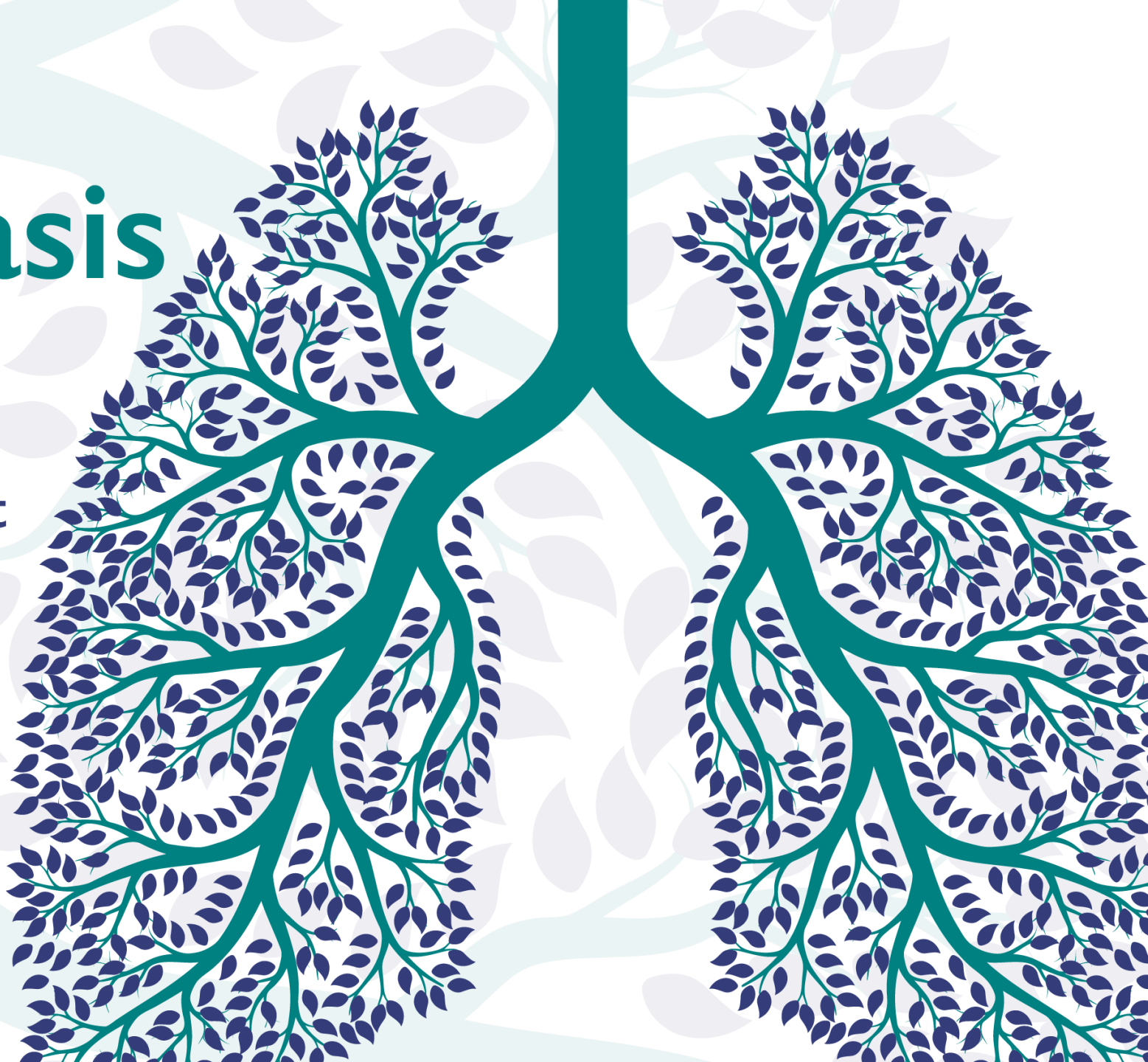
Bridging the Bronchiectasis GAP:

The Latest Emerging Multimodal Treatment Approaches



Provided by The France Foundation

Program Overview

Bronchiectasis is a growing yet under-recognized airway disease, and diagnostic delays continue to cost patients lung function and quality of life. This activity gives you the tools to change that.

- Recognize the cardinal symptoms and red flags that set bronchiectasis apart from asthma and COPD, so you can diagnose it earlier and more accurately
- Understand the neutrophilic inflammation that drives disease progression and pulmonary exacerbations
- Translate the latest clinical trial data on novel therapeutic agents into a practical, multimodal treatment plans
- Put it into practice through an interactive patient case and “What Do You Know?” knowledge checks led by expert pulmonary faculty

Planning Committee and Faculty

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Disclaimer

This educational activity is intended for healthcare professionals for educational purposes only. Information reflects data available at the time of release and may not represent the most current evidence, regulatory status, or prescribing information. Always consult current prescribing information, clinical guidelines, and institutional policies before making clinical decisions.

Educational Support

This activity is supported by an independent medical educational grant from Insmed.

Learning Objectives

- Summarize the epidemiology, patient risk factors, and disease progression of bronchiectasis
- Identify key symptoms to allow an early and accurate diagnosis of bronchiectasis
- Describe the role of neutrophilic inflammation and neutrophil serine proteases in the pathophysiology of bronchiectasis
- Apply evidence-based emerging therapies within a multimodal approach to bronchiectasis management

Knowledge Check!
Look for a brain symbol in the top right corner of the screen to find the answers to the "What Do You Know?" questions

Agenda

1. Minimizing Diagnostic Delays – A Focus on Cardinal Symptoms and Other Red Flags
2. Bronchiectasis Overview: The Role of Neutrophilic Inflammation and the Impact of Pulmonary Exacerbations
3. Examining Clinical Trial Data With Novel Therapeutic Agents
4. Patient Case Review: Implementing a Multi Modal Treatment Approach to Improve Outcomes

Minimizing Diagnostic Delays–A Focus On Cardinal Symptoms and Other Red Flags

What Do You Know?

In a patient with bronchiectasis, which chronic colonizing organism is most strongly associated with more rapid decline in lung function and frequent exacerbations?

A. *Pseudomonas aeruginosa*
B. *Moraxella catarrhalis*
C. *Streptococcus pneumoniae*
D. *Haemophilus influenzae*

What Do You Know?

Which symptom pattern is **most characteristic** of bronchiectasis rather than asthma?

A. Intermittent wheezing with sputum-poor cough
B. Chronic daily productive cough with mucopurulent sputum
C. Recurrent dry cough and chest tightness
D. Frequent nightly cough with clear sputum

How Is Bronchiectasis (BE) Defined?

BE is defined by:

Imaging, identified by HRCT

- Airway to **artery diameter ratio ≥ 1.0**
- **Lack of airway tapering**
- Airway visible in periphery

Clinical features

- **Cough with sputum production** most days of the week
- Frequent pulmonary infections
- Hemoptysis
- Purulence

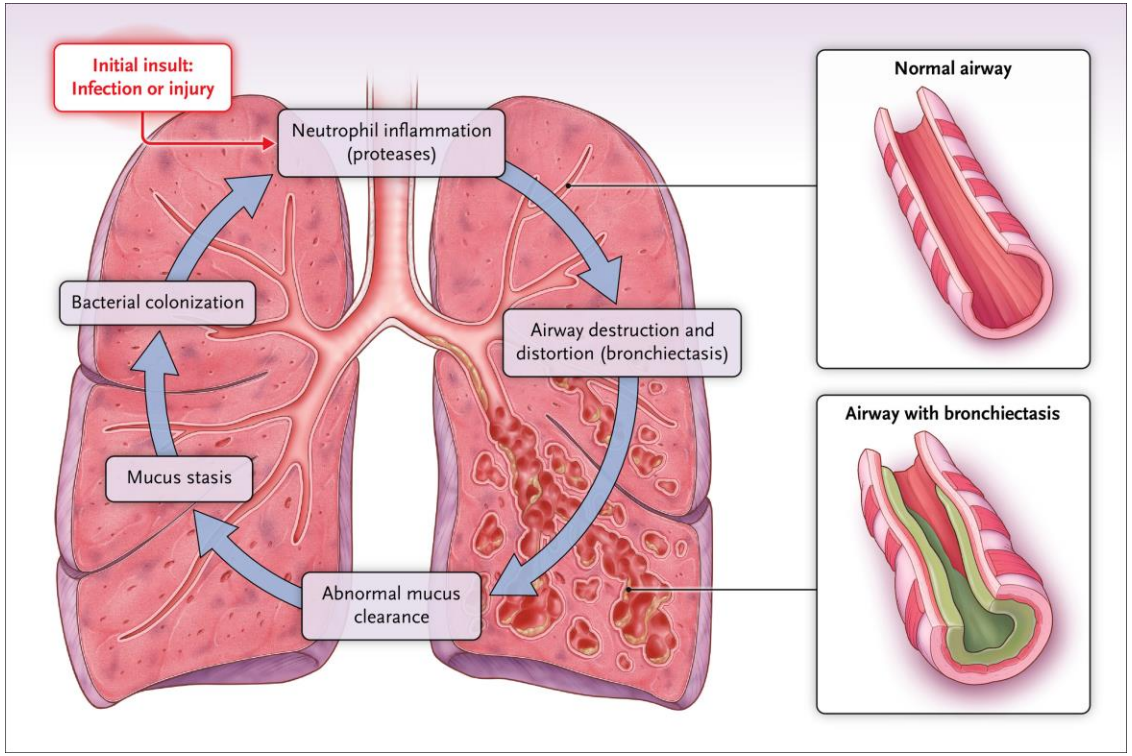
FEV_1 may decline with frequent exacerbations

BE = bronchiectasis; FEV = forced expiratory volume; HRCT= high resolution computed tomography

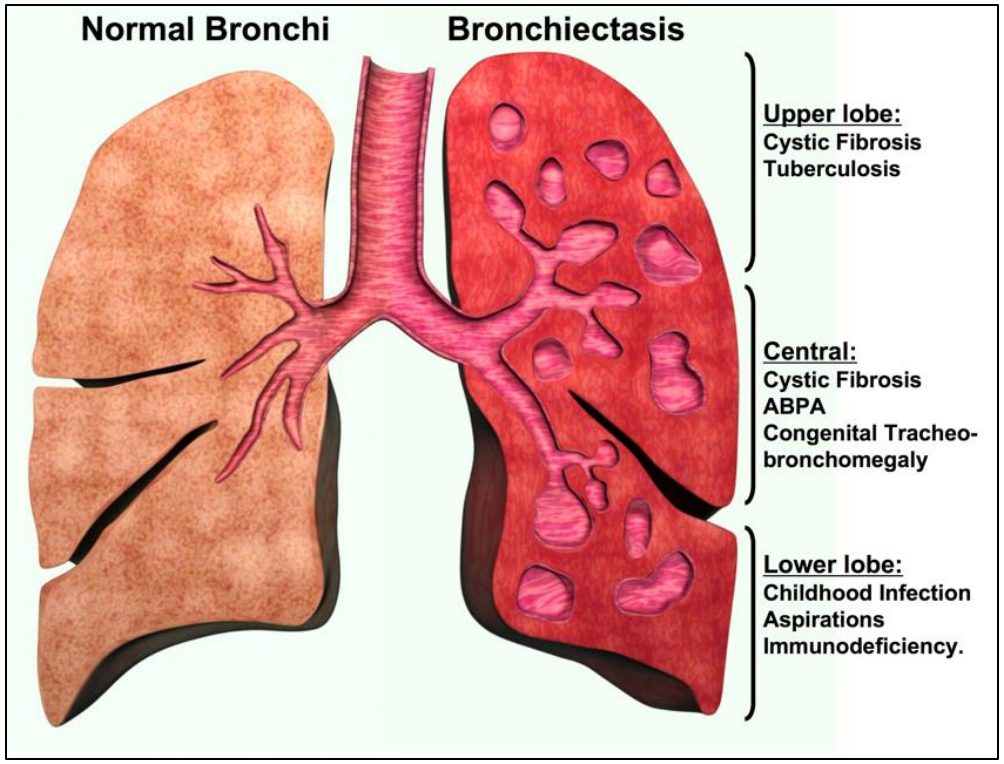
Hill AT, et al. *Thorax*. 2019;74 (suppl 1):1-69; O'Donnell AE. *N Engl J Med*. 2022;387(6):533-545.

