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Diagnosis and Management of Bronchiectasis

An APCCMPD Ambulatory-Care Curriculum Teaching Script

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Diagnosis and Management of Bronchiectasis

Scenario 1:

Ms. G is a 55-year-old woman with a history of hypertension and diabetes who presents to your outpatient practice with new-onset shortness of breath, cough and wheeze. She has no significant past pulmonary history and notes that these symptoms started about 5 months ago. Since that time, she has been treated 4 times for upper respiratory infections with a variety of antibiotics. She has also tried numerous inhalers without relief. The only time she felt better was following a short course of prednisone. She continues to have a persistent cough with abundant yellow sputum production. Her primary care physician ordered a chest x-ray (CT) and ultimately a computed tomography (CT) of the chest given the recurrence and persistence of her symptoms. She was told by her doctor that the report mentioned bronchiectasis, and she should see a pulmonologist for further evaluation.

Question 1: What are the classic signs and symptoms of bronchiectasis? What are some other key parts of the history that you would want to know as you begin to discuss a possible cause for her imaging findings?

Question 2: You review her imaging and agree that there is diffuse bronchiectasis present in a central distribution. What does bronchiectasis look like on chest imaging? How does the distribution of disease help you in determining the possible underlying cause(s)?

Scenario 1 (Continued):

Upon further history taking, you note that Ms. G is a never smoker. She currently works as an administrative assistant at a local bank. She has 2 children and never had any difficulty conceiving. She notes some mild asthma and intermittent sinus issues throughout her life, but no other extra-pulmonary symptoms are noted on her detailed review of symptoms. She has some mild GERD but no clinical history that is concerning for chronic aspiration. She has no known history of recurrent infections as a child. She was generally healthy up until the last 5 months. There is no sputum culture data for your review at this time.

Question 3: What is the pathophysiology of bronchiectasis?

Question 4: What is the recommended workup for bronchiectasis? How would you tailor your evaluation in this patient given the clinical history?

Scenario 2:

You are seeing a 55-year-old woman with a history of hypertension and diabetes in the office for management of her bronchiectasis. CT chest has shown focal bronchiectasis in the right lower lobe thought to either be attributable to chronic aspiration or past infection. She is seeing you now with mildly worsened cough, sputum production and stable dyspnea. She has no prior culture data available for your review.

Question 5: Based on the above history, how would you proceed with treatment?

Question 6: What are the different modes of airway clearance available? What are the data to support this?

Scenario 2 (Continued):

The above patient comes back to see you in 6 weeks, this time with worsening cough, fever, copious sputum production and dyspnea. You send a sputum culture, and it is positive for *Pseudomonas aeruginosa*, which is pan-sensitive.

Question 7: You are concerned for an acute exacerbation. What are the hallmarks of an acute exacerbation of bronchiectasis? What are the most common pathogens? How would you proceed with treatment?

Scenario 2 (Continued):

The patient completes a 14-day course of ciprofloxacin and has some clinical improvement. You see her back in the office 3 months later. She returns with another exacerbation, which would be her third this year alone.

Question 8: How should you approach this patient with recurrent exacerbations? What are your treatment options?

Question 9: When should you consider the use of a macrolide antibiotic?

Question 10: Beyond macrolide therapy, what additional pharmacologic strategies are available to target the inflammatory component of bronchiectasis?

Question 11: When should you consider lung transplant referral?

Diagnosis and Management of Bronchiectasis

Educational Objectives:

1. Review a systematic approach to the diagnosis and evaluation of bronchiectasis
2. Review radiographic findings and correlate with underlying cause
3. Discuss an initial approach to the management of bronchiectasis

Scenario 1:

Ms. G is a 55-year-old woman with a history of hypertension and diabetes who presents to your outpatient practice with new-onset shortness of breath, cough and wheeze. She has no significant past pulmonary history and notes that these symptoms started about 5 months ago. Since that time, she has been treated 4 times for upper respiratory infections with a variety of antibiotics. She has also tried numerous inhalers without relief. The only time she felt better was following a short course of prednisone. She continues to have a persistent cough with abundant yellow sputum production. Her primary care physician ordered a chest x-ray (CXR) and ultimately a computed tomography (CT) of the chest given the recurrence and persistence of her symptoms. She was told by her doctor that the report mentioned bronchiectasis and that she should see a pulmonologist for further evaluation.

Question 1: What are the classic signs and symptoms of bronchiectasis? What are some other key parts of the history that you would want to know as you begin to discuss a possible cause for her imaging findings?

