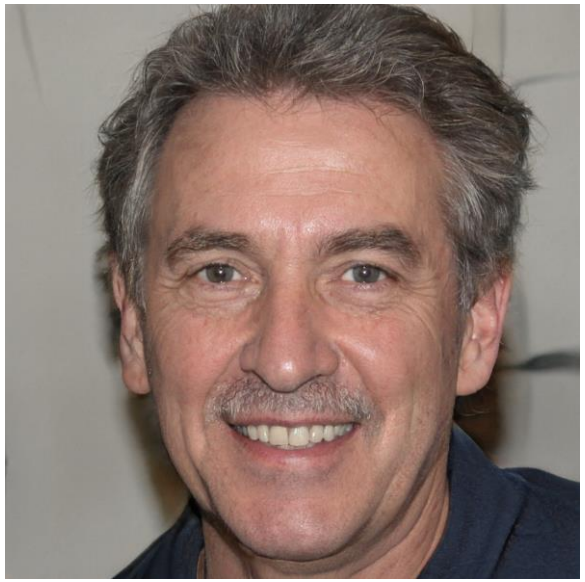
HPI

- Bronchiectasis
- Two sputum cultures positive for MAC, but unable to tolerate therapy
- On bronchodilators
- Currently using a positive expiratory pressure device and high-frequency chest wall oscillation therapy
- Recurrent flare ups

GERD: Gastroesophageal reflux disease
MAC: Mycobacterium avium complex

Name altered for presentation purposes

Case 2



AI generated image. Credit: thispersondoesnotexist.com/

“Dave”

68-year-old male

PMH

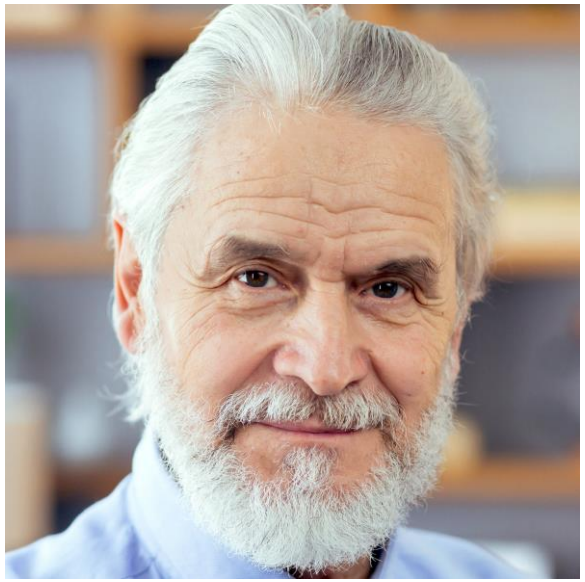
- Rheumatoid arthritis treated with immunosuppressants

HPI

- Developed persistent cough with purulent sputum
- CT showed bronchiectasis, predominant on right side

Name altered for presentation purposes

Case 3



Credit: elements.envato.com/close-up-photo-of-portrait-of-old-man-at-home-look-JRYUALJ

“Bill”

73-year-old male

PMH

- Asthma in younger years
- Non-smoker, but some second-hand smoke
- 10 years of worsening cough, wheezing, intermittent mucous production

HPI

- HRCT identified bronchiectasis
- A bronchoscopic specimen grew *M. avium*
- Immunoglobulin levels normal
- Persistent cough not much improved with bronchodilators
- Started on azithromycin, rifampin, and ethambutol; amikacin liposome inhaled suspension (ALIS) added after 6 months

HRCT: High-resolution computed tomography

Name altered for presentation purposes

Case 4

Credit: elements.envato.com/old-woman-smiling-at-the-beach-2VZSU34

“Mary”

75-year-old female

PMH

- Bronchiectasis
- Non-smoker

HPI

- Daily cough with mucous production
- Treated with inhaled corticosteroids, long-acting bronchodilators
- Uses high-frequency chest wall oscillation therapy daily
- CT stable
- Frequent hospital admissions with symptom exacerbation

Name altered for presentation purposes

Polling Question

What role do bronchodilators play in treating NCFBE?

A. They reduce exacerbation frequency
B. They improve quality of life and lung function
C. They reduce markers of inflammation in blood and sputum
D. They are an option for patients with comorbid asthma or COPD
E. They are never to be used in NCFBE

Role of Neutrophils

Elevated Neutrophils are Associated with:

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

Neutrophil Elastase is a Neutrophil Serine Protease (NSP) Associated with:

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

Inhibiting Dipeptidyl Peptidase 1 (DPP-1)

- DPP-1 activates neutrophil elastase and NSPs in the bone marrow during neutrophil maturation
- 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.