Bronchiectasis Features

Airway distortion and impaired mucus clearance are consequences of bronchiectasis pathobiology



Pulmonary distribution may suggest etiology, but overlap between causes is substantial



Based on the US Bronchiectasis Research Registry, ~33% of cases are positive for *Pseudomonas aeruginosa*

ABPA = allergic bronchopulmonary aspergillosis

O'Donnell AE. *N Engl J Med*. 2022;387(6):533-545; Medlibes Online Library. 2010. Accessed April 7, 2025. http://medlibes.com/entry/bronchiectasis; Aksamit T, et al. *Chest*. 2017;151:982-992.

Symptoms Indicative of BE

Unique features

- Productive cough
- Hemoptysis
- Recurrent infectious exacerbations & frequent antibiotics
- Persistent bacterial infection

Overlap with other pulmonary diseases

- COPD
- Asthma

May be part of other systemic diseases

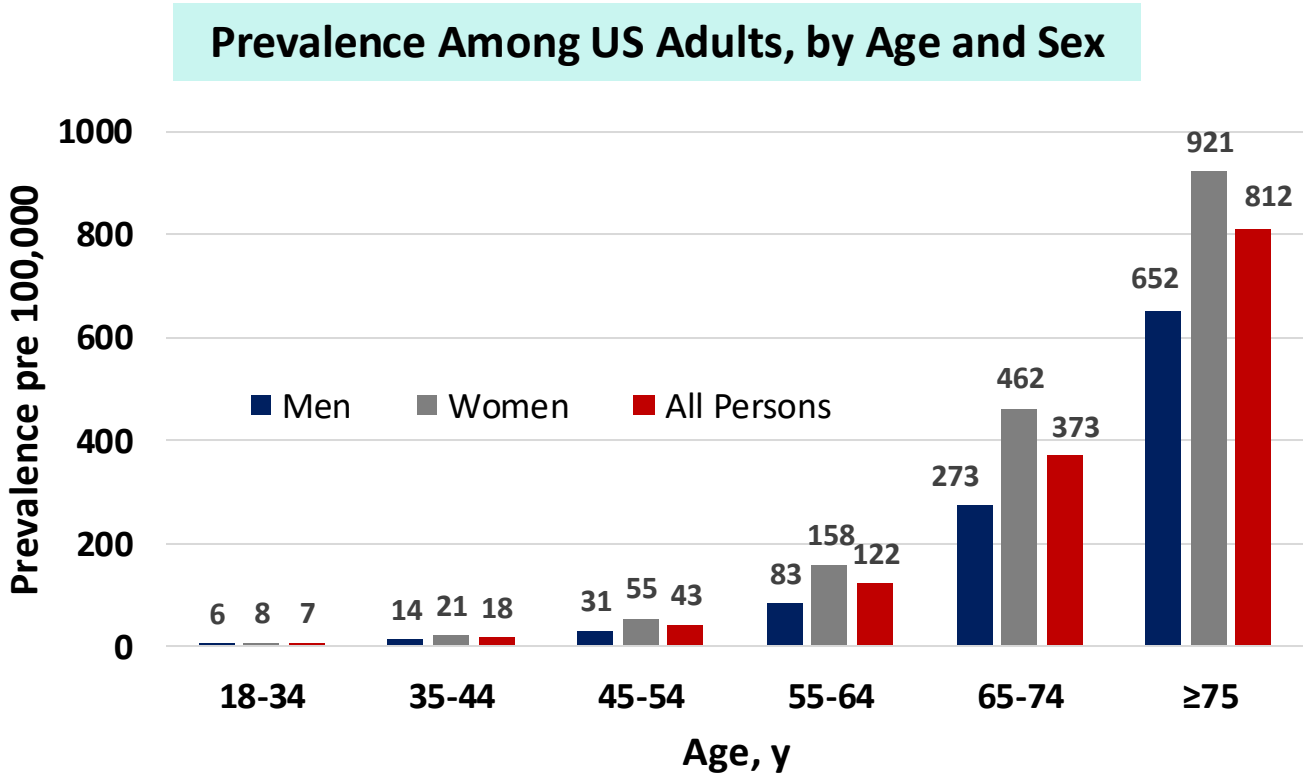
- Genetic and congenital causes
- Autoimmune
- Immunodeficiency
- Gastrointestinal (inflammatory bowel disease, gastroesophageal reflux)
- Persistent cough despite treatment

COPD = chronic obstructive pulmonary disease

McFarlane L, et al. *Clin Med (Lond)*. 2021;21(6):e571-e577; O'Donnell AE. *N Engl J Med*. 2022;387(6):533-545; Hill AT, et al. *Thorax*. 2019;74 (suppl 1):1-69.

BE Epidemiology

- Recent estimate: 340,000-522,000 US adults
  - 67% women
    - 76% aged ≥ 65 years
- Increasing incidence and prevalence
  - 8% annual increase in prevalence from 2001-2013



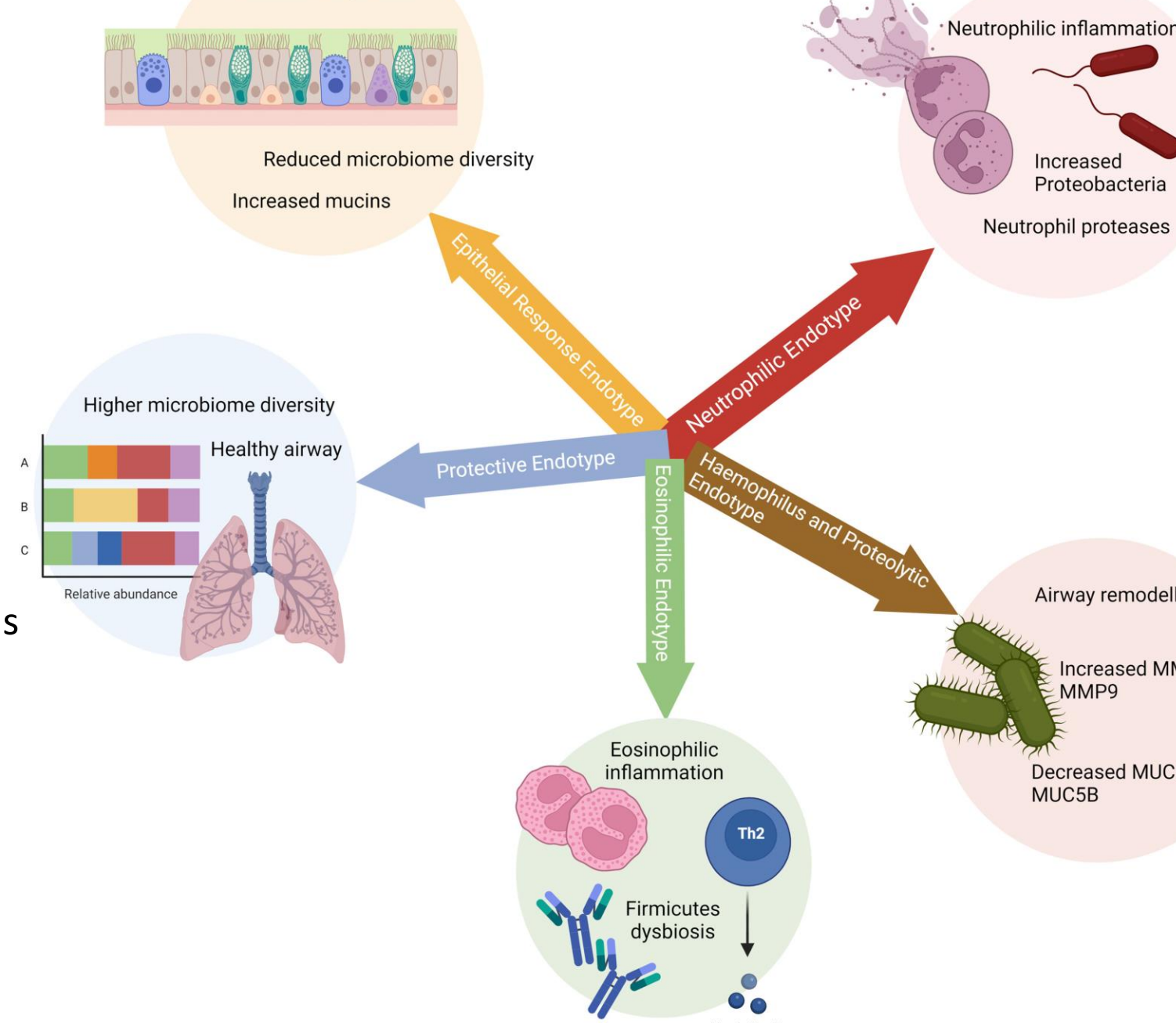
CF = cystic fibrosis; ELCAP = Early Lung and Cardiac Action Program

Weycker D, et al. *Chron Respir Dis*. 2017;14(4):377-384; Seitz AE, et al. *Chest*. 2012;142(2):432-439; Cai Q, et al. *Radiology*. 2022;304(2):437-447.

Understanding Heterogeneity: Endotypes

Endotype vs Phenotype:

- Phenotypes are observable characteristics related to clinically meaningful outcomes
- Endotypes are biological classifications based on specific pathophysiological processes or biomarkers
- BE has a broad constellation of phenotypes and endotypes
- Endotypes can drive treatment decisions



IL = interleukin; MMP = matrix metalloproteinase; MUC = mucin

Choi H, Gao YH. *J Thorac Dis*. 2025;17(4):2640-2654; Flume PA, et al. *Lancet*. 2018;392:880-890; Martins M, et al. *Pulmonology*. 2023;29(6):505-517.

Genetic Diseases and BE

Cystic fibrosis

- Extra-pulmonary involvement
- Sweat testing
- Genetic confirmation
- CFTR modulator therapy

Primary ciliary dyskinesia

- Extra-pulmonary involvement
- Ciliary ultrastructure/ exhaled nasal nitric oxide
- Genetic testing
- New therapeutics

Alpha-1 antitrypsin (AAT) deficiency

- COPD/emphysema/BE/liver disease
- Clinical liver disease develops in ~10% of patients
- Plasma-derived AAT has demonstrated benefits in emphysema
- New therapeutics

CFTR = cystic fibrosis transmembrane conductance regulator

O'Donnell AE. *N Engl J Med*. 2022;387(6):533-545; Goetz DM, Savant AP. *Pediatr Pulmon*. 2021;56(12):3595-3606; Goutaki G, Shoemark A. *Clin Chest Med*. 2022;43:127-140; Strange C. *Clin Chest Med*. 2020:41:339.