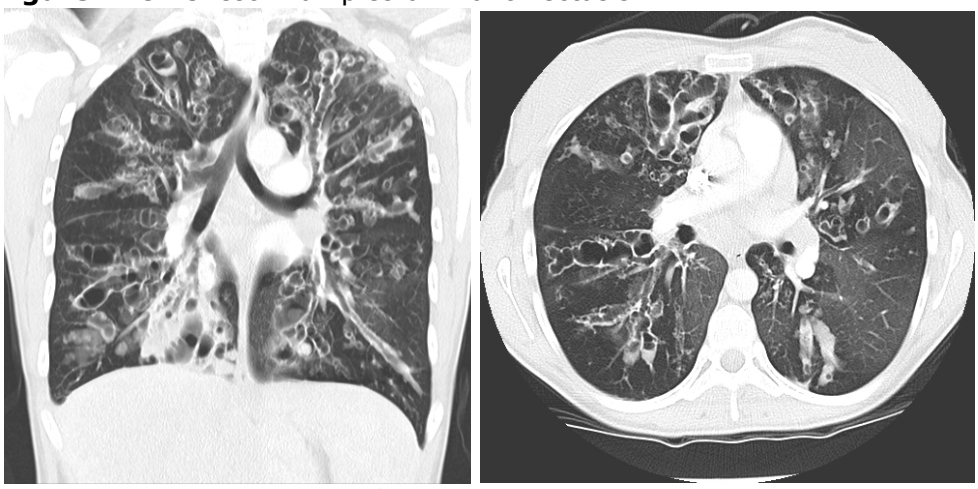
Bronchiectasis is a chronic respiratory disease characterized by a daily productive cough, chronic mucopurulent sputum, and a tendency towards exacerbations.[1] Other associated symptoms include hemoptysis, dyspnea, wheezing, and systemic symptoms (fever, sweats, weight loss, fatigue). Diagnosis is confirmed with high-resolution CT chest.

Given the heterogeneous nature of its etiologies, a detailed clinical history is important to determine the underlying cause of bronchiectasis.[2] A history of frequent infections as an adult or in childhood points to post infectious bronchiectasis and/or immunodeficiency, and extra-pulmonary symptoms may indicate presence of a systemic disease process (e.g., inflammatory bowel disease, rheumatoid arthritis, connective tissue disease, etc.) that is associated with bronchiectasis. History should also look for comorbid conditions of asthma, chronic obstructive pulmonary disease (COPD), and gastroesophageal reflux disease (GERD). While asthma and COPD can have overlap conditions, they are also common disease mimics which bronchiectasis may be mislabeled as; potentially contributing to diagnostic delays. A detailed social history including occupational exposures, tobacco use, and ability to conceive in the past is also important. Finally, a detailed family history with particular attention to any family members with cystic fibrosis, primary ciliary dyskinesia, or a pattern of respiratory disease in the family is pertinent.

Question 2: You review her imaging and agree that there is diffuse bronchiectasis present in a central distribution. What does bronchiectasis look like on chest imaging? How does the distribution of disease help you in determining the possible underlying cause(s)?

A non-contrast chest CT is required for the diagnosis of bronchiectasis which is defined as bronchial airway diameter larger than the diameter of an adjacent blood vessel as shown in Figure 1.[2,3] Other imaging features include lack of airway tapering with a presence of radiographically visible airways in the periphery. Additional findings may include tree-in-bud opacities caused by mucus impaction in small airways and cysts at ends of airways. There are several different airway morphologies that may exist in bronchiectasis; including cylindrical, varicose, and cystic.

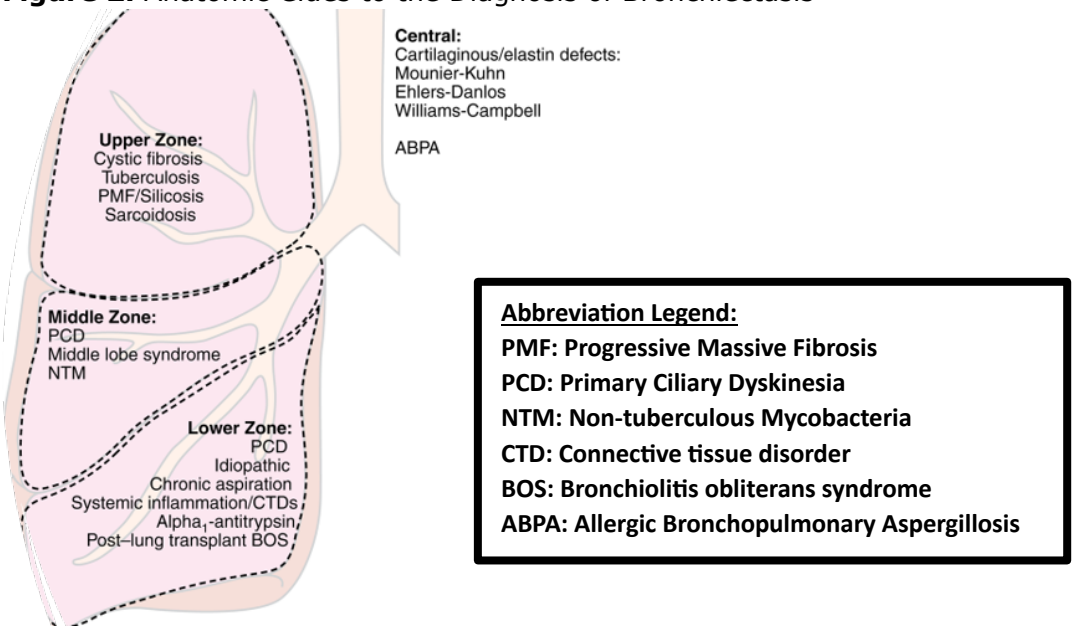
Figure 1. CT Chest Examples of Bronchiectasis



Case courtesy of Dr. Rohit Sharma.[3]

As seen in Figure 2, anatomic location of bronchiectasis can suggest the underlying cause.

