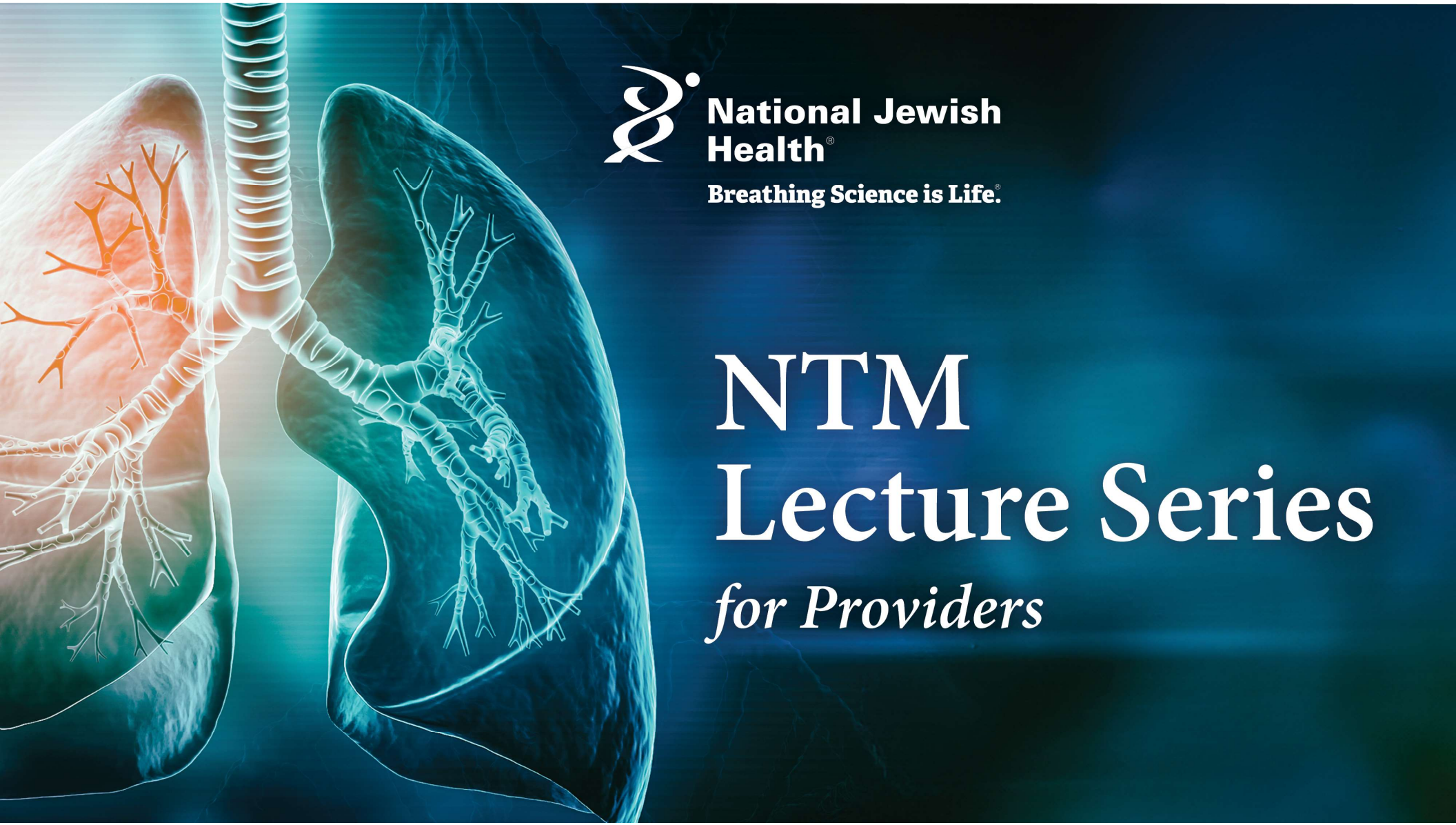
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Overview of Bronchiectasis

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Associate Professor
Co Director PCD Clinic
National Jewish Health

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Objectives

- Definition of bronchiectasis
- Pathophysiology of bronchiectasis
- Diagnostic evaluation
- Treatment (including exacerbations)
- Future Directions

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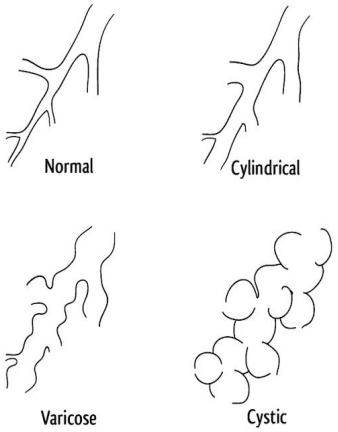
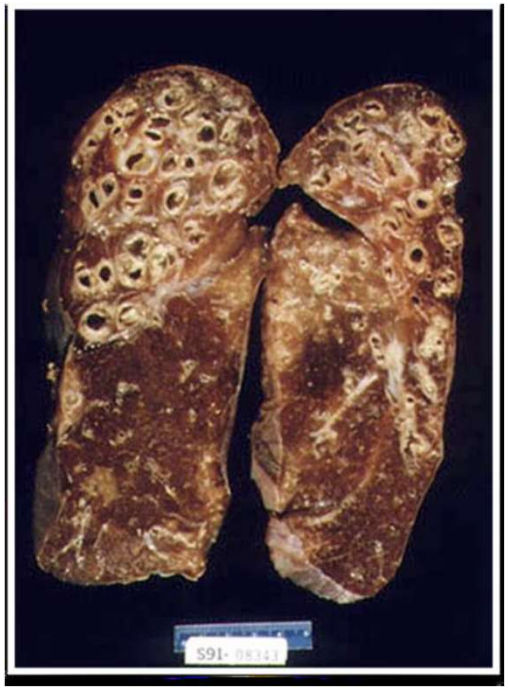
Definition of Bronchiectasis

- Name come from Greek
  - “bronkhos” (windpipe or bronchial tubes)
  - “ektasis” (dilatation)
- Name of the disease and a radiographic finding that may or may not be associated with the disease
- Progressive respiratory disease
  - characterized by permanent dilatation of the bronchi
  - clinical syndrome of cough, sputum production, and recurrent respiratory infections





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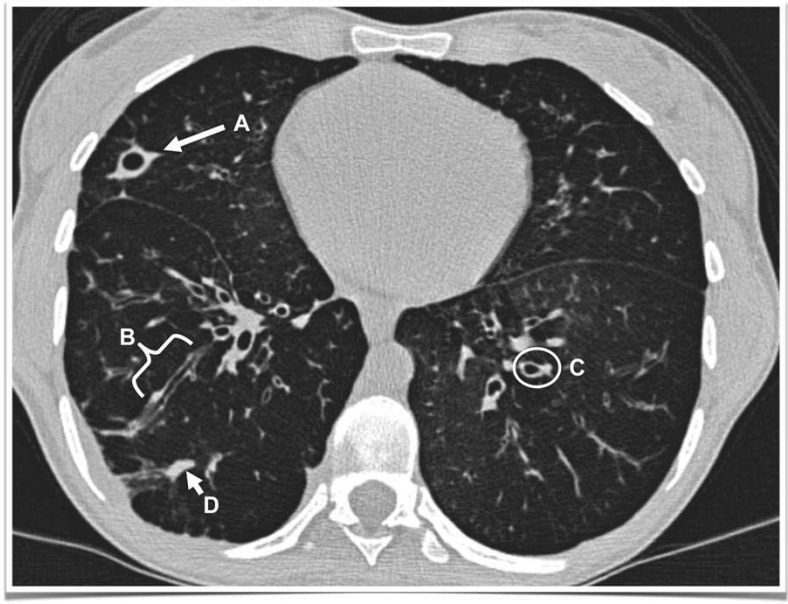
Definitive diagnosis - HRCT

CT features of bronchiectasis

- Defined by bronchial dilatation as suggested by one or more of the following:
    1. Bronchoarterial ratio >1 (internal airway lumen vs adjacent pulmonary artery)
    2. Lack of tapering
    3. Airway visibility within 1cm of costal pleural surface or touching mediastinal pleura

The following indirect signs are commonly associated with bronchiectasis:

- Bronchial wall thickening
- Mucus impaction
- Mosaic perfusion / air trapping on expiratory imaging