What Do You Know?

A 40-year-old man with chronic daily productive cough and recurrent chest infections has a normal chest X-ray. Which statement **most accurately** describes the role of chest radiography in suspected bronchiectasis?

A. When combined with normal spirometry, a normal chest X-ray excludes bronchiectasis.

B. Chest X-rays are more sensitive and reliable for detecting early- and late-stage bronchiectasis than other strategies.

C. **Chest X-rays are insensitive and often normal even in patients with established bronchiectasis; HRCT is required for definitive diagnosis.**

D. Chest X-rays are insensitive because they cannot reliably distinguish bronchiectasis from chronic bronchitis on plain films, so spirometry should determine the need for HRCT.

Diagnostic Evaluation

Confirm diagnosis:
HRCT

Basic Work-Up:

- Pulmonary function tests (PFTs)
- Laboratory testing including:
  - CBC, differential (neutrophilic vs eosinophilic inflammation)
  - Immunoglobulins (IgG, IgM, IgA, IgE, IgG sub-classes)
  - Sputum culture (bacterial, mycobacterial, fungal)
  - Alpha-1 antitrypsin

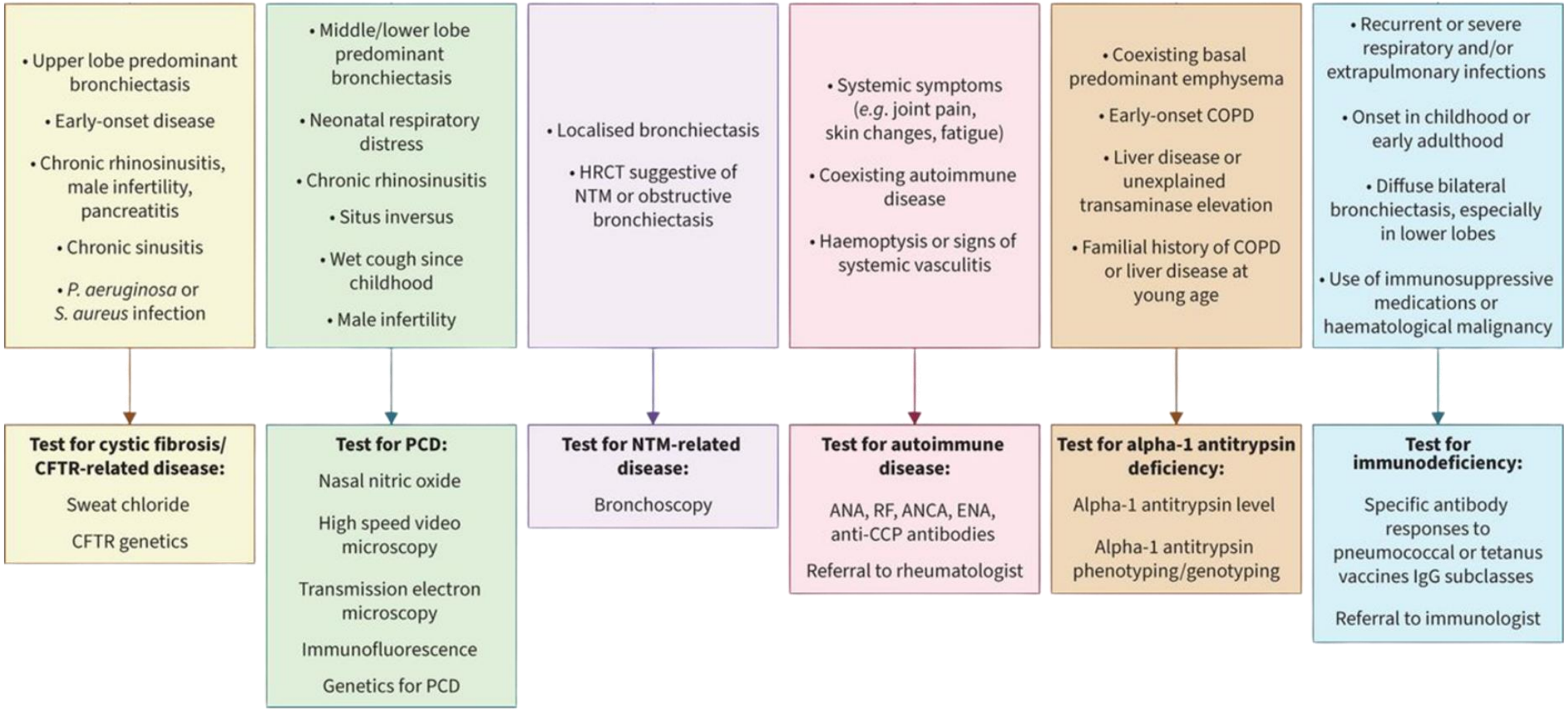
Targeted Testing:

- ABPA testing (IgE, *Aspergillus,* eosinophils)
- Cystic fibrosis (sweat test, *CFTR* genetics)
- PCD (nasal nitric oxide, ciliary biopsy, genetics)
- Autoimmune panel (ANA, RF, ANCA)
- Gastrointestinal evaluation (if aspiration/reflux suspected)
- Induced sputum collection (for those who do not produce)

ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibodies; IgG, IgM, IgA, IgE = immunoglobulin G, M, A, and E; PCD = primary ciliary dyskinesia; RF = rheumatoid factor

O'Donnell AE. *N Engl J Med*. 2022;387(6):533-545; Polverino E, et al. *Eur Respir J*. 2017;50(3):1700629; Hill AT, et al. *Thorax*. 2019;74(suppl 1):1-69; Chalmers JD, et al. *Eur Respir J*. 2025;66(6):2501126.

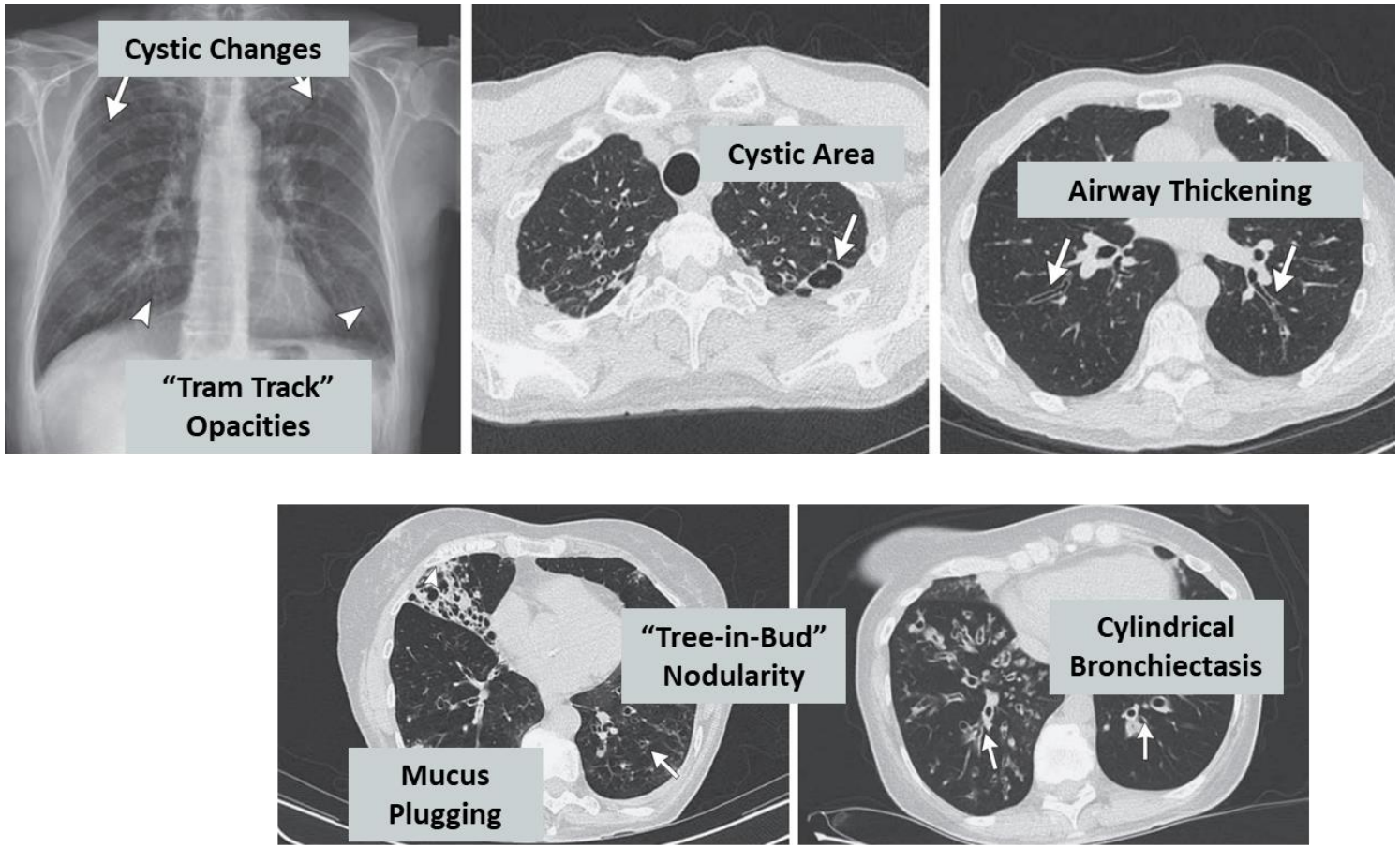
Targeted Assessments for Patients With BE



CCP = cyclic citrullinated peptide; ENA = extractable nuclear antigen; NTM = nontuberculous mycobacteria

Chalmers JD, et al. *Eur Respir J*. 2025;66(6):2501126.

BE Features Seen on Imaging



O'Donnell AE. *N Engl J Med*. 2022;387(6):533-545.

Key Tips and Strategies for Diagnosis

- Consider bronchiectasis when treatments for other obstructive diseases fail (eg, with asthma) or a diagnosis doesn’t fit (COPD w/o smoking)
- Chest X-ray is insufficient for diagnosis; an HRCT is always needed
- Think of bronchiectasis as the "third obstructive disease"
- Always review primary imaging; reports may miss the finding
- A history of recurrent cough and bronchitis should trigger a CT scan
  - Recurrent cough requires frequent empiric antibiotic prescribing for "bronchitis"/sinusitis

Risk Stratification: BE Severity Index (BSI) and FACED Scale

BSI Variable	Points	FACED Variable	Points
Age (years)			
<50	0	<70	0
50–69	2	≥70	2
70–79	4		
≥80	6		
FEV1% predicted			
>80	0	≥50	0
50–80	1	<50	2
30–49	2		
<30	3		
MRC dyspnea score		**Modified MRC dyspnea score**	
1–3	0	0–2	0
4	2	3–4	1
5	3		
Radiological severity			
≥3 lobes involved or cystic bronchiectasis	1	1–2 lobes involved	0
<3 lobes involved	0	>2 lobes involved	1
Chronic colonization by *Pseudomonas aeruginosa*			
N/A	N/A	Yes/No	1

BSI Predicts risk of future mortality, hospitalization, exacerbations, and quality of life

Scoring: 0-4, mild; 5-8, moderate; > 8, severe

FACED Predicts 5-year mortality

Scoring: 0-2, mild; 3-4, moderate; 5-7, severe

FACED = FEV1% predicted, age, chronic colonization by *Pseudomonas aeruginosa*, radiological extent of the disease, and dyspnea

O'Donnell AE. *N Engl J Med*. 2022;387(6):533-545; Martinez-Garcia MA, et al. *Eur Respir J*. 2014;43:135.