Figure 2. Anatomic Clues to the Diagnosis of Bronchiectasis



Abbreviation Legend:
PMF: Progressive Massive Fibrosis
PCD: Primary Ciliary Dyskinesia
NTM: Non-tuberculous Mycobacteria
CTD: Connective tissue disorder
BOS: Bronchiolitis obliterans syndrome
ABPA: Allergic Bronchopulmonary Aspergillosis

Taken from Murray and Nadel's *Textbook of Respiratory Medicine*.[4]

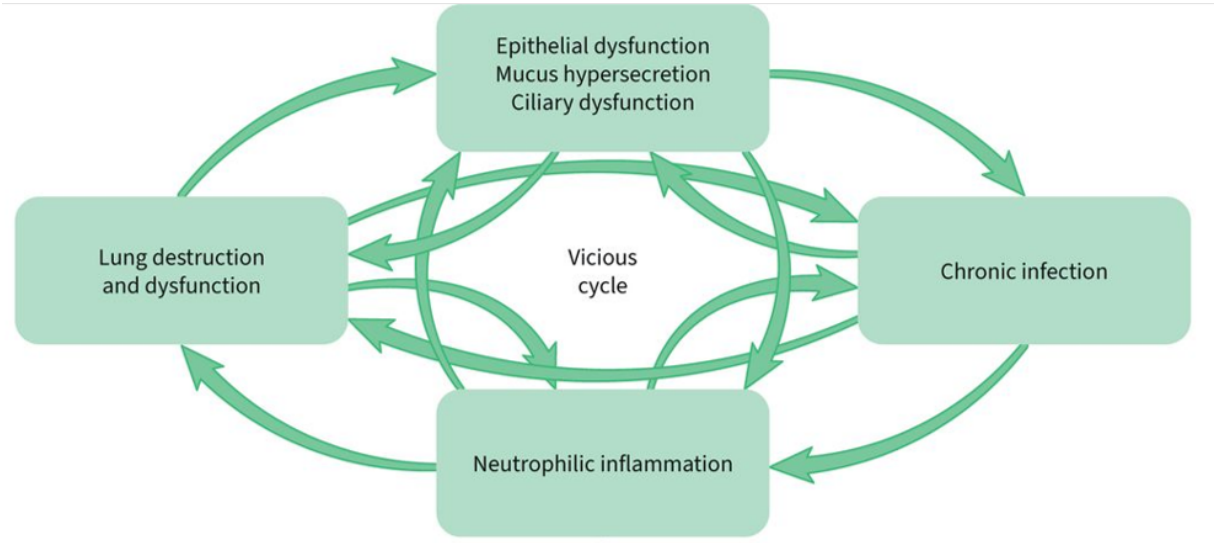
Scenario 1 (Continued):

Upon further history taking, you note that Ms. G is a never smoker. She currently works as an administrative assistant at a local bank. She has 2 children and never had any difficulty conceiving. She notes some mild asthma and intermittent sinus issues throughout her life, but no other extra-pulmonary symptoms are noted on her detailed review of symptoms. She has some mild GERD but no clinical history that is concerning for chronic aspiration. She has no known history of recurrent infections as a child. She was generally healthy up until the last 5 months. There is no sputum culture data for your review at this time.

Question 3: What is the pathophysiology of bronchiectasis?

Many different inciting factors can initiate what has been termed the "vicious cycle" but is now more accurately described as the "vicious vortex" of bronchiectasis.[5] Figure 3 reflects that interactions between mucociliary dysfunction, chronic infection, chronic inflammation (predominantly neutrophilic), and lung destruction are not linear and stepwise, but that each one of these is closely interlinked with the others. To stop this cycle, it is not enough to target just one factor. Treatment needs to target all components of the vicious vortex.