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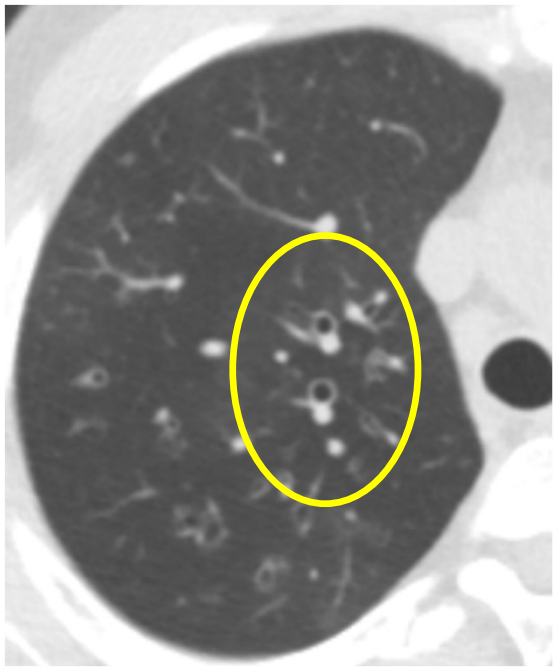
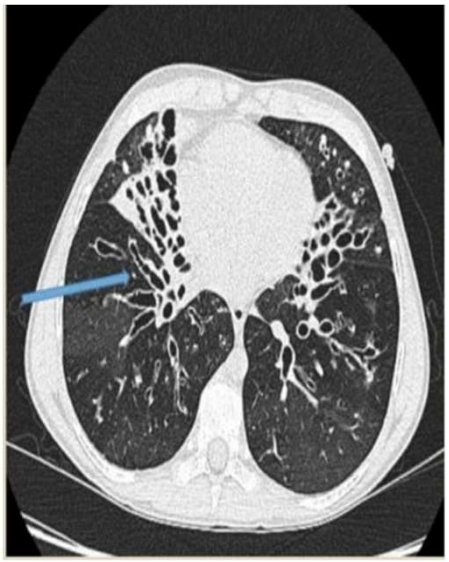
High Resolution CT Findings

- CT *without* high resolution slices has a sensitivity of 79% and specificity of 99% compared to bronchography[1]
- HRCT has a sensitivity of 98% and specificity of 99% compared to bronchography[2]
- Chest x-ray sensitivity lower but may be used to follow changes
- Multiple findings have been described on HRCT
  - Bronchial dilatation — "Signet ring" sign
  - Failure to taper — "Tram track" sign
  - Bronchial wall thickening
  - Cystic dilatation
  - Air-fluid levels
  - Mucoid impaction
  - Air trapping

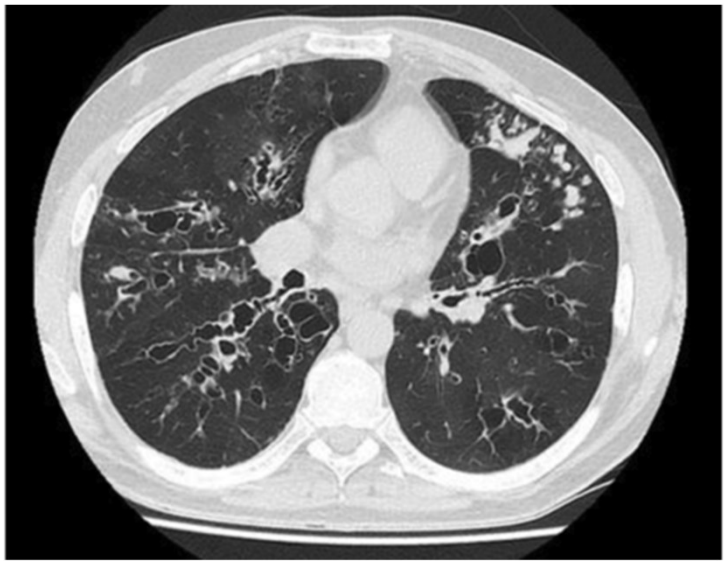


1. Phillips MS, et al. *Clin Radiol.* 1986;37:321-325.
2. Young K, et al. *Acta Radiol.* 1991;32:439-441.

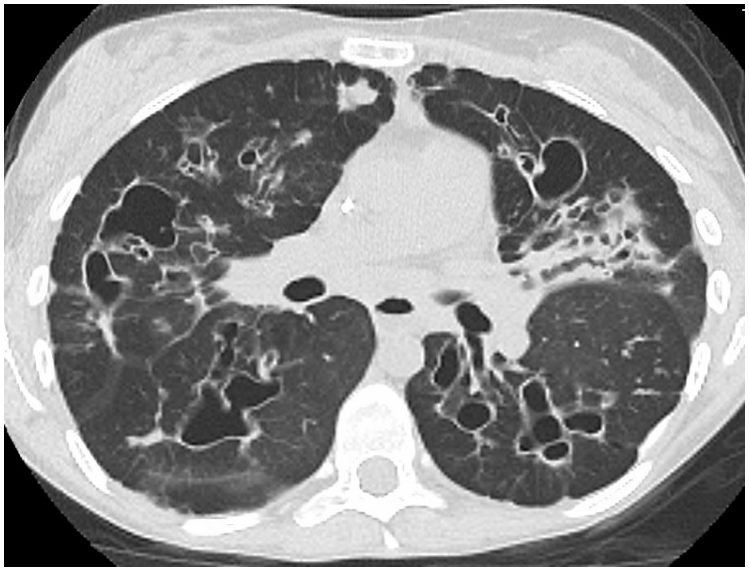
Radiographic Phenotypes



Cylindrical/tubular



Varicose



Saccular/cystic

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Pathophysiology

- Mucociliary Defects
  - CF
  - PCD
- Immune Defects
  - Primary – CVID
  - Secondary - Chemo
- Other conditions
  - RA
  - Sjogren's
  - IBD

- Acute/ Severe Insult
  - Viral infection
  - Radiation
- Recurrent
  - Aspiration
  - Infections
- Persistent
  - ABPA
  - TBM
  - Bronchial Obstruction

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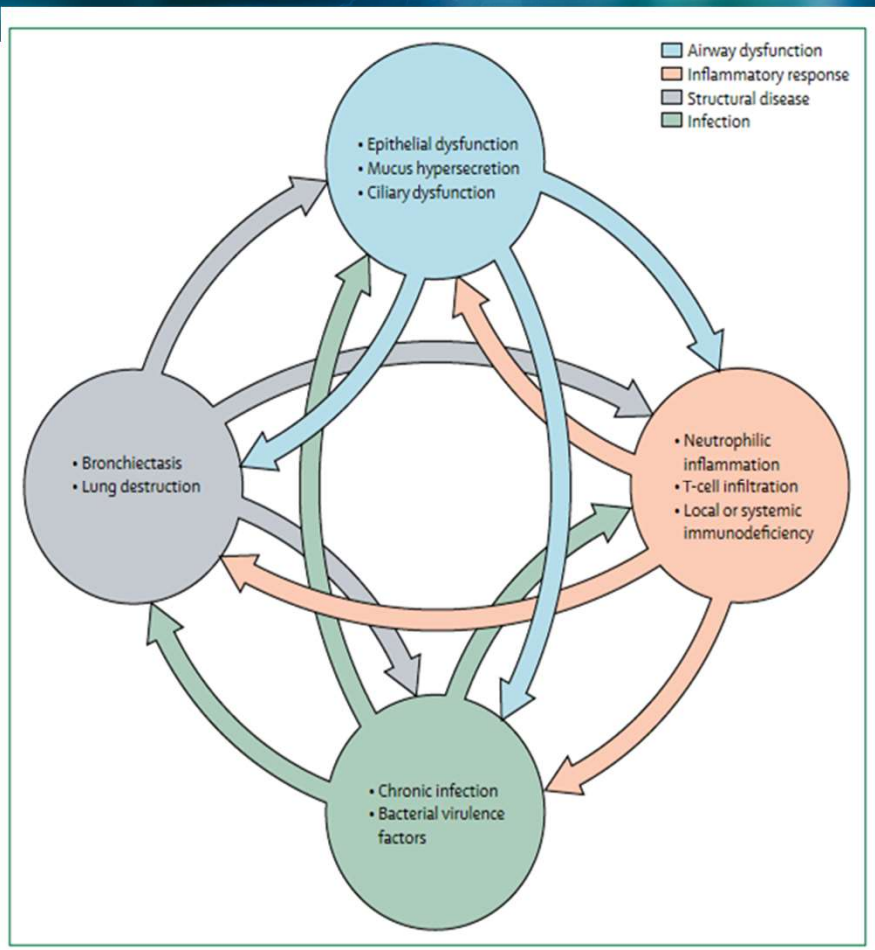
Pathophysiology



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

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Diagnosis

Characteristics of patients in whom bronchiectasis should be considered	**Persistent production of mucopurulent/purulent sputum**
	Chronic cough or recurrent infection in setting of rheumatoid arthritis
	Chronic obstructive pulmonary disease and frequent exacerbations
	Sputum culture with *Pseudomonas aeruginosa*
	Inflammatory bowel disease and chronic productive cough
	Immunosuppression (post-transplant), HIV, vasculitis, lymphoma, or prior radiation treatment
	Chronic sinusitis with chronic productive cough
	Connective tissues disease with chronic productive cough
	Otherwise healthy people with chronic productive cough lasting >2 months

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Bronchiectasis Etiologies

- Most common etiologies
  - Idiopathic (34%-53%)
  - Post-infectious (26%-29%)
  - COPD-related (11%)
  - Connective tissue disease related (8%)

- Possible barriers to early diagnosis
  - Cough is common symptom of many pulmonary disorders
  - Early bronchiectasis is not often seen on chest x-ray
  - Lack of computed tomography scan, sputum cultures, and other testing
  - Misdiagnoses (asthma, COPD, chronic cough, etc)

1. Aliberti S, et al. *Eur Respir J.* 2016;47:1113-1122.
2. Pasteur MC, et al. *Am J Respir Crit Care Med*. 2000;162:1277-1284.