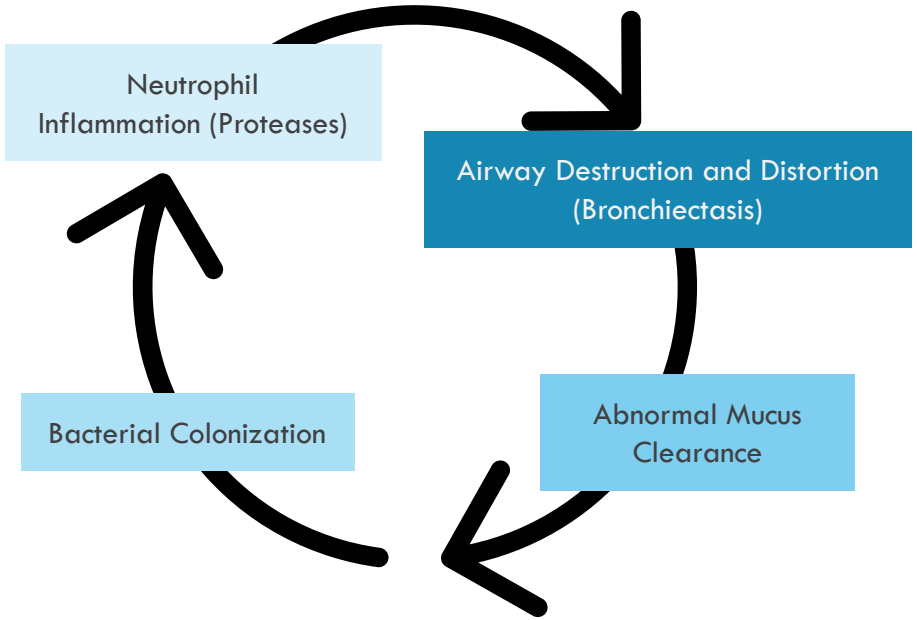
Question

What is the role of DPP-1 in the pathophysiology of NCFBE?

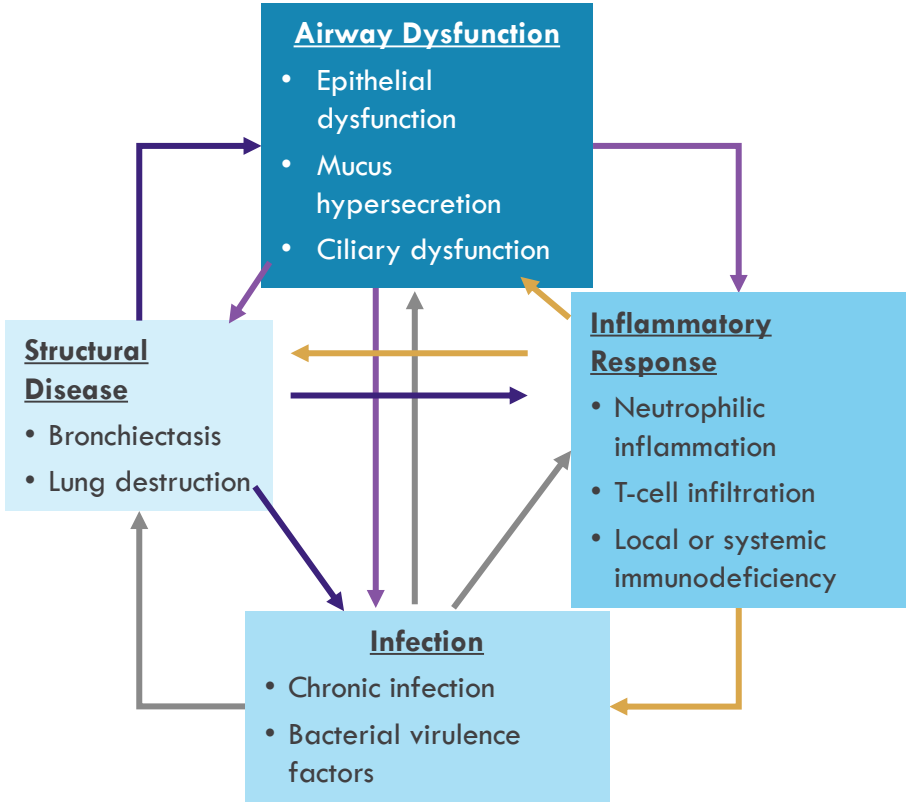
A. It activates neutrophil elastase in the bone marrow
B. It reduces extracellular matrix degradation
C. It increases ciliary beating rate
D. It reduces mucus production

Pathology

Cole's Vicious Cycle[1]



Vicious Vortex[2]



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.