Figure 3. Pathophysiology of the Vicious Vortex in Bronchiectasis



Taken from Chalmers JD et al.[6]

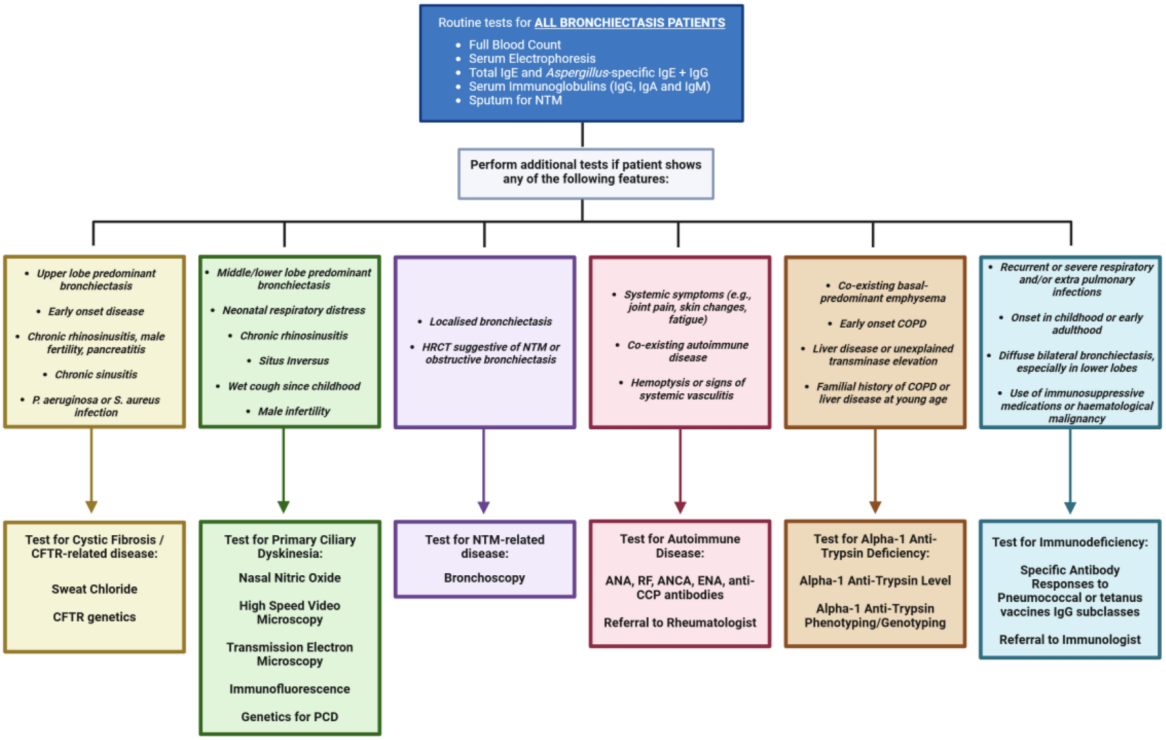
Question 4: What is the recommended workup for bronchiectasis? How would you tailor your evaluation in this patient given the clinical history?

Various bronchiectasis guidelines[7-10] recommend the following testing on all bronchiectasis patients:

- CBC with differential
- Serum immunoglobulins (G/A/M/E)
- Aspergillus serology (IgG precipitins, specific IgE, skin testing)
- Sputum cultures bacterial, mycobacterial, fungal

Figure 4 shows the updated European Respiratory Society (ERS) guideline recommendations for routine tests and additional testing to consider in certain populations. A detailed history and physical is imperative to guide further testing beyond the routine tests in an aim to provide individualized and cost-effective care.

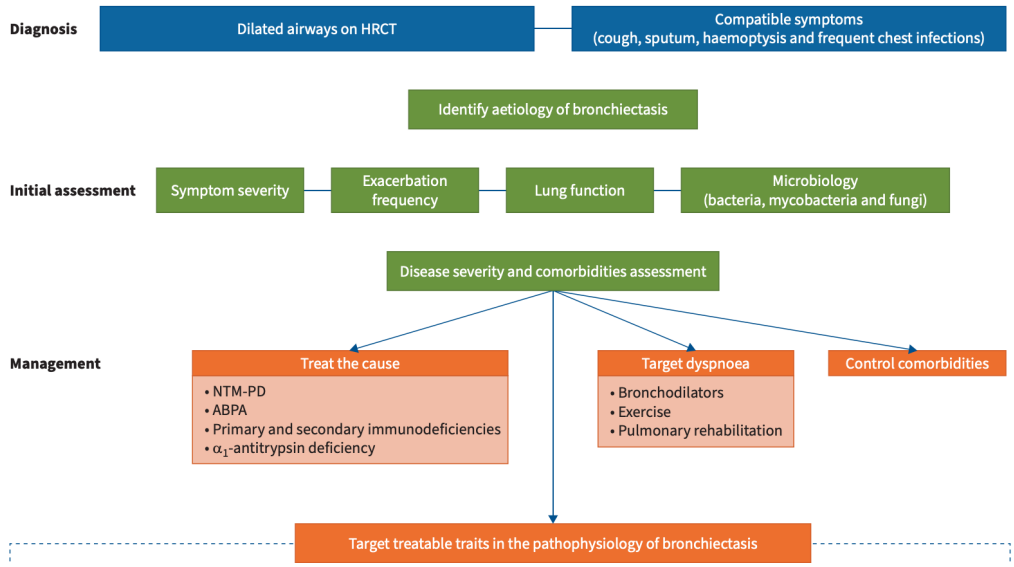
Figure 4. Approach to Identifying an Underlying Cause for Bronchiectasis



Taken from Chalmers JD et al. [7]

In addition to sending blood work to identify an etiology of bronchiectasis, the initial assessment and broad overview of management should include other components as outlined in Figure 5.