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General considerations

- Definitive diagnosis
- Determining etiology
- Underlying/ associated conditions
- Severity of disease
- Microbiology
- Other non- respiratory issues

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Diagnostic Work up

Test	Comment
History and Physical	Guide additional testing
HRCT	Location, location, location
PFTs	Management and prognosis
CBC with differential	Eosinophils (ABPA), leukocytosis, anemia (IBD)
Quantitative Immunoglobulins	CVID, IgG4 disease, etc
Total IgE, Aspergillus specific IgE	ABPA
ESR/CRP, RA/CCP, SSA/SSB	Abnormalities may suggest vasculitis or CVD
Sputum bacterial culture	Treatment options, may require special handling
Sputum AFB cultures	NTM as cause or complication
Sputum fungal culture	Helpful in asthma when aspergillus identified
Sinus CT scan	Aid in diagnosis (CF,PCD, immunodeficiencies)

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History and physical

- **History**
  - Neonatal symptoms
  - Childhood pneumonia / viral illnesses
  - Recurrrent oto-sino-pulmonary infections
  - Aspiration
  - Asthma
  - Autoimmune disease
  - Family history
- **Exam**
  - Wheezing
  - Clubbing
  - Situs Abnormalities
  - Arthritis
  - Nail abnormalities

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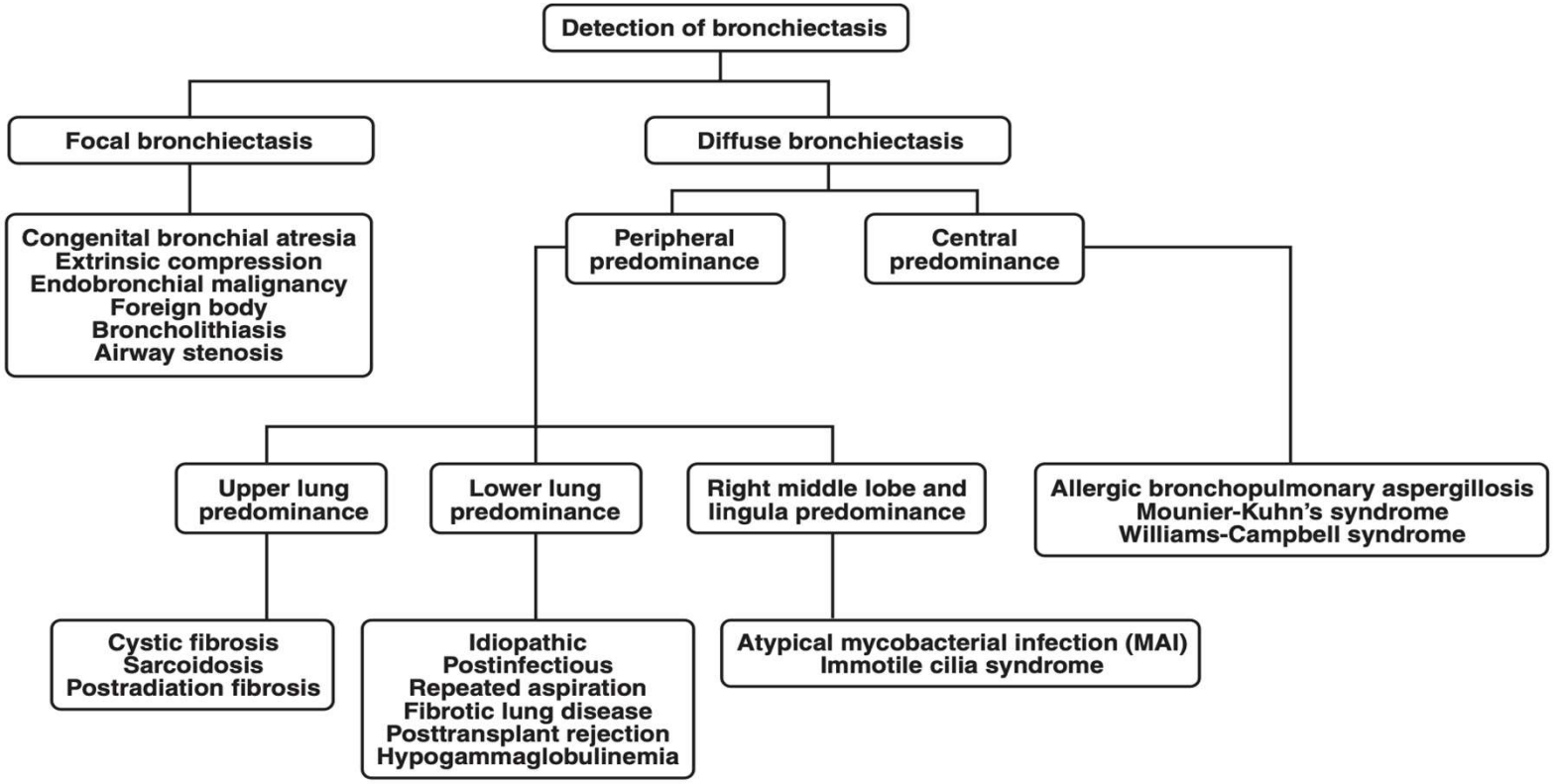
Radiographic Algorithm



Cantin L, et al. *AJR Am J Roentgenol*. 2009;193:W158-W171.

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Other tests

- Sweat chloride
- A1At levels and genotyping
- Ciliary biopsy
- Nasal nitric oxide measurements
- Genetic testing (CF, PCD)
- Barium swallow/ esophageal manometry/ pH probe
- Antibody titers to pneumococcal antibodies

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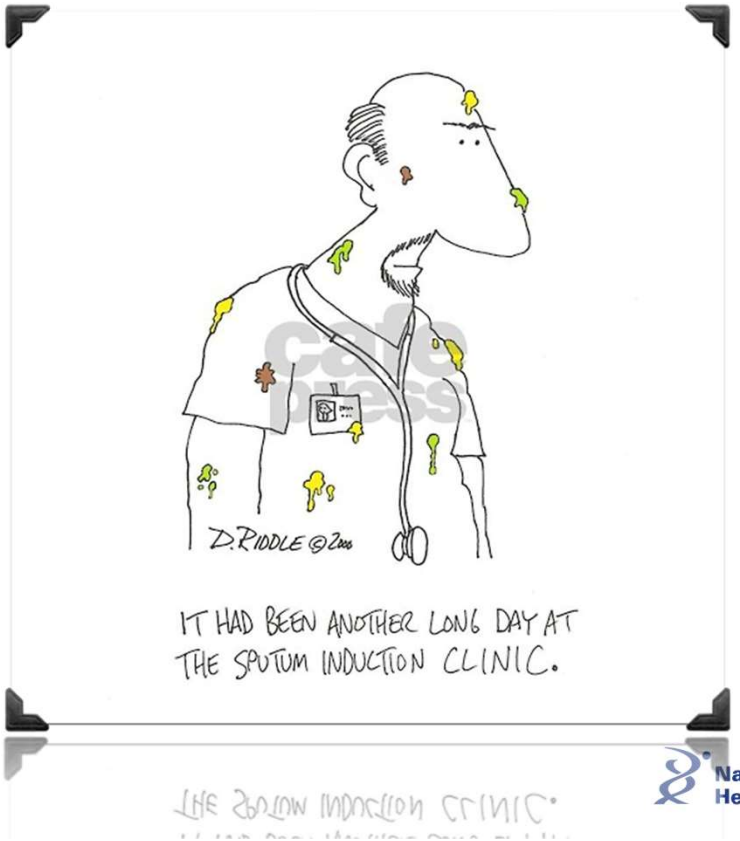
Sputum Cultures