Emerging Therapies Inhibiting Neutrophils

1. NCT04656275.. 2. NCT05238675. 3. Chalmers JD, et al. *N Engl J Med*. 2020;383(22):2127-2137. 4. NCT04594369. 5. NCT05344508

Brensocatib

Mechanism of Action

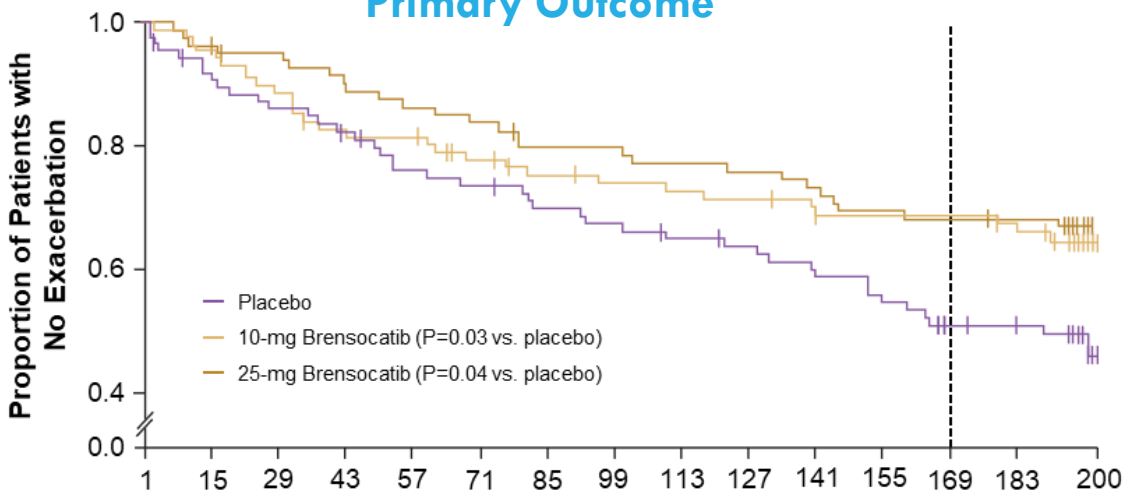
- Selective reversible DPP-1 inhibitor
- Oral small molecule
- Blocks NSP activation

Other Ongoing Study: Phase 3 ASPEN [2,3]

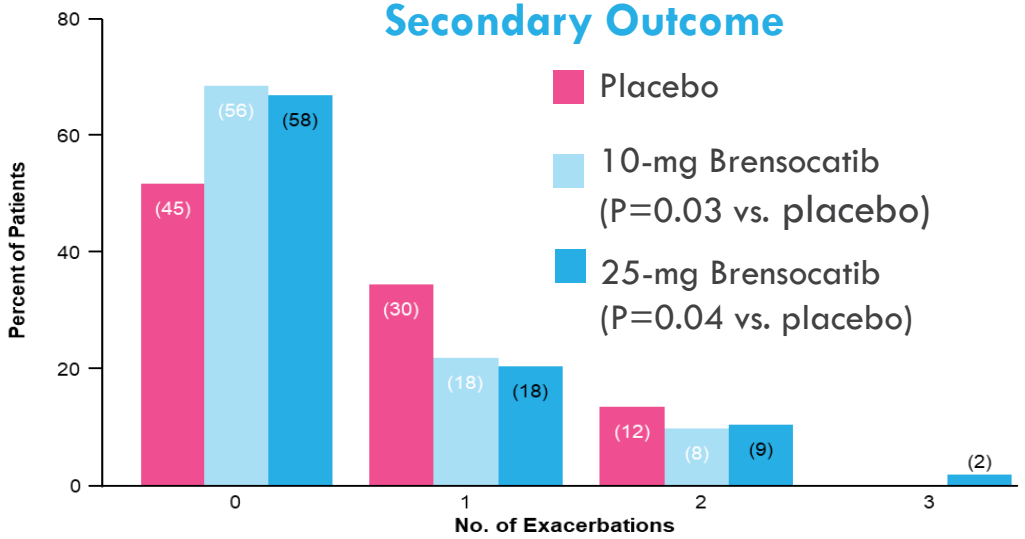
Assess safety, efficacy, and tolerability in persons with NCFBE over 52 weeks

Phase 2 WILLOW

Primary Outcome



Secondary Outcome



NSP, neutrophil serine protease

1. Chalmers JD, et al. *N Engl J Med*. 2020;383(22):2127-2137. 2. ClinicalTrials.gov: NCT04594369. 3. ClinicalTrials.gov: NCT05344508

Thank you!

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