Figure 5. Summary of Initial Diagnosis, Assessment, and Management in Bronchiectasis



Taken from Choi H et al.[11]

Scenario 1 Completion:

You send a variety of blood studies and testing is consistent with a diagnosis of ABPA.

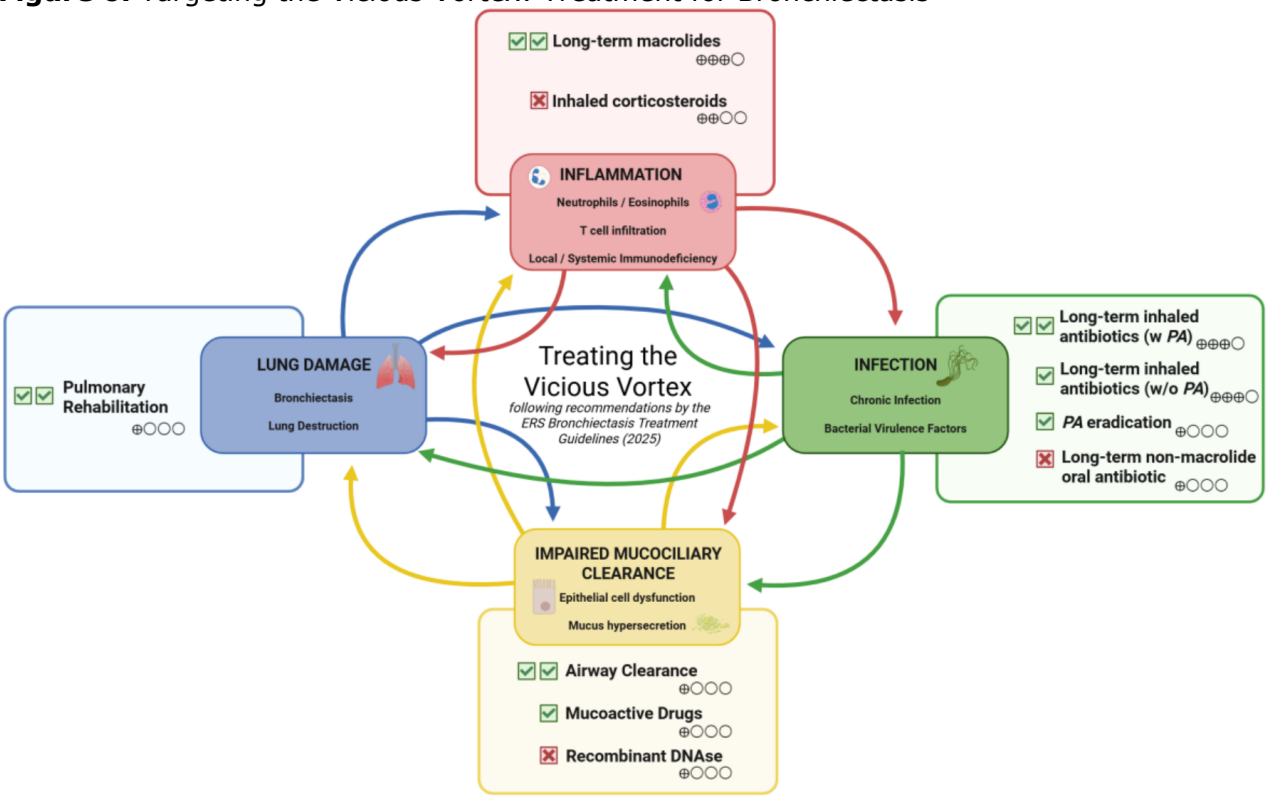
Scenario 2:

You are seeing a 55-year-old woman with a history of hypertension and diabetes in the office for management of her bronchiectasis. CT chest has shown focal bronchiectasis in the right lower lobe thought to either be attributable to chronic aspiration or past infection. She is seeing you now with mildly worsened cough, sputum production and stable dyspnea. She has no prior culture data available for your review.

Question 5: Based on the above history, how would you proceed with treatment?

Treatment should target all components of the vicious vortex. The recently updated ERS guidelines[7] provide a framework for optimal management, as outlined in Figure 6. Airway clearance should be considered for all patients. In this setting, management may include initiation of airway clearance while obtaining culture data and review of exacerbation history to determine if additional treatments may be beneficial.