- Sputum sample
  - Expectorated
  - Induced
  - Bacterial, AFB cultues

- Bronchoaveolar lavage
  - Unable to induce
  - Suspect infection
  - Suspect NTM with negative sputa

* Bronchoscopy allows to visualize / exam airways / rule out obstruction



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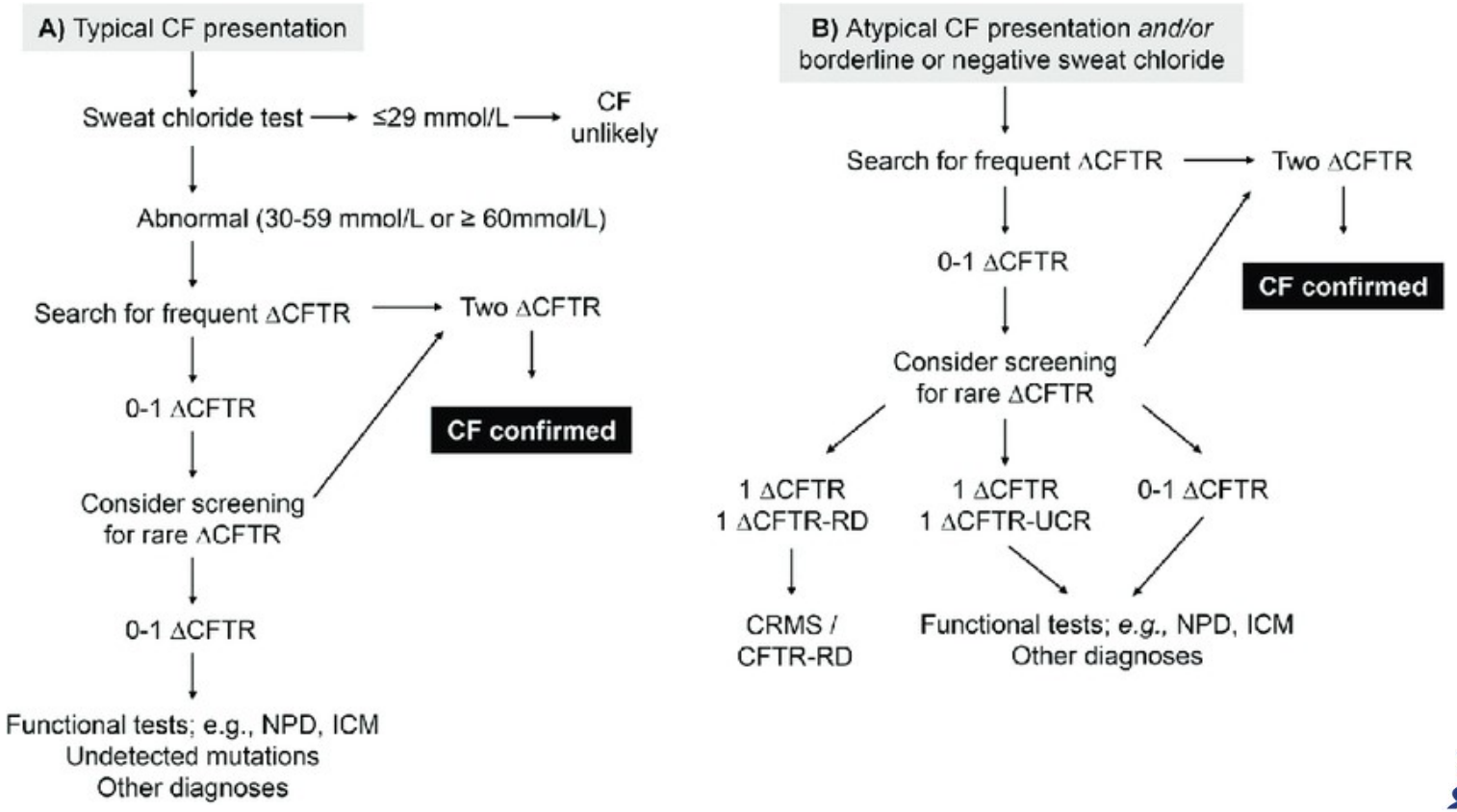
Testing for cystic fibrosis



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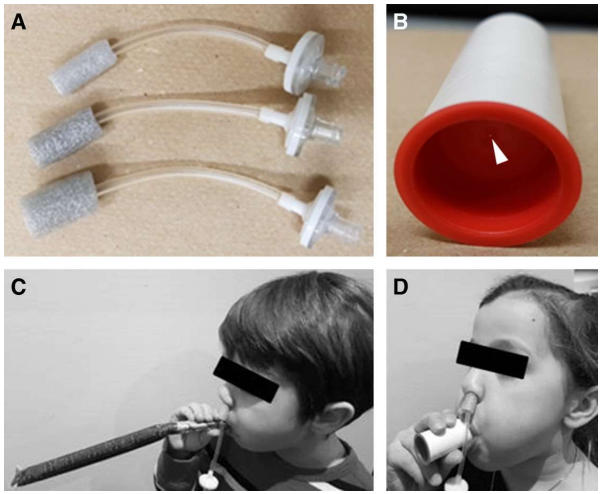
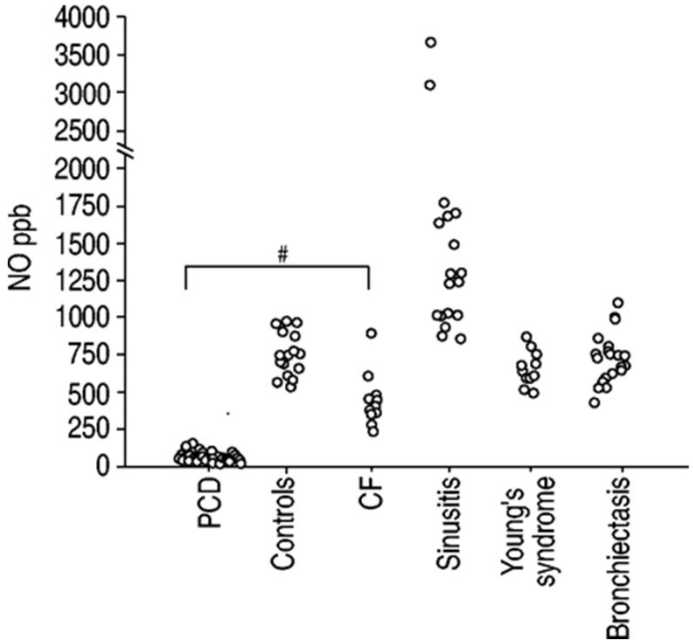
Testing for PCD

- Presence of ≥ 2clinical features associated with PCD
  - Neonatal respiratory distress
  - Year round daily ‘wet’ cough
  - Year round daily rhino-sinusitis
  - Abnormal organ laterality