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D. Chest X-ray is insensitive mainly because it cannot reliably distinguish bronchiectasis from chronic bronchitis on plain films, so spirometry should determine need for HRCT.

Section Takeaways

- Key symptoms of bronchiectasis include chronic cough and recurrent/chronic airway infections
- Bronchiectasis is diagnosed by HRCT
- Lab assessments for bronchiectasis often include routine and expanded testing
- Testing is focused on identifying underlying endotypes to help provide targeted treatments

The Role of Neutrophilic Inflammation and the Impact of Pulmonary Exacerbations

What Do You Know?

Which mechanism best explains how neutrophil serine proteases, such as neutrophil elastase, cathepsin G, and proteinase 3, contribute to airway remodeling in bronchiectasis?

A. **They degrade extracellular matrix components and disrupt epithelial-barrier integrity**
B. They increase eosinophil degranulation and type 2 cytokine release in the airway
C. They promote goblet cell metaplasia, leading to increased sputum
D. They accelerate extracellular matrix turnover rapidly, leading to scaffolding collapses of the airway

The Role Inflammation in Bronchiectasis

Neutrophilic

- More severe disease
- Lower FeNO
- Weaker bronchodilator response
- Higher levels of IL-8

Eosinophilic

- Less severe disease
- Higher FeNO
- Stronger bronchodilator response
- Higher levels of IL-13

- IL-8 levels correlated with exacerbation frequency
- IL-13 levels correlated with bronchodilator response

FeNO = fractional exhaled nitric oxide; IL = interleukin

Tsikrika S, et al. *Cytokine*. 2017;99:281-286.

Neutrophils in Bronchiectasis

- Inflammation in bronchiectasis is typically driven by neutrophils
- Neutrophil numbers and markers of activation correlate with bacterial load
- Higher neutrophil levels = higher rate of exacerbations

Neutrophilic Inflammation in Bronchiectasis

Measure in Bronchoalveolar Lavage Fluid	Control Group (n = 9)	Bronchiectasis Group (n = 49)
Total cell count, 10^5 cells/mL	11 (7-35)	21 (2-477)
Neutrophils, %	1 (0-4)	37 (0-98)*
Neutrophils, 10^5 cells/mL	0.1 (0-0.48)	1.92 (0-376)*
Elastase, µg/L	34 (9-44)	90.5 (8-2,930)*

*$P < 0.03$

Pembridge T, Chalmers JD. *Breathe*. 2021;17:210119; Chalmers JD, Elborn S, Greene CM. *Eur Respir Rev*. 2023;32:230015; Chalmers JD, et al. *Am J Respir Crit Care Med*. 2012;186(7):657-665; Angrill J, et al. *Am J Respir Crit Care Med*. 2001;164(9):1628-1632.

Mechanisms of Neutrophilic Inflammation

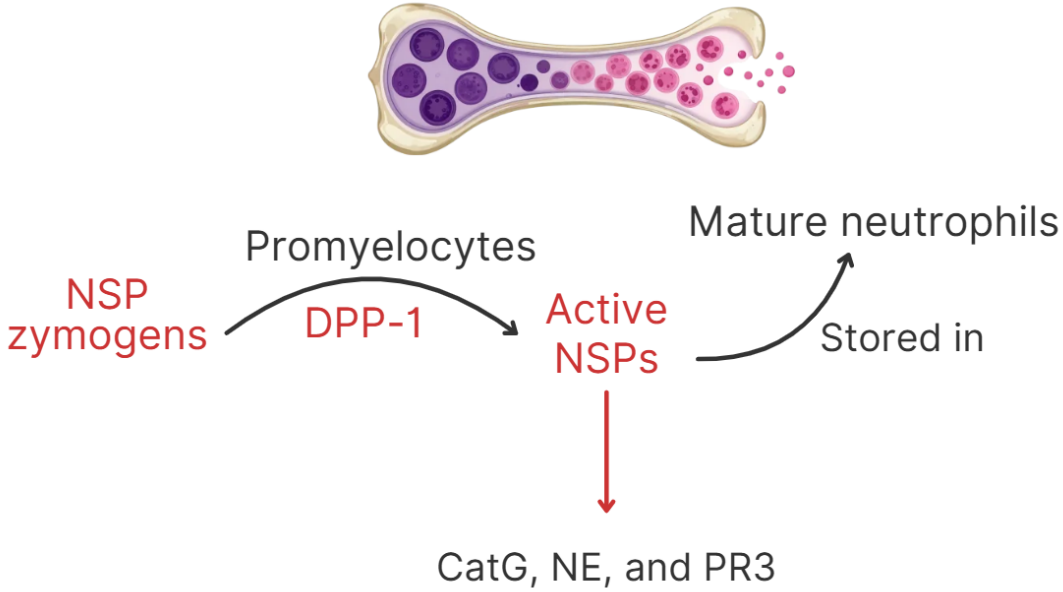
DPP-1 activates neutrophil serine proteases (NSPs)

→ Which activate:

- Neutrophil elastase (NE)
- Proteinase 3 (PR3)
- Cathepsin G (CatG)

→Which:

- Degrade extracellular matrix components
- Disrupt epithelial–barrier integrity



DPP = dipeptidyl peptidase

Tang RD, et al. *J Thorac Dis*. 2025;17(7):5347-5360.

NSPs Contribute to the Vicious Vortex

Mucus hypersecretion

- Results in impaired mucociliary clearance

Structural lung destruction caused by:

- Cleavage of SLPI and elafin
- Degradation of elastin and collagen
- Activation of MMPs

Elevated release of pro-inflammatory cytokines

- Leads to chronic infection and inflammatory responses

DPP = dipeptidyl peptidase

Tang RD, et al. *J Thorac Dis*. 2025;17(7):5347-5360.

Definition of Bronchiectasis Exacerbations

Patient-Focused Definition

- A change in respiratory symptoms significant enough that they seek care
- Novel patient-focused exacerbation diaries
- Can be subjective
- Symptom changes are subtle and hard to recognize

Clinical Trial Definition

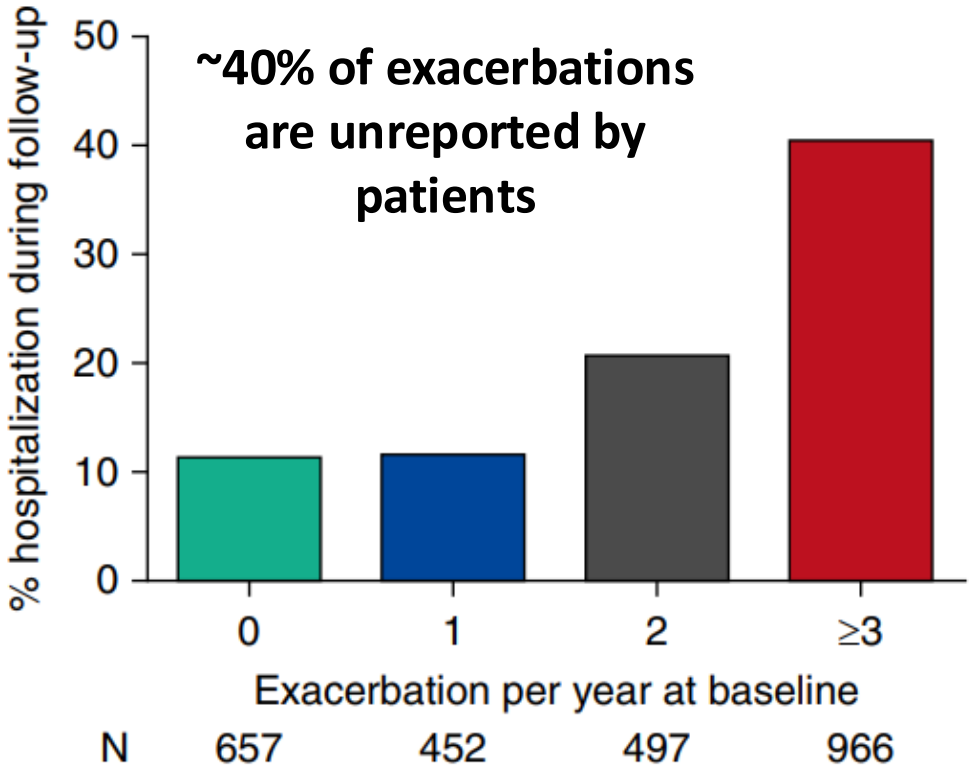
- Deterioration of 3 or more key symptoms for > 48 hours
  - Cough
  - Sputum volume/consistency
  - Sputum purulence/color
  - Breathlessness and/or exercise intolerance
  - Fatigue/malaise
  - Hemoptysis
- Physician agreement that these constitute an exacerbation (eg, treatment change is needed)

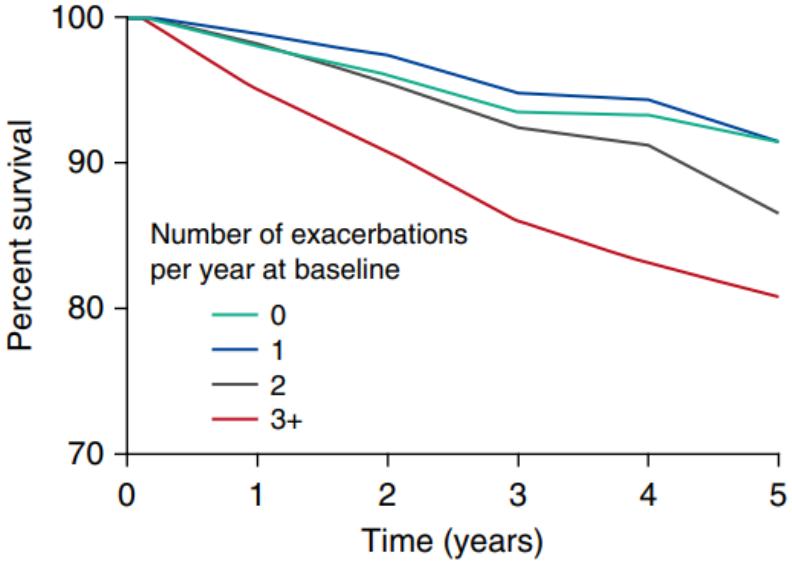
Frequent exacerbations are associated with poorer QoL scores

Choi H, Chalmers JD. *Ann Transl Med*. 2023;11(1):25; Hill AT, et al. *Eur Respir J*. 2017;49:1700051.