Figure 6. Targeting the Vicious Vortex: Treatment for Bronchiectasis



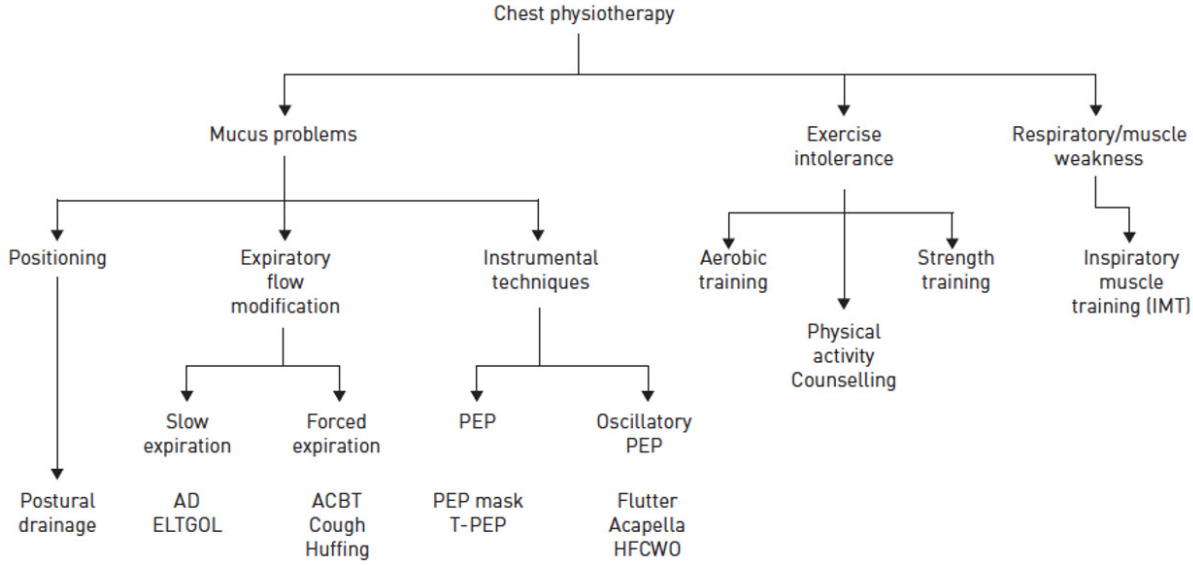
**Green indicates treatments with a favorable recommendation (bold with 2 ticks is strong recommendation, non-bold with one tick is conditional recommendation). Red indicates treatments that receive a recommendation against (Red cross indicates conditional recommendation against). The certainty of evidence is indicated by the cross circles after each topic (1 cross=very low certainty 2=low certainty, 3=moderate certainty, 4=high certainty).*

Taken from Chalmers JD et al.[7]

Question 6: What are the different modes of airway clearance available? What are the data to support this?

Impaired mucociliary clearance is one of the main defects leading to bronchiectasis and disease progression. We recommend consideration of airway clearance therapies in all symptomatic patients with cough and sputum production that impairs their quality of life and/or who suffer from frequent acute exacerbations.[12] Patients with dry cough and mucus plugging on chest CT may also benefit from airway clearance.[7] No single technique has proven superior; therefore selecting a modality that is easy to use and well tolerated is essential for adherence. Airway clearance techniques may use techniques focused at multiple levels including mucus hypersecretion, dyspnea, and weakness. Figure 7 shows different airway clearance interventions.

Figure 7. Chest Physiotherapy Interventions for Bronchiectasis



Chest physiotherapy interventions flow chart based on clinical experience from the task force panel. AD: autogenic drainage; ELTGOL: total slow expiration with open glottis and infralateral position; ACBT: active cycle of breathing techniques; PEP: positive expiratory pressure; T-PEP: temporary positive expiratory pressure; HFCWO: high frequency chest wall oscillation.

Taken from Polverino et al. [9]

Airway clearance can be mechanical via devices and/or using active breathing techniques or postural drainage. Commonly used chest physical therapy devices include oscillatory positive expiratory pressure (oPEP) devices (e.g., Acapella, Aerobika). Additionally, high frequency chest wall oscillation via a percussive vest (commonly used in cystic fibrosis) may benefit patients with greater mucus burden and/or mucus plugging. Pharmacologic options include mucoactive drugs such as hypertonic saline, which often comes in the form of 3% sodium chloride or 7% sodium chloride nebulizer solutions. Small studies show hypertonic saline improves FEV1 and quality of life and reduces health care utilization.[13] A common approach to the sequence of airway clearance includes use of nebulized solutions (short acting bronchodilation followed by nebulized sodium chloride) prior to airway clearance techniques (PEP or HFCWO), and huff cough techniques at the end to assist with mucus expectoration. DNase has not proven to be effective and may be harmful in non-CF bronchiectasis, although it is important to remember that each non-CF cause of bronchiectasis is potentially distinct.[14] Exercise and pulmonary rehabilitation can also help with airway clearance.

Scenario 2 (Continued):

The above patient comes back to see you in 6 weeks, this time with worsening cough, fever, copious sputum production and dyspnea. You send a sputum culture, and it is positive for *Pseudomonas aeruginosa*, which is pan-sensitive.

Question 7: You are concerned for an acute exacerbation. What are the hallmarks of an acute exacerbation of bronchiectasis? What are the most common pathogens? How would you proceed with treatment?