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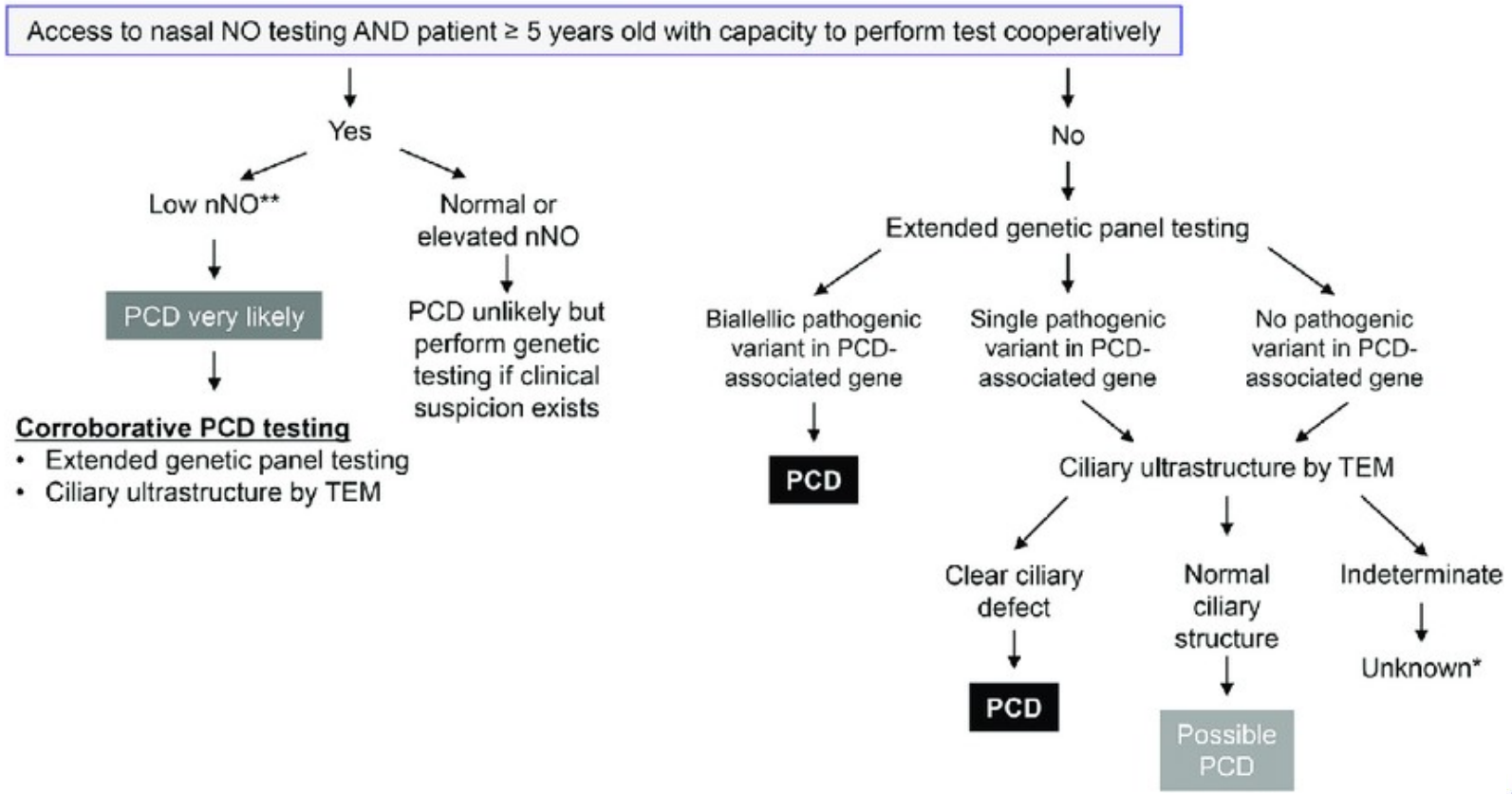
Testing for PCD



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Assessing Severity

Bronchiectasis Severity Index

1. Age
2. BMI
3. FEV1
4. Hospitalizations
5. Number of exacerbations per year
6. Breathlessness score
7. + Pseudomonas in sputum
8. Presence of other organisms
9. Number of lobes involved

0-4 Mild Bronchiectasis
1 year outcomes: 0 - 2.8% mortality; 0- 3.4% hospitalization rate
4 year outcomes: 0- 5.3% mortality; 0- 9.2% hospitalization rate

5-8 Moderate Bronchiectasis
1 year outcomes: 0.8 - 4.8% mortality; 1.0 - 7.2% hospitalization rate
4 year outcomes: 4 - 11.3% mortality; 9.9 - 19.4% hospitalization rate

9+ Severe Bronchiectasis
1 year outcomes: 7.6 - 0.5% mortality; 16.7 - 52.6% hospitalization rate
4 year outcomes: 9.9 - 29.2 % mortality; 41.2 – 80.4% hospitalization rate

Chalmers JD, et al. AJRCCM 2014, 2014 Mar 1; 189(5): 576-585

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Conclusion

- Bronchiectasis is common but underrecognized
- A high index of suspicion is needed to trigger investigation
- Bronchiectasis is defined as irreversible airway damage leading to dilation (bronchoarterial ratio >1) of airways
- Various laboratory testing, pulmonary function tests, and culture data are important to identify associated conditions and severity of disease
- Imaging is paramount for diagnosis and can provide clues to help diagnose underlying or associated causes

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Objectives

- Definition of bronchiectasis
- Pathophysiology of bronchiectasis
- Diagnostic evaluation
- **Treatment (including exacerbations)**
- Future Directions

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Treatment

- There are currently no guidelines for the management of bronchiectasis in the United States
  - British Thoracic Society guideline, 2019 (updated from 2010)
  - Thoracic Society of Australia and New Zealand position statement, 2023 (updated from 2015)
  - European Respiratory Society guidelines, 2017
- There are no therapies that are currently FDA approved for the airway condition of bronchiectasis
- Much of the treatment of NCFBE has been influenced by cystic fibrosis research and management recommendations

Thorax. 2019 Jan; 74 (Suppl 1): 1-69. British Thoracic Society Guidelines for bronchiectasis in adults.
Eur Respir J. 2017 Sep 9; 50(3). European Society Guidelines for the management of bronchiectasis.

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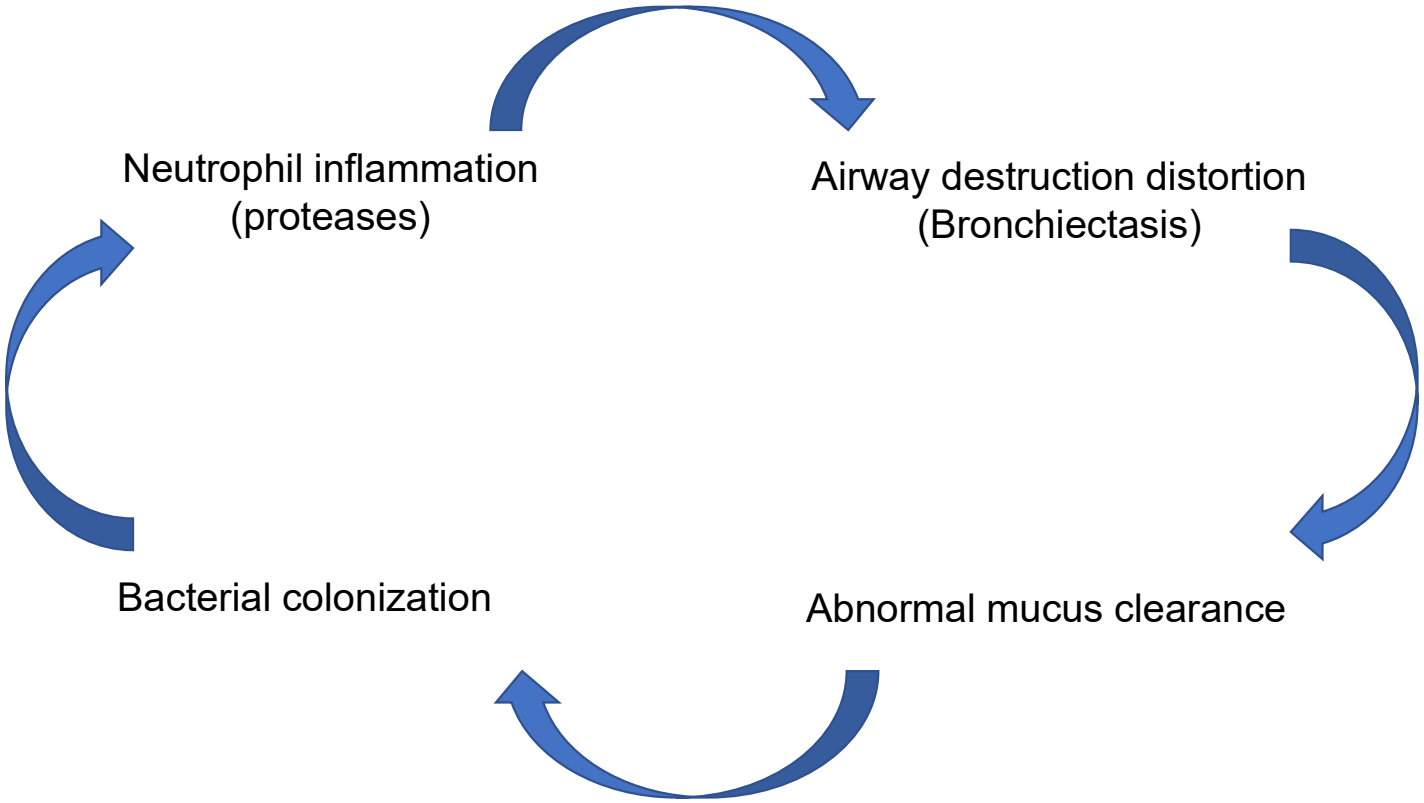
Therapeutic principles



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Components of Treatment

1. Mucus Management
2. Inflammation Attenuation
3. Infection Control

- Decreases progression of airway distortion and scarring
- Maintains better lung function