Frequent Exacerbations Are Associated With Poorer Outcomes

5-Year Follow-Up of Hospitalization Rate and Survival Stratified by Number of Exacerbations Per Year at Baseline





Numbers at risk

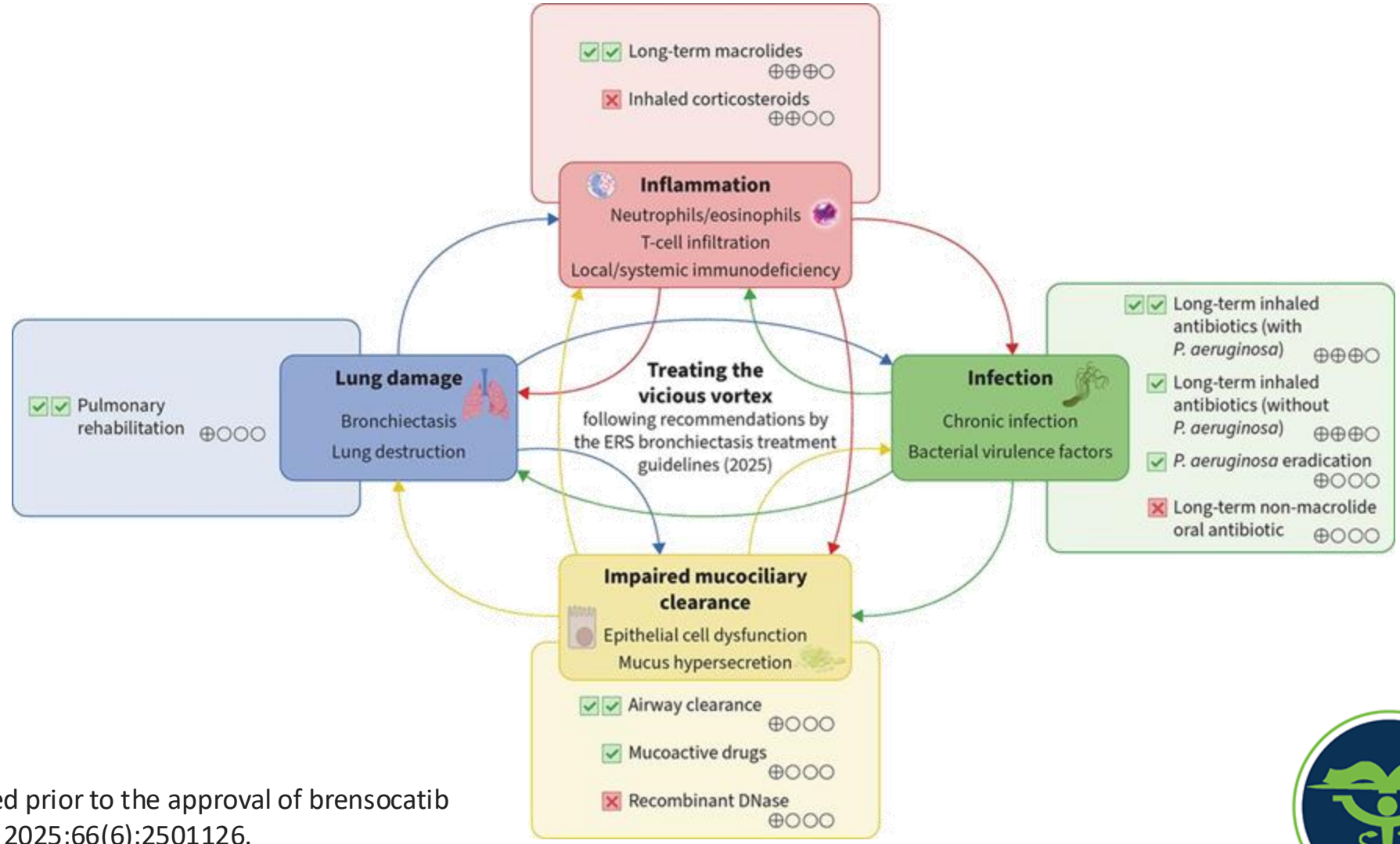
0	657	654	600	554	522	153
1	452	444	402	381	351	134
2	497	490	437	407	376	196
3 or more	966	958	836	771	694	365

Chalmers JD, et al. *Am J Respir Crit Care Med*. 2018;197(11):1410-1420; Artaraz A, et al. *Respir Res*. 2020;21(1):18.

Treating the Vicious Vortex*

Recommendations:

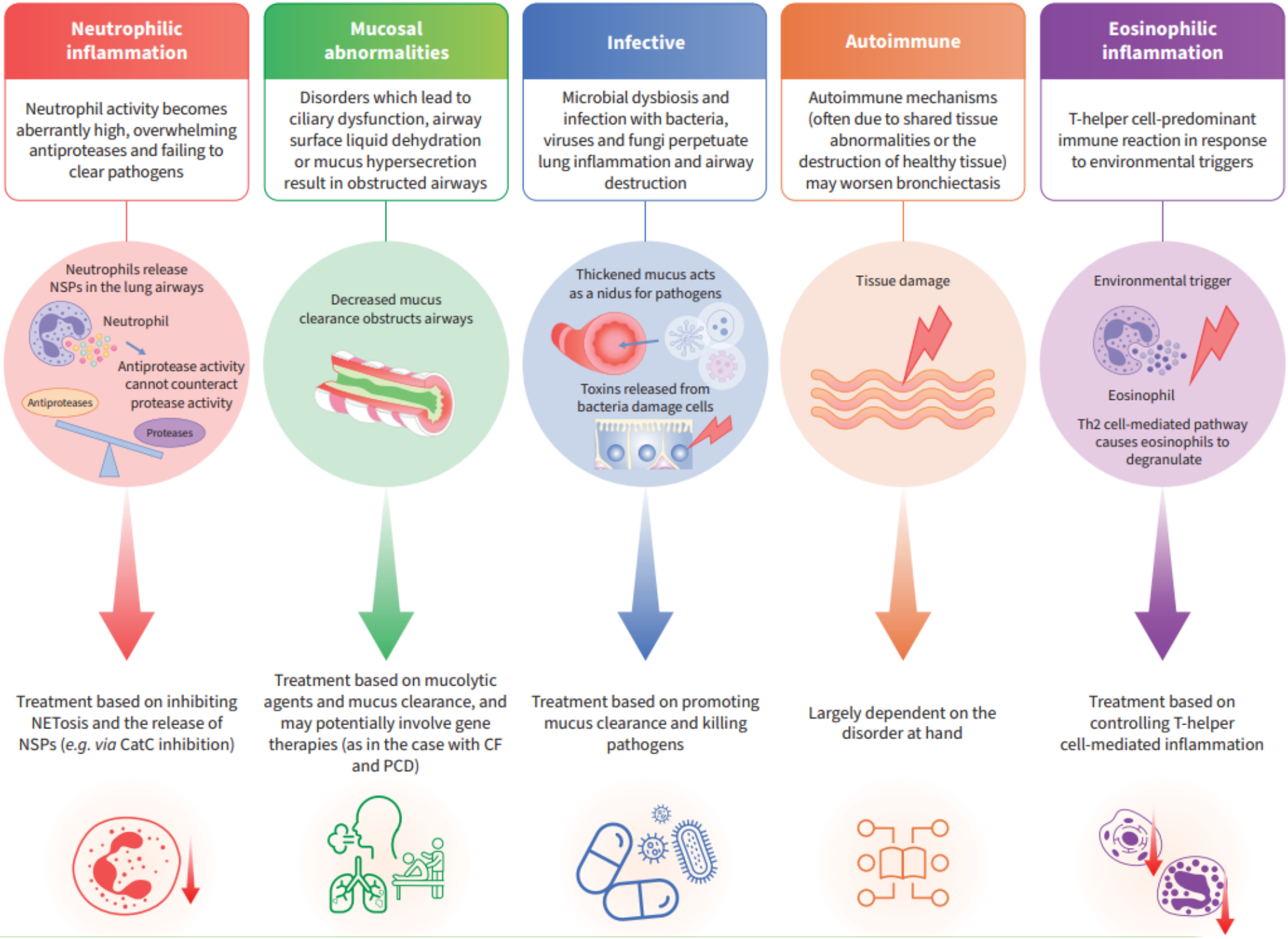
- **Green** = in favor (✓✓ strong, ✓ conditional)
- **Red** = against (✕ conditional)
- Evidence certainty: 1–4 crosses = very low → high



*These guidelines were released prior to the approval of brensocatib

Chalmers JD, et al. *Eur Respir J*. 2025;66(6):2501126.

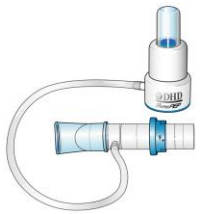
Treatment Strategies by BE Endotype



Chalmers JD, et al. *Eur Respir J*. 2025;65(1):2401050.

The Cornerstone of Treatment: Airway Clearance

- Mucus plugging leads to:
  - Local tissue hypoxia
  - Decreased ion channel function
  - Bacterial infection and overgrowth
- Airway clearance strategies promote mucus clearance via mechanical stress and hydration
- These strategies reduce cough, improve QoL, and reduce exacerbations
  - No data exist for the optimum frequency or duration



Strategies for Airway Clearance	
Device-Mediated	**No Device Needed**
Positive expiratory pressure (PEP) device	Active cycle breathing (ACB)
O-PEP (oscillating)	Forced expiratory technique (FET)
High-frequency chest wall oscillation (HFCWO), eg, “the Vest”	Manual percussion/vibration
-	Autogenic drainage

Herrero-Cortina B, et al. *Eur Respir J*. 2023;62(1):2202053; McShane PJ, et al. *Am J Respir Crit Care Med*. 2013; 18:647–656.

Overview of Pharmacological Treatment Strategies

There is no one treatment for bronchiectasis. Instead, we rely on several pharmacologic and non-pharmacologic treatments.

Order of administration:

1st: Short-acting bronchodilators
2nd: Mucolytics
3rd: Airway clearance techniques
4th: Inhaled antibiotics
5th: Inhaled corticosteroids

BCOS = bronchiectasis and COPD overlap; ICS = inhaled corticosteroid; NAC = N-acetylcysteine

Bronchodilators

FEV_1 ↑ (in BCOS)

Inhaled antibiotics

Bacteria load ↓, QOL ↑, exercise capacity ↑, exacerbation ↓

Mucoactive drugs

- Isotonic saline/humidification – sputum clearance ↑
- Hypertonic saline – QOL ↑, sputum clearance ↑
- Inhaled dry powder mannitol – sputum clearance ↑, antibiotics usage ↓, QOL ↑, time to next exacerbation ↑
- NAC – exacerbation risk ↓

Anti-inflammatory drugs

- ICS – benefits in eosinophilic bronchiectasis
- Long-term macrolides: QOL ↑, exacerbation
- Brensocatib
- Additional therapies in clinical trials

Choi JY. *Tuberc Respir Dis*. 2023;86(3):183-195; Agent P, et al. *Breathe (Sheff)*. 2015;11(2):110-118.