Hill et al.[15] published a consensus definition of an acute exacerbation described as an acute clinical deterioration, requiring a change in therapy, presenting with at least three of the following symptoms:

- Increased cough
- Increased sputum volume and/or consistency
- Increased sputum purulence
- Increased dyspnea
- Fatigue/malaise
- Hemoptysis

Chronic infection drives airway inflammation and worsens outcomes in bronchiectasis. Globally, *Pseudomonas aeruginosa* is a common airway colonizer in bronchiectasis including in the United States registry where *Pseudomonas aeruginosa* is the most common pathogen and is associated with increased exacerbations. For acute exacerbations, ERS guidelines recommend a 14-day course of antibiotics, tailored to susceptibility profiles, typically with an oral fluoroquinolone. However, optimal duration remains uncertain and shorter durations may be considered particularly in non-pseudomonal infectious exacerbations.[7]

If *Pseudomonas* is isolated for the first time, ERS guidelines recommend an eradication attempt through one of three pathways outlined below in Figure 8.

Figure 8. *Pseudomonas* Eradication Therapy in Bronchiectasis

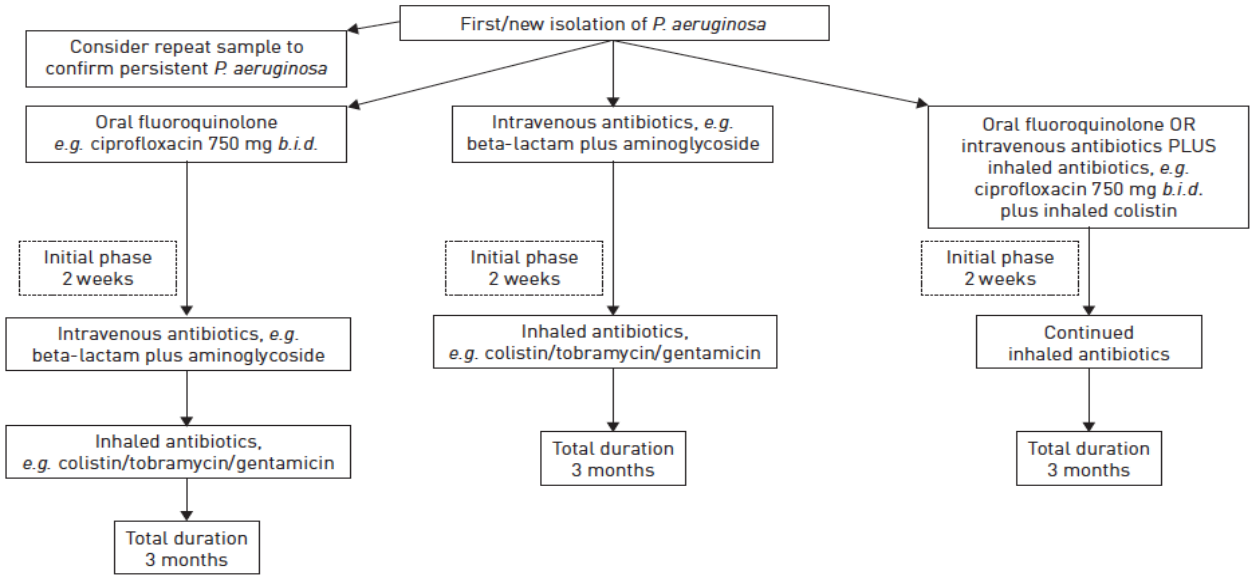


Figure taken from Polverino et al.[9]

A meta-analysis by Conceição et al.[16] found eradication success in approximately 40% of cases at 12 months, with significant reductions in exacerbation rates.

Scenario 2 (Continued):

The patient completes a 14-day course of ciprofloxacin and has some clinical improvement. You see her back in the office 3 months later. She returns with another exacerbation, which would be her third this year alone.

Question 8: How should you approach this patient with recurrent exacerbations? What are your treatment options?

Sputum samples should be sent for microbiological analysis at the time of exacerbation. If culture is positive, antimicrobial therapy should be initiated and tailored to the sensitivity of the pathogen with consideration of chronic suppressive antibiotics for recurrent pseudomonas infections. The treatment for non-tuberculous mycobacterial pulmonary disease (NTM-PD)is addressed separately.

European Respiratory Society guidelines suggest a treatment approach for frequent exacerbations as seen in Figure 9.