- Helps control patient symptoms
- Prevents illness/hospitalization
- Decreases likelihood of needing oxygen therapy

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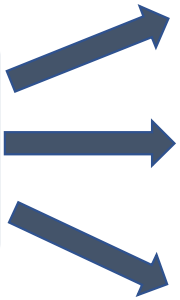
Components of Treatment

1. Mucus Management
2. Inflammation Attenuation
3. Infection Control



1.Underlying cause
2. Mucus Management
    - Mechanical
    - Pharmacologic
3. Bronchodilators
4. Anti-inflammatory agents
5. Macrolides
6. Antibiotics
7. Pulmonary rehabilitation
8. Emerging therapies

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1. Treatment Starts With Identifying Cause

Condition / Disease	Treatment
ABPA	Oral steroids +/- oral antifungal
Alpha-1 antitrypsin deficiency	Alpha-1 protein replacement
Aspiration/GERD	Treat GERD and speech therapy
Cystic fibrosis	CFTR modulator therapy
Immunodeficiency (CVID)	IVIG replacement therapy
Infection (TB, NTM, etc)	Antibiotics
Rheumatologic/autoimmune/ inflammatory diseases (RA, Sjogren's, IBD, etc)	Immunosuppression

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2. Mucus Management: Methods & Goals

- Goals
  - Mobilize secretions → interrupt cycle of inflammation and infection
  - Decrease symptoms
  - Decreased exacerbations and inflammation
- Methods
  - Mechanical
  - Pharmacologic
  - Physical activity

Cannot stress enough the importance of AIRWAY CLEARANCE as the cornerstone of treatment for bronchiectasis

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2. Mucus Management: Recommendations

Recommended

- Short-acting beta agonist prior to physiotherapy[1]
- Hypertonic saline nebulization[2]
- Mechanical airway clearance
- Aerobic exercise
- Use 1-2 times per day

Not Recommended

- Dornase alfa nebulization (indicated for CF patients)[3]
- Routine use of anticholinergics[4] – unless there is another indication, such as COPD

1. Polverino E, et al. *Eur Respir J.* 2017;50:1700629.
2. Hill AT, et al. *Thorax.* 2019;74:1-69.
3. O'Donnell AE, et al. *Chest.* 1998;113:1329-1334.
4. Lasserson T, et al. *Cochrane Database Syst Rev.* 2001:CD002162.

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2. Mucus Management: Mechanical Methods

METHODS	• 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
CHOICE OF METHOD	• Choice of therapy based on patient characteristics and support • Best to teach multiple modalities for varying situations
FREQUENCY	• At least daily! • May need to ramp up intensity during exacerbation

Involvement of respiratory therapists is paramount

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2. Mucus Management Mechanical Methods

- PEP Device
  - Improved quality of life scors and exercise capacity
- HFCWO
  - Improved SOB, cough, sputum , FEV1 and FVC
- Postural Drainage
  - Augments amount of soutum expectorated / cleared during airway clearance
- Any modality can be tailored to fit specific preference of the patient but in all cases,

patient education is paramount factor for success

Maggie McIlwaine , et al. Cochrane Database Syst Rev. 2019 Nov 27;2019 (11)

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2. Mucus Management: Pharmacologic Strategies

- Several mucoactive agents can improve airway hygiene in patients with bronchiectasis
  - Isotonic saline (0.9%) nebulization
  - Hypertonic saline (3%, 7%, and 10%) nebulization
  - Mannitol dry powder

- Recommendation: trial of long term mucoactive treatment in patients who have difficulty expectorating sputum and poor quality of life and standard airway clearance has failed to control symptoms
  - Weak recommendation, low quality evidence
  - Benefits:
    - Frequent exacerbations
    - Difficulty clearing secretions
    - Chronic colonization of bacteria, esp *Pseudomonas aeruginosa*

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

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2. Mucus Management: Pharmacologic Strategies

- No evidence to support the use of guaifenesin in bronchiectasis, but some patients endorse benefits
- No evidence to support the use of N-acetylcysteine in bronchiectasis
- Avoid recombinant DNase in adult patients with Non-CF bronchiectasis
  - Strong recommendation, moderate quality evidence
  - Dornase, the recombinant DNase, has been evaluated in 2 trials showing no benefit
    - In one trial there was worsening of FEV1
    - Other trial there was an increase in frequency of exacerbations

O'Donnell AE, et al. Chest. 1998 May;113(5):1329-34.
Wills PJ et al. AMJCCM 1996 Aug;154(2 Pt 1):413-7.
Desai M et al. Pediatr Pulmonol. 1995 Nov;20(5):307-8.
El-Abiad NM, et al. Respir Med. 2007 Oct;101(10):2224-6.

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2. Mucus Management: Hypertonic Saline

- 7% hypertonic saline vs 0.9% saline -- Mixed Results
  - 4 weeks
    - More effective in promoting expectoration
    - Improved quality of life
    - Improved lung function
    - Reduced ER visits
  - 12 month study
    - No difference in exacerbation rates
    - No difference in quality of life score
    - No change in FEv1
    - No reduction in bacterial colonization

Kellett F, et al. Respir Med 2005; 99: 27–31
Kellett F, et al. Respir Med 2011; 105: 1831–1835.
Nicolson et al. Respir Med 2012; 106: 661–667
Paff et al. Eur Respi J Feb 23; 49(2)

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3. Bronchodilators

- No evidence to support routine use of bronchodilators
- No evidence to support routine use of anticholinergics
- LABA in symptomatic pts with airflow obstruction
- Spanish guidelines recommend SABA prior to airway clearance, inhaled hypertonic saline and/or inhaled abx

Arch Bronconeumol (Engl Ed). 2018 Feb;54(2):88-98. Spanish Guidelines on Treatment of Bronchiectasis in Adults

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Attenuate Inflammation

Recommended

- Chronic macrolide therapy (azithromycin, erythromycin) for those with frequent exacerbations, defined as ≥3 exacerbations/year[1]

Not Recommended

- Routine daily use of oral systemic steroids; unless there is another indication[2]
- Routine use of inhaled steroids; unless there is another indication[1-3]
- Ibuprofen; no established role in NCFBE[4]
- Chronic daily statins[1]

- Abbreviation: NCFBE, non-cystic fibrosis bronchiectasis.
- 1. Polverino E, et al. *Eur Respir J.* 2017;50:1700629. 2. Lasserson T, et al. *Cochrane Database Syst Rev.* 2001:CD002162. 3. Kapur N, et al. *Cochrane Database Syst Rev.* 2018;5:CD000996.
- 4. Koser U, et al. *F1000Res.* 2017;6:527.

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4. Attenuate Inflammation: Corticosteroids

- Should not be prescribes unless coexisting asthma
- Placebo controlled studies of ICS -no benefit
- 200 –fold increase of acquiring NTM infection
  - Compared to general population
  - Increased risk 29- fold to 50- fold depending on dose of ICS

Lasserson, T, et al. Oral steroids for bronchiectasis (stable and acute exacerbations). Cochrane Database Syst Rev. 2001; 4: CD002162
Kapur N, et al. Inhaled Corticosteroids for Bronchiectasis. Cochrane Database of Systematic Reviews. 2018, Issue 5. Art. No.: CD000996.

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5. Attenuate Inflammation: Macrolides

- Macrolide antibiotics target both inflammation and infection and have been shown to have beneficial clinical effects in patients with bronchiectasis.
- Macrolide antibiotics (erythromycin, clarithromycin, azithromycin) have antimicrobial, anti-inflammatory and immunomodulatory properties
- They are efficiently delivered to sites of infection and achieve high tissue concentrations, particularly Azithromycin.
- Three major randomised controlled trials in adults and one in children have shown that azithromycin and erythromycin are effective in preventing pulmonary exacerbations (reduced by 40-60%). (Wong et al 2012, Altenburg et al 2013, Serisier et al 2013, Valery et al 2013).
- Meta-analyses of these and smaller studies also show modest improvements in quality of life and lung function (Wu et al 2014, Gao et al 2014).

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Meta-Analysis of Long-Term Macrolide Use for Inflammation Attenuation

- 3 randomized studies of long-term macrolides in adults with NCFBE
- BAT, BLESS, EMBRACE
  - N = 341 patients
- Primary outcome – frequency of exacerbations requiring antibiotics
  - Secondary outcomes
    - time to first exacerbation
    - change in quality of life according to SGRQ,
    - change in FEV1
- 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%-88% developed antimicrobial resistance

Chalmers JD, et al. *Lancet Respir Med.* 2019;7:845-854. Altenburg J, et al. *JAMA.* 2013;309:1251-1259.