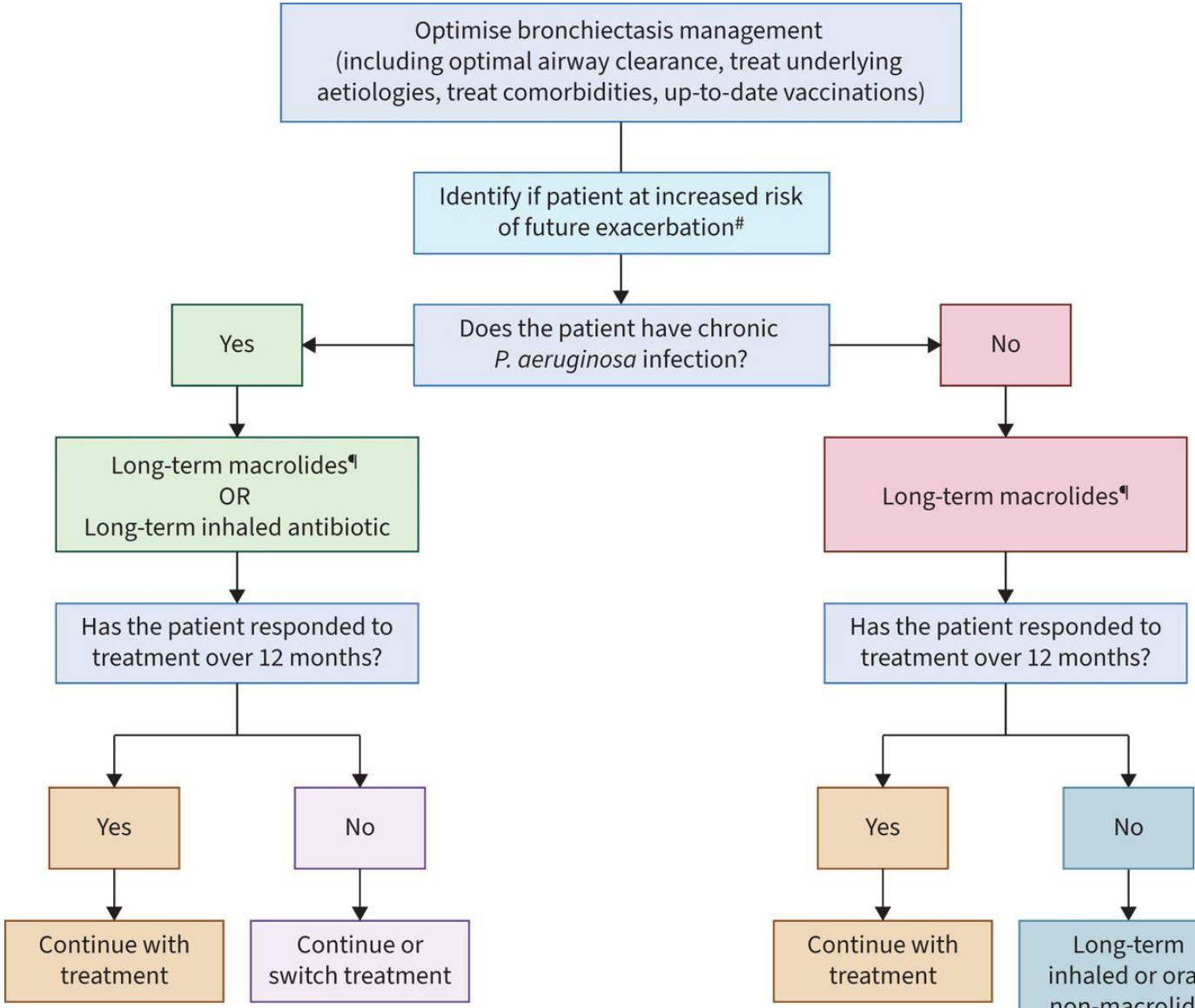
Adverse Events Associated With Pharmacological Treatment Strategies

Drug Class	Common Adverse Events	Serious Adverse Events	Important Safety Considerations
Bronchodilators	Tachycardia, arrythmias, palpitations, anxiety jitteriness	Tachycardia arrythmias	Use caution in patients with cardiac disease; review cardiac history for arrythmias
Mucoactive drugs	Cough, hoarseness, oropharynx irritation	Bronchospasm	Consider close monitoring in those with hyperreactive airways disease
Inhaled antibiotics	Cough, bronchospasm, hoarseness, dysphonia	Ototoxicity, nephrotoxicity, antibiotic resistance, bronchospasm	Monitor hearing/renal function if prolonged aminoglycoside use is a concern
Anti-inflammatory drugs	**ICS:** Thrush, hoarseness, throat irritation	Pneumonia risk, systemic steroid effects with higher exposure	Use selectively; balance benefit against infection risk
	Long-term macrolides: GI upset, taste disturbance	QT prolongation, arrhythmias, hearing loss, severe rash/SCAR, antibiotic resistance	Check drug interactions and QT risk; consider ECG and hearing monitoring; watch for antimicrobial resistance
	Brensocatib: Rash, dry skin, hyperkeratosis, gingival/dental changes, headache, URTI symptoms	Dental/gingival complications, elevated liver enzymes, possible skin cancer signal, severe infection events reported in trials	Monitor skin, oral/dental health, and liver tests; review drug interactions, especially CYP3A4-related interactions

Chalmers JD, et al. Eur Respir J. 2025;66(6):2501126; Martinez-Garcia MA, et al. *Drugs*. 2022;82(14):1453-1468; Tarrant BJ, et al. *Respirology*. 2017;22(6):1084-1092; Chalmers JD, et al. *ERJ Open Res*. 2023;9(3):00695-2022. Mihălțan FD, et al. *J Clin Med*. 2026;15(3):1257; King P. *Drugs*. 2007;67(7):965-974; Vanoverschelde A, et al. *J Antimicrob Chemother*. 2021;76(10):2708-2716.

Optimizing Management of Bronchiectasis

- While a 12-month re-evaluation is suggested, earlier reassessment is needed
  - Specifically in the case of adverse events or clinical deterioration
- Patients at high risk of future exacerbation if experiencing ≥2 exacerbations per year, 1 exacerbation per year plus severe symptoms or ≥1 severe exacerbation requiring hospitalization per year;
- Following exclusion of non-tuberculous mycobacteria. *P. aeruginosa*



Chalmers JD, et al. *Eur Respir J*. 2025;66(6):2501126.

What Did You Learn?

Which mechanism best explains how neutrophil serine proteases, such as neutrophil elastase, cathepsin G, and proteinase 3, contribute to airway remodeling in bronchiectasis?

A. **They degrade extracellular matrix components and disrupt epithelial-barrier integrity**

B. They increase eosinophil degranulation and type 2 cytokine release in the airway

C. They promote goblet cell metaplasia, leading to increased sputum

D. They accelerate extracellular matrix turnover so rapidly that airway scaffolding collapses

Section Takeaways

- Neutrophilic inflammation plays a key role in BE
- Neutrophil serine proteases have been identified as a therapeutic target for treating BE
- BE treatments are centered around preventing exacerbations, which are associated with disease progression
- Targeted treatments require a multimodal approach to interrupt the vicious vortex

Examining Clinical Trial Data With Novel Therapeutic Agents

What Do You Know?

Which of the following best describes the mechanism of action of brensocatib?

A. Neutrophil elastase inhibitor that reduces airway bacterial burden and acute infections

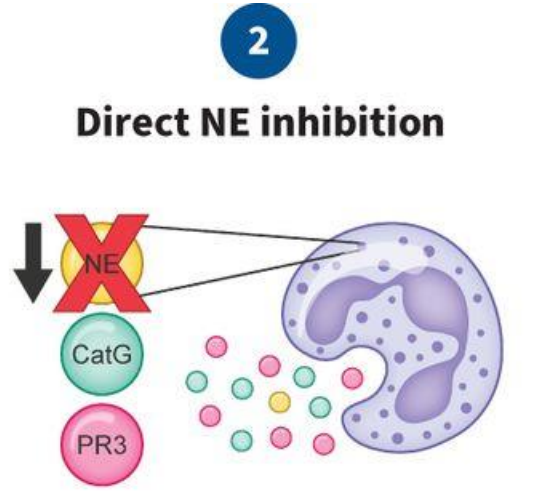
B. **DPP-1 inhibitor that reduces activation of neutrophil serine proteases, decreasing neutrophil-driven airway inflammation**

C. IL-5 receptor antagonist that reduces eosinophilic inflammation and airway hyperresponsiveness

D. Inhaled bronchodilator that improves mucociliary clearance and reduces airflow obstruction

Approved Therapy for BE: Brensocatib

- Brensocatib is a small molecule inhibitor of DPP-1
- DPP-1 activates NSPs during neutrophil maturation
- Brensocatib reduces neutrophil-driven inflammation, leading to lower levels of neutrophil elastase and other proteases
  - Lung function improvement (measured by FEV_1)
  - Reduction pulmonary exacerbations
  - Improved respiratory symptoms



Approved in August 2025 to treat NCFBE in patients aged ≥ 12 years

NCFBE = non-cystic fibrosis bronchiectasis

Bell SC, Grimwood K. *Engl J Med*. 2025;392(17):1635-1637; Chalmers JD, et al. *N Engl J Med*. 2025;392(16):1569-1581. https://www.ajmc.com/view/brensocatib-becomes-first-fda-approved-therapy-for-bronchiectasis; Chalmers JD, et al. *Eur Respir J*. 2025;65(1):2401050; Clinicaltrials.gov

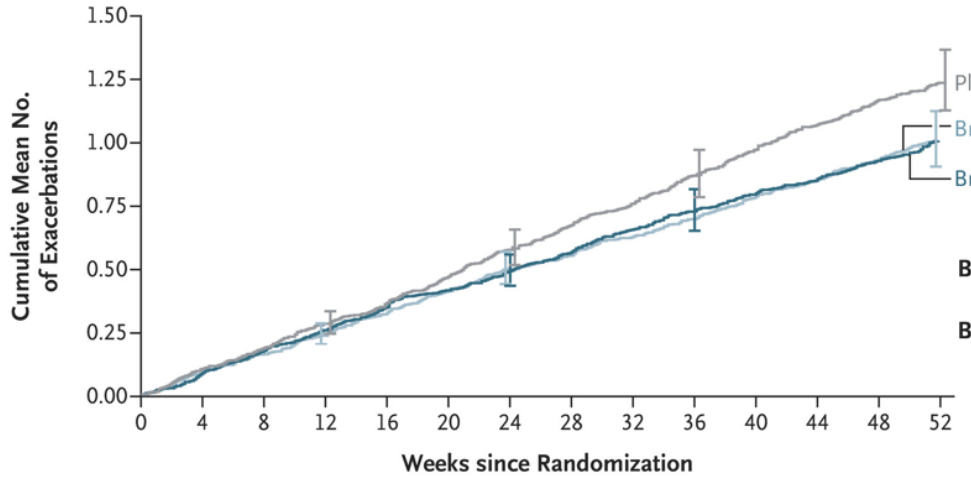
Overview of Brensocatib in ASPEN Clinical Trial

Clinical Trial: Phase 3 (ASPEN trial)	• International, double-blind, randomized, placebo-controlled trial for adults and adolescents with BE to evaluate the efficacy and safety of 52 weeks of once-daily 10-mg or 25-mg added to existing clinical management
Select Inclusion/Exclusion Criteria	• Non-cystic fibrosis bronchiectasis • Included patients with > 2 pulmonary exacerbations that required antibiotics • Excluded those with COPD, asthma, CF, or those being treated for NTM
Key Result	• **Treatment with brensocatib** led to **lower annualized rate of exacerbations than placebo** in patients with bronchiectasis • **Lung function decline was less** with the **25-mg dose** than placebo – Mean FEV_1 decline: −50 ± 9 mL (10 mg brensocatib), −24 ± 10 mL (25 mg brensocatib), −62 ± 9 mL (placebo)
Side Effects	• Generally well tolerated • Safety profile comparable to placebo