Figure 9. Treatment of Frequent Exacerbations in Bronchiectasis

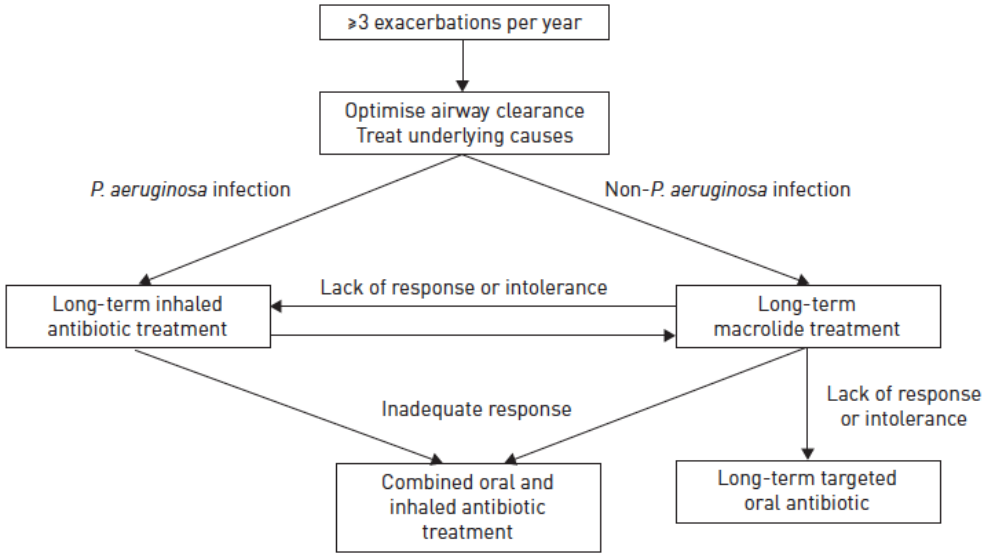


Figure taken from Polverino et al. [9]

Guidelines[7,9] recommend inhaled suppressive antibiotic treatment for patients with bronchiectasis, chronic *P. aeruginosa* infection, and a history of frequent exacerbations. Inhaled antibiotics can achieve high local concentrations with a lower risk of toxicity though they may be associated with bronchospasm. Trials performed with a variety of antibiotics (inhaled aminoglycosides [tobramycin, gentamicin, amikacin], inhaled fluoroquinolones [ciprofloaxin, levofloxacin], inhaled aztreonam, inhaled colistin) have shown mixed results and no antibiotics are approved for non-CF bronchiectasis which may impact availability of formulations in various countries. Nevertheless a recent meta-analysis demonstrated a decrease in exacerbations and in severe exacerbations with improved symptoms and quality of life.[17]

Question 9: When should you consider the use of a macrolide antibiotic?

In addition to their antibacterial properties, macrolides have potent anti-inflammatory effects. International guidelines recommend macrolides for patients with more than 3 exacerbations per year. Macrolides have been shown to significantly reduce exacerbations, including in those with *Pseudomonas*.[18] A recent Cochrane review[19] showed that the long-term use of macrolide therapy reduced the frequency of exacerbations and improved quality of life based on studies mainly using azithromycin. It is important to counsel patients regarding potential cardiac risk (including QTc prolongation), gastrointestinal symptoms, antibiotic resistance, and ototoxicity. Macrolides should be avoided in patients with known or suspected NTM infection and periodic surveillance cultures can be considered to monitor for NTM isolates while on chronic macrolides.

Question 10: Beyond macrolide therapy, what additional pharmacologic strategies are available to target the inflammatory component of bronchiectasis?

Emerging therapies target the inflammatory cascade in bronchiectasis. Neutrophilic inflammation is a key driver of airway damage and neutrophil serine protease levels (including neutrophil elastase) are associated with disease severity, bacterial load, and clinical outcomes including exacerbations and hospitalizations.[20] Brensocatib, an oral dipeptidyl peptidase 1 (DPP1) inhibitor, works by reducing activation of neutrophil enzymes that contribute to tissue injury. In the phase 3 ASPEN trial[21], in patients with non-cystic fibrosis bronchiectasis who had 2 or more exacerbation in the past year, brensocatib significantly lowered the annualized rate of pulmonary exacerbations and prolonged time to first exacerbation compared with placebo. The higher dose (25mg) also showed a slower decline in lung function. Brensocatib is now FDA-approved for adults with non-cystic fibrosis bronchiectasis, offering a novel anti-inflammatory approach beyond macrolide therapy. Additional therapeutics are in development including those targeting both neutrophilic and eosinophilic endotypes.

Question 11: When should you consider lung transplant referral?

There are several indicators of severe lung disease in bronchiectasis. Generally, lung transplant should be considered when[22]:

- Postbronchodilator FEV1<30%,
- Postbronchodilator FEV1 >40% AND additional complications such as
    - hypoxemia
    - pulmonary hypertension
    - 6MWT <400m
    - pCO2>50mm Hg
    - >2 exacerbations/year requiring IV antibiotics
    - massive hemoptysis
    - pneumothorax
    - malnutrition
- FEV1<50% and rapidly declining trajectory
- Severe exacerbation requiring positive pressure ventilation

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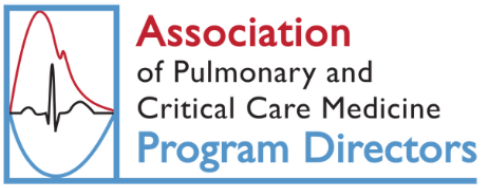

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