Serisier DJ, et al. *JAMA.* 2013;309:1260-1267. Wong C, et al. *Lancet.* 2012;380:660-667.

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5. Attenuate Inflammation: Macrolides Risks and Benefits

Benefits

- Proven to decrease exacerbations
  - EMBRACE trial (azithromycin)[1]
  - BAT trial (azithromycin)[2]
  - BLESS trial (erythromycin)[3]
- Proven to improve FEV1[2,3]
- Proven to attenuate FEV1 decline[3]
- Proven to reduce sputum production[3]

Risks

- Associated with increased risk of bacterial resistance[2,3]
  - Avoid use in patients with NTM coinfection[4]
- Prolonged QTc[5]
- Hearing decrements[6]

1. Wong C, et al. *Lancet.* 2012;380:660-667. 2. Altenburg J, et al. *JAMA.* 2013;309:1251-1259. 3. Serisier DJ, et al. *JAMA.* 2013;309:1260-1267. 4. Polverino E, et al. *Eur Respir J.* 2017;50:1700629. 5. Albert RK, et al. *Am J Respir Crit Care Med.* 2014;189:1173-1180. 6. Albert RK, et al. *N Engl J Med.* 2011;365:689-698.

5. Attenuate Inflammation: Macrolides

- Dose regimens vary and are not standardized
- Optimal duration is unclear
  - Max benefit after at least 3 months
- Azithromycin
  - 500 mg MWF
  - 250 mg MWF
  - 250 mg daily

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5. Attenuate Inflammation: Macrolides

Checklist

- Frequent exacerbations
  - 3 or more in the past year
- Exclude NTM
  - Sputum AFB cultures every 3 months
- Assess cardiac risk
  - ECG -- QTc interval, arrhythmia

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6. Infection Control: Antibiotics

Antibiotics (oral, intravenous, or nebulized) are typically used in 3 scenarios	To treat exacerbations
	To attempt eradication of new airway isolates
	As a long-term maintenance for suppression of chronic infection ("colonization")

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

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6. Antibiotics
Acute Exacerbation

- Exacerbation is a significant worsening of 3 or more of the following symptoms over 48 hours
  - Cough
  - Sputum volume and/or consistency
  - Sputum purulence
  - Shortness of breath and/or exercise intolerance
  - Fatigue and/or malaise
  - Coughing up blood

- Chronic infection with *P. aeruginosa*
  - Associated with more frequent hospital admissions
  - Longer hospital stays
  - Worse pulmonary function
  - Higher mortality

- Predictors of higher mortality among inpatients
  - Male gender
  - Use of systemic corticosteroids
  - Lower FEV1 at baseline
  - Increased creatinine
  - History of smoking
  - Need for mechanical ventilation.

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6. Antibiotics
Acute Exacerbation

- Summary of evidence: No direct data longer vs shorter course of antibiotics
  - Usual practice = 14 days
    - based on patient's prior sputum culture data, and severity of exacerbation
  - Shorter course
    - Mild exacerbation
    - Associated with pathogens sensitive to antibiotics
    - Rapid return to baseline
  - Lack of recovery
    - Re-evaluate clinical condition
    - Change antibiotics, new micro data
  - Severe exacerbation
    - IV antibiotics
    - Requiring hospitalization, meeting sepsis criteria
    - Hypoxemia, fever, hemoptysis

Polverino et al. Eur Respir J. 2017 Sep 9;50(3)

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6. Antibiotics
Pseudomonas aeruginosa Infection

- *P. aeruginosa* is associated with the following
  - More exacerbations
  - More rapid lung function decline
  - More imaging progression of disease
  - More hospitalizations
  - Worsening of quality of life
  - Higher mortality risk
- *P. aeruginosa* may be present in approximately 16% to 33% of patients with bronchiectasis

Finch S, et al. *Ann Am Thorac Soc.* 2015;12:1602-1611.

Elborn JS, et al. *Respir Med.* 2022;192:106728.

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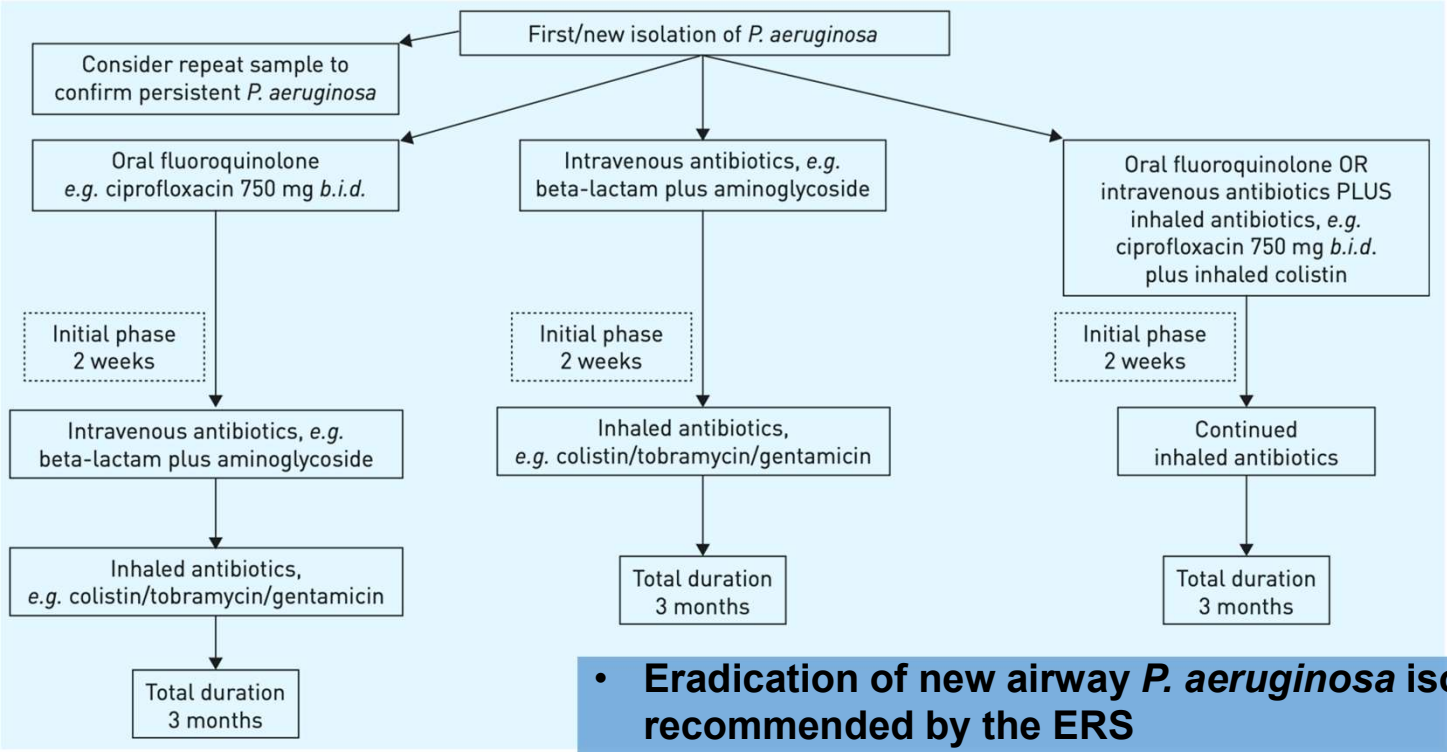
6. Antibiotics
Pseudomonas aeruginosa Infection



- **Eradication of new airway *P. aeruginosa* isolates is recommended by the ERS**
- **Currently, there is no evidence to support eradication of other organisms**

Polverino et al. Eur Respir J. 2017 Sep 9;50(3)

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6. Antibiotics:
Suppressive Antibiotic Therapy for Patients With Frequent Exacerbations

For Patients With *P. aeruginosa* Infection

- Long-term inhaled antibiotic
- Long-term macrolide antibiotic* for those who cannot take an inhaled antibiotic
- Long-term macrolide antibiotic* plus or instead of an inhaled antibiotic for those with a high exacerbation frequency despite an inhaled antibiotic

For Patients Without *P. aeruginosa* Infection

- Long-term oral macrolide* for those who cannot take an inhaled antibiotic
- Long-term oral antibiotic of choice for those who cannot take a macrolide antibiotic
- Long-term inhaled antibiotic for those who cannot take an oral antibiotic

Long-term antibiotic therapy should be offered to all adult patients with bronchiectasis at ≥3 exacerbations per year. However, consider only after optimizing airway clearance and treating modifiable underlying causes.