Chalmers JD, et al. *N Engl J Med*. 2025;392(16):1569-1581; https://clinicaltrials.gov/study/NCT04594369

ASPEN: Efficacy Endpoints

Exacerbations over 52-Weeks

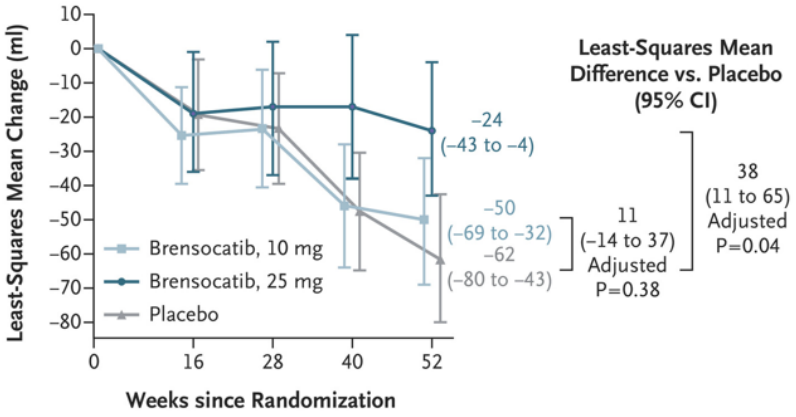


	Rate Ratio vs. Placebo (95% CI)	Adjusted P Value
Brensocatib, 10 mg (N=583)	0.79 (0.68 to 0.92)	0.004
Brensocatib, 25 mg (N=575)	0.81 (0.69 to 0.94)	0.005
Placebo (N=563)	—	—

No. at Risk

Brensocatib, 10 mg	583	582	582	576	570	565	564	555	546	540	533	529	522	516
Brensocatib, 25 mg	575	572	568	566	563	552	550	543	540	537	528	523	520	515
Placebo	563	562	556	551	547	544	539	534	529	522	519	509	507	499

Change in Postbronchodilator FEV_1 from Baseline



No. with Data

Brensocatib, 10 mg	579	545	529	513	475
Brensocatib, 25 mg	571	529	523	494	487
Placebo	563	522	513	494	468

Chalmers JD, et al. *N Engl J Med*. 2025;392(16):1569-1581.

ASPEN: Safety Summary

Most common adverse events n (%)	Brensocatib 10 mg (N = 582)	Brensocatib 25 mg (N = 574)	Placebo (N = 563)
Covid-19	92 (15.8)	120 (20.9)	89 (15.8)
Nasopharyngitis	45 (7.7)	36 (6.3)	43 (7.6)
Cough	41 (7.0)	35 (6.1)	36 (6.4)
Headache	39 (6.7)	49 (8.5)	39 (6.9)
Most common serious adverse events n (%)			
Bronchiectasis	47 (8.1)	48 (8.4)	67 (11.9)
Pneumonia	11 (1.9)	13 (2.3)	16 (2.8)
Any adverse event of special interest	42 (7.2)	56 (9.8)	53 (9.4)
Hyperkeratosis	8 (1.4)	17 (3.0)	4 (0.7)
Periodontitis or gingivitis	8 (1.4)	12 (2.1)	15 (2.7)
Severe infection	4 (0.7)	7 (1.2)	4 (0.7)
Pneumonia	23 (4.0)	27 (4.7)	33 (5.9)

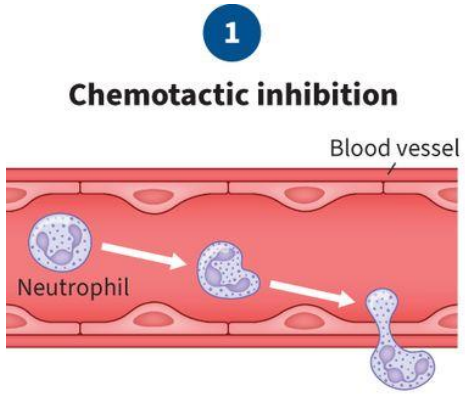
Adverse events resulting in death were:

- **10-mg group** (n = 3)**:** aspergillus infection, acute respiratory failure, and bronchiectasis
- **25-mg group** (n = 4)**:** pneumonia, myocardial infarction, general physical health deterioration, and road traffic accident
- **Placebo** (n = 7)**:** pneumonia, acute respiratory failure, bronchiectasis, hemoptysis, cardiac arrest, cardiorespiratory arrest, and cervical vertebral fracture

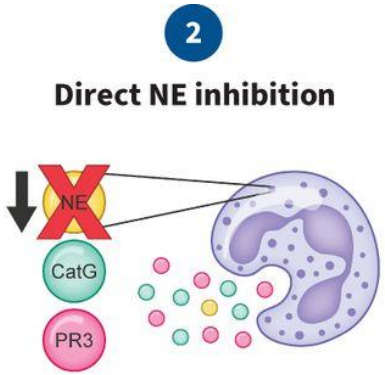
Chalmers JD, et al. *N Engl J Med*. 2025;392(16):1569-1581.

Investigational BE Therapies

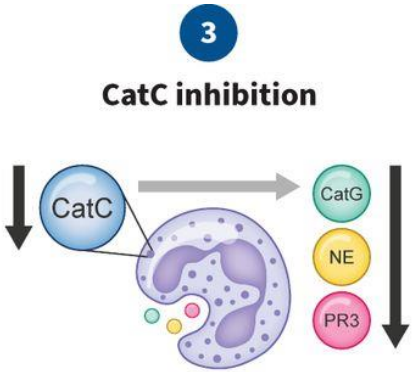
Emerging Treatment	Mechanism of Action
II33mAb (Itepekimab)	Anti-interleukin-33 (IL-33) monoclonal antibody
Ensifentrine	PDE3/PDE4 inhibitor
HSK31858	DPP-1 inhibitor
BI 1291583 (verducatib)	DPP-1 inhibitor



Reduction of neutrophil infiltration into the airway by inhibition of chemotaxis



Limiting overall protease activity by direct inhibition of NE

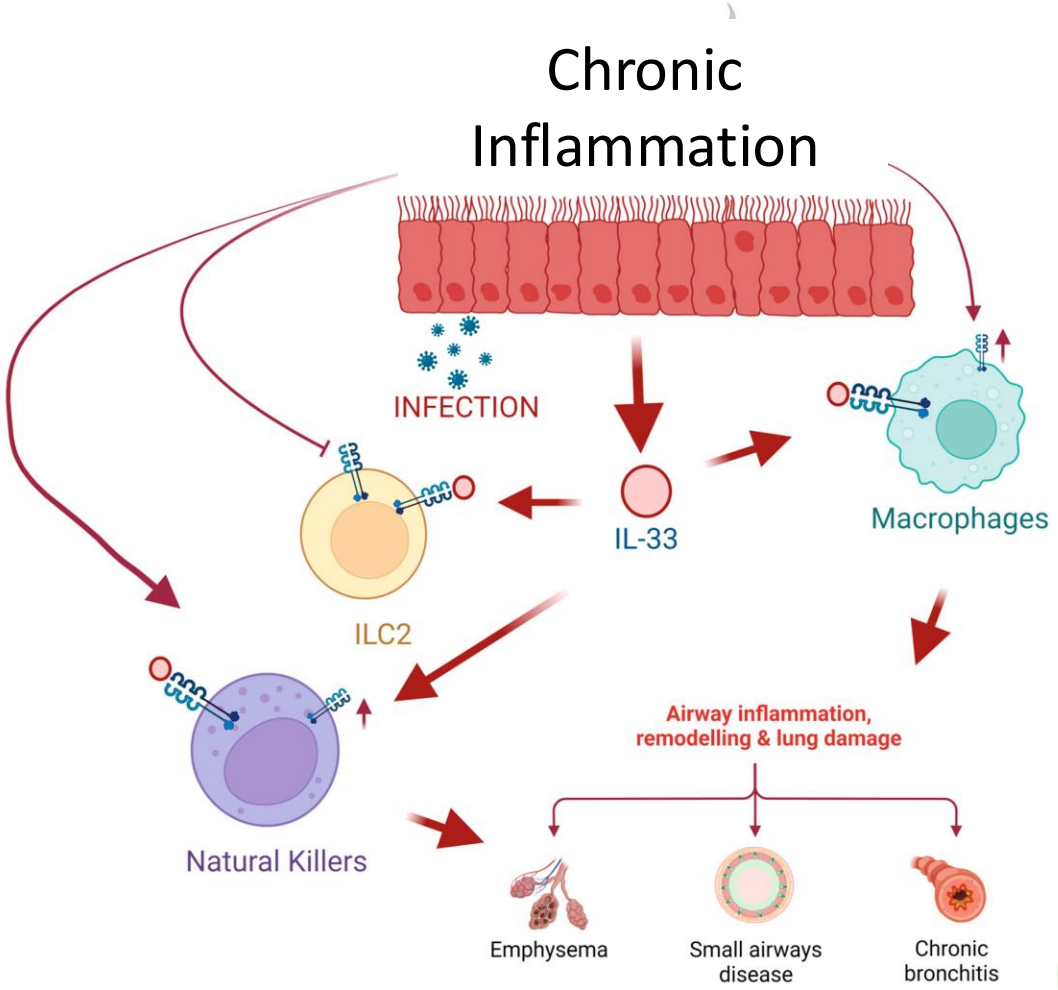


Inhibition of CatC to limit activation of NSPs in the bone marrow, thereby lessening their effects as well

Chalmers JD, et al. Targeting neutrophil serine proteases in bronchiectasis. *Eur Respir J*. 2025;65(1):2401050; Clinicaltrials.gov