Polverino et al. Eur Respir J. 2017 Sep 9;50(3)

7. Pulmonary Rehab/ Physical Exercise

- Incremental shuffle walk distance and QOL score improved, but not sustained at 6 months
- Frequency of exacerbations over 12 months was reduced
- No effect on cough or symptoms related to quality of life
- Pulmonary rehab initiated during an exacerbation had not impact on exacerbation frequency or mortality
- European guidelines recommend participation in pulmonary rehab for patients with exertional limitation
  - (mMRC scale ccore > 1)

Polverino et al. Eur Respir J. 2017 Sep 9;50(3)

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Follow up and Monitoring

- Spirometry with bronchodilator at least every 6 months
- Measure lung volumes annually
- 6MW test annually
- Sputum samples at regular intervals, 3-4 months
  - Bacterial, fungal, AFB
- Sputum samples during exacerbations
- Calculate severity score at time of diagnosis
  - Repeat annually to aid in therapeutic management

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Patient Care Strategies

- Multidisciplinary approach (RT's)
- Patient education
  - Engagement in therapy
- Ongoing monitoring
  - Symptoms, spirometry, sputum cultures, and imaging with CT scans
- Pulmonary rehabilitation programs
- Assess O_2 needs
- Manage associated conditions, such as asthma, COPD, GERD, and sinusitis
- Treat symptoms, such as shortness of breath (bronchodilators)

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8. Emerging Treatment Strategies: WILLOW

- Brensocatib is an oral, reversible dipeptidyl peptidase (DPP-1) inhibitor that has demonstrated the ability to inhibit NSP activity
  - Neutrophils are the dominant inflammatory cell in the airway
  - Neutrophil serine proteases (NSPs), including neutrophil elastase (NE), are activated during neutrophil maturation in the bone DPP-1
  - NE levels are associated with disease severity, bacterial load, and clinical outcomes (exacerbations)
  - Patients with bronchiectasis have frequent exacerbations that are usually associated with neutrophilic inflammation
- The goal of the WILLOW trial: examine whether brensocatib reduced the incidence of exacerbations in patients with NCFBE.

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

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8. Emerging Treatment Strategies: WILLOW

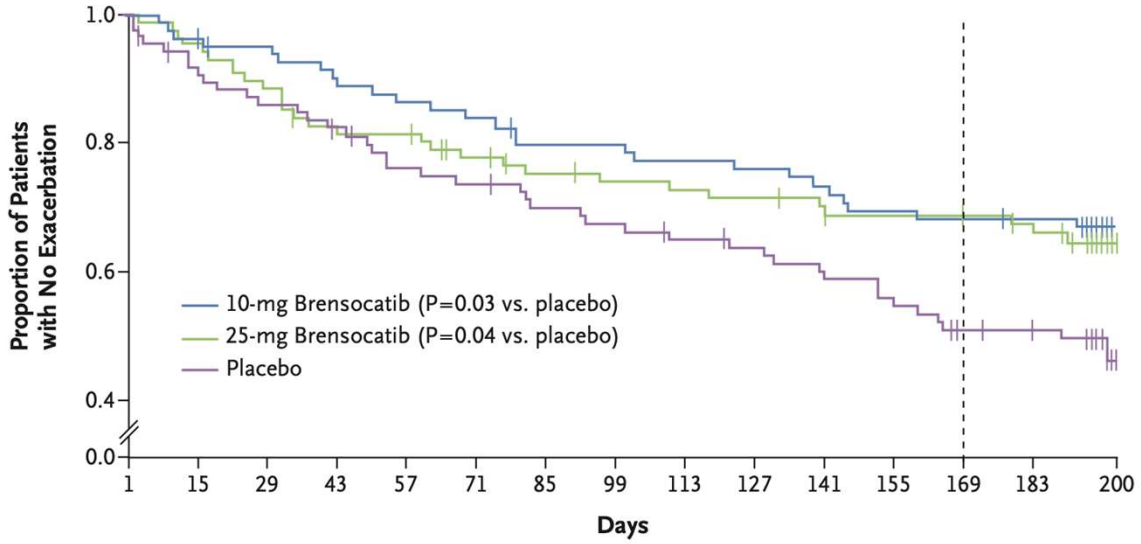
- Phase II, international, double-blind, placebo-controlled 24-week trial enrolling 256 patients with NCFBE
- Patients randomized to receive brensocatib 10 mg, brensocatib 25 mg, or placebo for 24 weeks
  - Enrolled patients had ≥2 exacerbations in previous 12 months, history of sputum expectoration, and mucopurulent or purulent sputum at screening
  - Baseline concentration of NE in sputum was below LLQ in approximately 25% of each treatment group
- Primary endpoint – time to 1st exacerbation
- Secondary endpoints – rate of exacerbations (event/patient-year), and change in predicted FEV1 after bronchodilator use, change in QOL, and change in NE from baseline

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

SGR9
SGR10

8. Emerging Treatment Strategies: WILLOW

Brensocatib Prolonged Time to 1st Exacerbation vs Placebo



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

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

Primary Endpoint

The 25th percentile of the time to the first exacerbation:

- Brensocatib 10 mg: 134 days (*P* = .03 vs placebo)
- Brensocatib 25 mg: 96 days (*P* = .04 vs placebo)
- Placebo 67 days

Rate of Exacerbations (≥ 1)

- Brensocatib 10 mg: 32% (*P* = .03 vs placebo)
- Brensocatib 25 mg: 33% (*P* = .04 vs placebo)
- Placebo: 48%

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SGR9 Note to Speakers, it is important to cover the content in both boxes, as one of the CME test questions will focus on this information, see question and correct answer (c) below
Sallie Reinmund, 8/8/2023

SGR10 4. In the phase II WILLOW trial, brensocatib showed which of the following outcomes compared with placebo in patients with NCFBE?

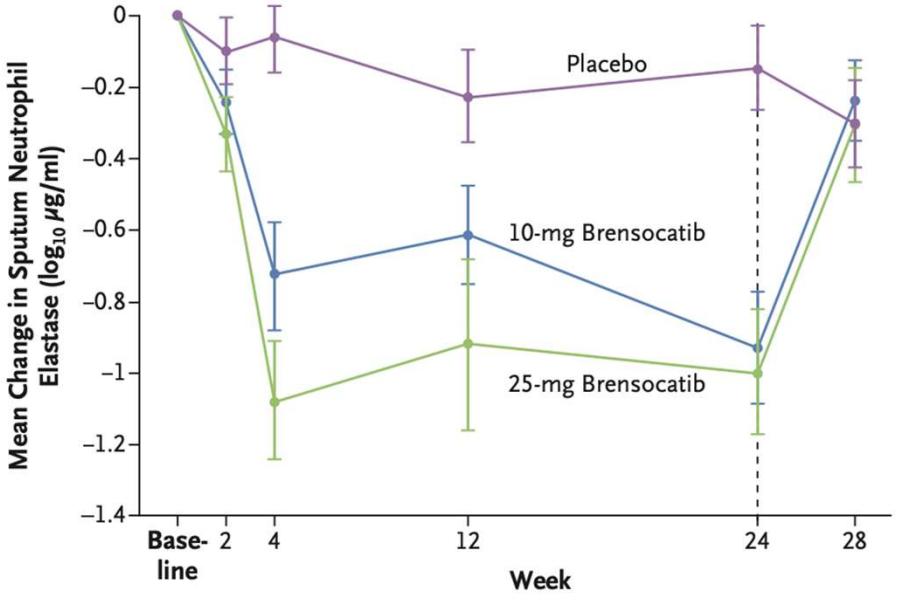
a. Reduced 24-hour sputum volume and proinflammatory cytokines
b. Reduced rate of exacerbations and infections
c. Reduced time to first exacerbation as well as rate of exacerbations
d. Time to first exacerbation and reduced markers of eosinophilic inflammation
e. I do NOT know

Sallie Reinmund, 8/8/2023

SGR13

8. Emerging Treatment Strategies: WILLOW

Change in Sputum Neutrophil Elastase Concentration



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

Cipolla D, et al. Respir Res. 2023;24(1):133.

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Slide 56

SGR13 Note to Speaker: “the second referenced article highlights that Brensocatib reduced all of the following serine proteases: neutrophil elastase (NE), proteinase 3 (PR3), and cathepsin G (CatG), in a dose related fashion. Brensocatib produced the greatest reduction in the sputum activity of CatG, followed by NE and then PR3.”
Sallie Reinmund, 8/9/2023

8. Emerging Treatment Strategies: ASPEN

- A 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

- Primary objective evaluate the effect of brensocatib at 10 mg and 25 mg compared with placebo on the rate of pulmonary exacerbations (PEs) over the 52-week treatment period.

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