Mechanism of Action of Itepekimab

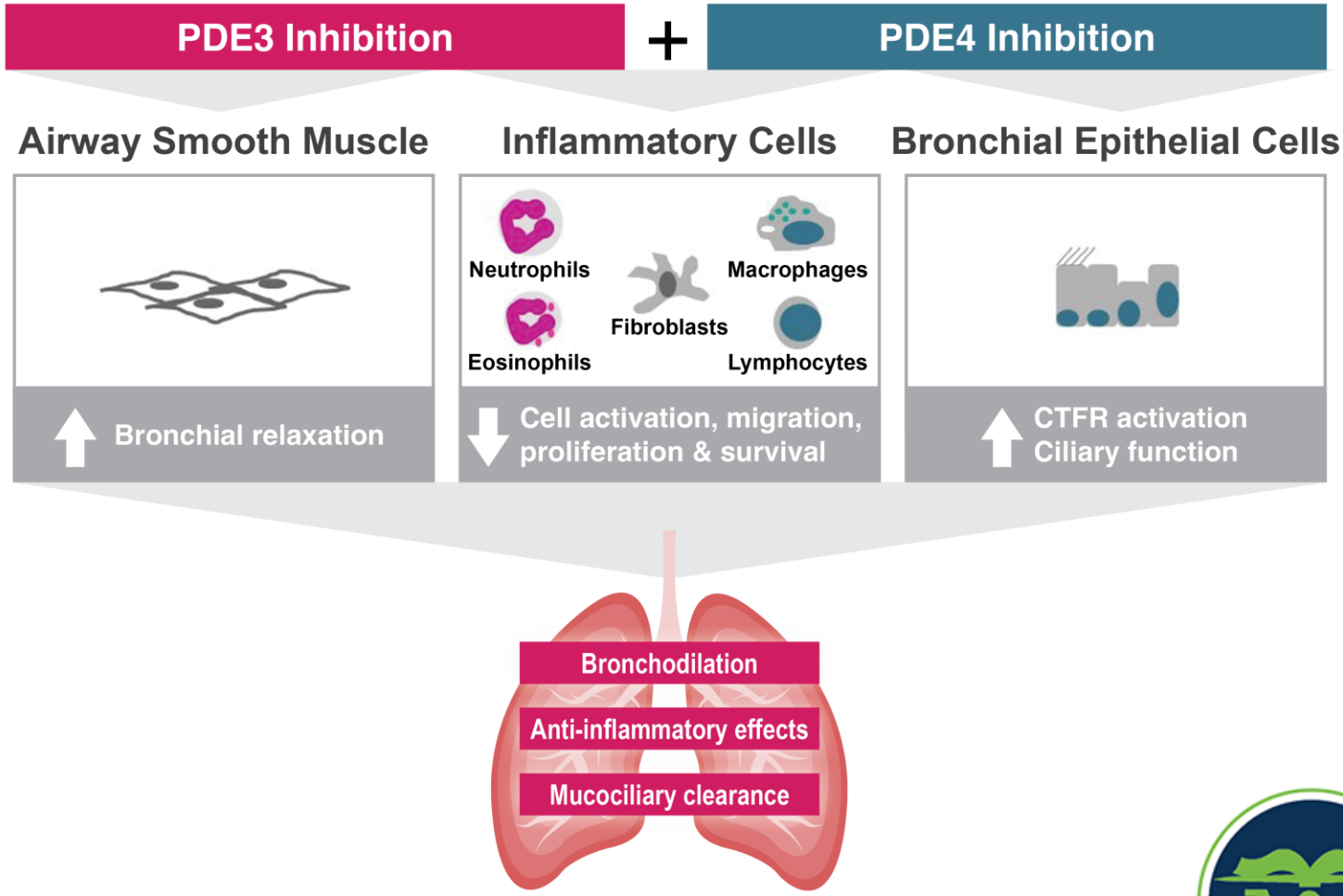
- Inhibits IL-33 from activating the downstream inflammatory cascade through its receptor, ST2/IL1RL1
  - Reduces inflammation and immune cell recruitment to the damaged tissue
- Currently in Phase 2 clinical trials for non-cystic fibrosis bronchiectasis



Kosloski M, et al. *Clin Transl Sci*. 2022;15(2):384-395; Riera-Martínez L, et al. *Int J Mol Sci*. 2023;24(10):8702.

Mechanism of Action of Ensifentrine

- In bronchial epithelia, it combines enhanced effects on
  - Inflammation
  - Bronchodilation
  - Mucociliary clearance
- Approved for maintenance treatment of COPD in adults
- Currently in Phase 2 clinical trials for non-cystic fibrosis bronchiectasis



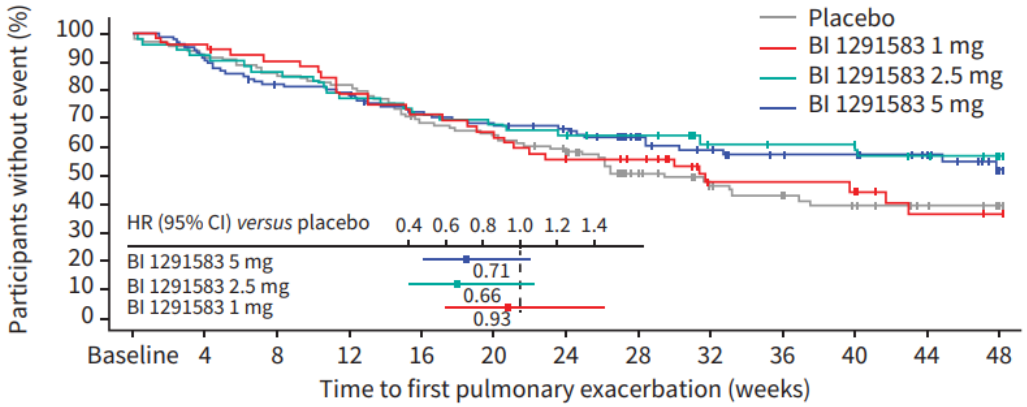
PDE = phosphodiesterase

Donohue JF et al. *J Chron Obstruct Pulmon Dis*. 2023 Jul 28;18:1611–1622.

Overview of Verducatib: DPP-1 Inhibitor

Clinical Trial: Phase 3 (AIRTIVITY™ Study)	• International, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of verducatib
Study Design	• Participants will be randomized to receive either 2.5 mg verducatib or placebo administered once daily for up to 76 weeks
Key Inclusion	• CF or NCFBE • Pulmonary exacerbations requiring antibiotic treatment
Primary Outcome Measure	• Annualized rate of pulmonary exacerbations

Time to First Pulmonary Exacerbation in Ph2 AIRLEAF Trial



Chalmers JD, et al. *Eur Respir J*. 2025;65(1):2401050; https://clinicaltrials.gov/study/NCT06872892

Overview of HSK31858: DPP-1 Inhibitor

Clinical Trial: Phase 3 (NCT06660992)	• International, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety in non-cystic fibrosis bronchiectasis
Study Design	• Participants will be randomized to receive either HSK31858 40mg or placebo once daily for up to 52 weeks
Primary Outcome Measure	• Frequency of pulmonary exacerbations

https://clinicaltrials.gov/study/NCT06660992

What Did You Learn?

Which of the following best describes the mechanism of action of brensocatib?

A. Neutrophil elastase inhibitor that reduces airway bacterial burden and acute infections

B. DPP-1 inhibitor that reduces activation of neutrophil serine proteases, decreasing neutrophil-driven airway inflammation

C. IL-5 receptor antagonist that reduces eosinophilic inflammation and airway hyperresponsiveness

D. Inhaled bronchodilator that improves mucociliary clearance and reduces airflow obstruction

Section Takeaways

- Brensocatib is the first FDA-approved medication for bronchiectasis
  - Reduces neutrophil-driven inflammation by inhibiting DPP-1
- Additional therapeutics targeting neutrophilic inflammation are in development
- Endotypes may help guide anti-inflammatory therapy with other treatment modalities in development targeting alternative pathways

Patient Case Review: Implementing a Multi Modal Treatment Approach to Improve Outcomes

Meet Darlene: Patient With HRCT-Confirmed Bronchiectasis

- Darlene is a 59-year-old woman who presents with a chronic productive cough (> 12 months), frequent bronchitis requiring antibiotics, intermittent hemoptysis, and exertional dyspnea
- BMI is 21.5
- On examination, inspiratory wheezes are noted
- Sputum culture grows *Pseudomonas aeruginosa*
- 1 positive culture for NTM
- HRCT shows dilated, thick-walled bronchi
- **Spirometry:** FEV_1 62% predicted

Has their airway clearance been optimized?

Have they had RT instruction?

RT = respiratory therapy

How Severe Is Darlene's Case?

What additional tests are required to confirm bronchiectasis and identify its etiology?

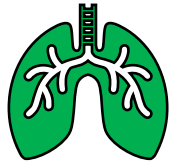
- CBC with differential
- Blood test to measure total IgG, IgA, IgM, IgE
- Repeat/review sputum cultures for bacteria, mycobacteria, fungi
- Screen for comorbidities—connective tissue disease, IBD, immunodeficiency, asthma/COPD overlap

How severe is Darlene's case, based on BSI or E-FACED scoring?

- Darlene's FEV_1 (62%), age (59), daily symptoms, chronic *Pseudomonas*, and frequent exacerbations indicate moderate-to-severe risk (BSI: likely 5–8, moderate)
- High risk for future exacerbations and mortality, warranting intensive multidisciplinary management

O'Donnell AE. *N Engl J Med*. 2022;387(6):533-545; Martinez-Garcia MA, et al. *Eur Respir J*. 2014;43:135.

How to Manage Darlene



What is the best airway clearance strategy for this individual?

Airway clearance is standard of care: all patients should be taught techniques by a respiratory physiotherapist

Options: Active cycle of breathing technique (ACBT), oscillatory PEP device, or high-frequency chest wall oscillation

Supervised instruction improves efficacy and adherence; re-education should be documented at every review and exacerbation

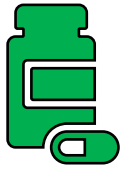
What is the expected trajectory of lung function, and how often should spirometry and imaging be repeated?

Annual spirometry is recommended; frequency should be increased if more severe symptoms, frequent exacerbations, or accelerated decline

Repeat sputum cultures every 3–6 months and at each exacerbation

Repeat HRCT only if clinical deterioration or substantial change in symptoms

Creating an Action Plan for Darlene



What might be included in Darlene's Action Plan?

- Airway clearance: minimum daily, technique individualized and confirmed by trained physiotherapist
- Prompt antibiotics for exacerbation: tailored to sputum culture
- Long-term macrolide or inhaled antibiotic therapy for chronic Pseudomonas and frequent exacerbations
- Inhaled bronchodilators as needed for airway obstruction

Given her moderate disease severity, chronic *Pseudomonas* infection, and frequent exacerbations, Darlene is an appropriate candidate for brensocatib.

Enhancing Darlene's QoL

What additional support may enhance Darlene’s quality of life?

Individualized care: refer to respiratory physiotherapist, psychologist/counselor, dietitian, social worker, respiratory nurse, patient support groups

Support mental health and facilitate self-management strategies

Initiating Treatment for Darlene With Brensocatib

- Airway clearance remains standard of care, and **brensocatib 25 mg orally once daily** was added
- Over the following 6 to 12 months, Darlene reported fewer bronchiectasis exacerbations and reduced need for antibiotic courses
  - Developed mild dry skin and intermittent facial rash early in treatment, which were managed conservatively without discontinuation
  - No serious adverse events occurred, and she did not develop clinically significant gingival complications or hypertension
  - Her **FEV_1 remained stable at 63% predicted**, with no clinically meaningful decline

Domain	10 mg	25 mg	Clinical implication
Exacerbations	Reduced vs placebo	Reduced vs placebo	Similar primary efficacy
FEV_1 decline	No significant benefit	Significant benefit	25 mg better for lung-function preservation
Symptoms	Smaller, not clearly significant benefit	Greater improvement on QoL-B and BEST	25 mg better symptom relief
Safety	Slightly fewer skin AEs	More hyperkeratosis, still usually mild	10 mg may be used if toxicity limits 25 mg

Chalmers JD, Daley CL. *Am J Respir Crit Care Med*. Published online March 30, 2026.

Key Takeaways

- Early diagnosis is important, and clinicians should consider bronchiectasis in patients with chronic cough and recurrent chest infections
- Airway clearance is key and foundational
  - Airway clearance comes in many shapes and sizes—consistency is key
  - Needs to be discussed with the patients, revisited at each encounter, and possibly logged or tracked for adherence
- Early identification of exacerbations can lead to better patient outcomes