Diagnosis and Management of Bronchiectasis

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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 female 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 and ultimately a 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?

A possible diagnosis of bronchiectasis should be considered in patients with a daily productive cough, in particular if patients note a large volume of sputum production. In addition, a sputum culture history of Pseudomonas aeruginosa, unexplained hemoptysis, persistence of symptoms for many years and recurrent respiratory tract infections are all consistent with bronchiectasis. (Pasteur, et al; Thorax 2010)

A detailed clinical history is important to determine the underlying cause of bronchiectasis. 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 (ex: inflammatory bowel disease, connective tissue disease, etc.) that is associated with bronchiectasis. 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 or a pattern of respiratory disease in the family is pertinent. A laboratory review for any immunodeficiencies and cultures (bacterial, fungal, and acid fast) for new or colonizing organisms should be done.
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)?

Figure 1. Sample representative cuts of CT scans of the chest showing bronchiectasis.
Figure 2. Correlation of radiographic distribution of bronchiectasis with underlying disease states. (Barker, Mysliwiec, Pasteur)
Question 3: What is the pathophysiology of bronchiectasis?

Many different inciting factors can initiate what has been termed the "vicious cycle" of bronchiectasis, whereby airway inflammation leads to mucus stasis, predisposing to infections, ultimately perpetuating ongoing inflammation and remodeling. The role of increased neutrophil elastase activity has been further elucidated in recent studies and is being investigated as a target for treatment. (Chalmers, NEJM 2020; 383: 2127)

![Pathophysiology of bronchiectasis](image)

**Figure 3. Pathophysiology of bronchiectasis. (O'Donnell, NEJM 2022; 387:533)**

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

The British Thoracic Society 2019 guidelines recommend the following testing:

- Blood testing (all patients):
  - Full blood count (CBC)
  - Serum total IgE
  - Sensitisation (specific IgE or skin prick test) to Aspergillus fumigatus
  - Serum immunoglobulins (IgA, IgM, IgG)
  - Sputum cultures (routine and mycobacterial)
  - Serum electrophoresis (if raised immunoglobulins present)
  - Baseline specific antibody levels against capsular polysaccharides of Streptococcus pneumoniae
  - HIV

Scenario 1 (cont.):

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 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.
Testing to consider in certain populations:

- Cystic fibrosis testing in patients with supporting clinical features (ex: early onset, male infertility, malabsorption, pancreatitis)
- Primary Ciliary Dyskinesia (PCD) testing in patients with supporting clinical features, (ex: neonatal distress, symptoms from childhood, recurrent otitis media, rhinosinusitis, or infertility)
- Rheumatoid factor, ANCA, ANA in patients with coexisting clinical features of arthritis, connective tissue disease and/or systemic vasculitis
- Alpha 1 antitrypsin (A1AT) deficiency in patients with coexisting basal panacinar emphysema
- Workup for gastric aspiration in select patients (ex: barium swallow)
- Bronchoscopy if:
  - Concern for endobronchial lesion/foreign body in localized disease
  - More definitive evaluation for NTM if high suspicion and patient unable to adequately expectorate

Of note, the ERS 2017 guidelines recommend a minimum bundle of CBC with differential, serum immunoglobulins and testing for ABPA. Patients should also have a sputum culture collected to monitor for infection. Testing for mycobacterial disease may be of utility in select cases.

**Scenario 1 Completion:**
You send a variety of blood studies and testing is consistent with a diagnosis of ABPA.
Bronchiectasis: Treatment

Antibiotics
- Systemic
- Inhaled

- Macrolides
- Steroids
- Elastase inhibitors
- CXCR2 antagonists
- Cytokine inhibitors

Airway clearance

Surgery

Treatment of underlying conditions

+ Infection

Figure 5. Overview of treatment modalities for bronchiectasis. (McShane, Am J Resp Crit Care Med 2023; 188:647)

Scenario 2:
You are seeing a 55-year-old female 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?
Figure 6. Treatment algorithm for bronchiectasis. (McShane, Am J Resp Crit Care Med 2023; 188:647)

Based on the algorithm above, we recommend obtaining a sputum culture and starting a regular airway clearance regimen. 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 NTM is addressed separately in another conference handout.

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

We recommend that you consider 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 exacerbation. Selection of a modality that the patient can use easily and tolerate is important to improving overall adherence. Airway clearance can be via mechanical means, with the use of chest physical therapy/postural drainage or devices. Commonly used devices are oscillatory PEP (Positive expiratory pressure) devices, such as the Acapella or Aerobika (see below). High frequency chest wall oscillation via a Vest (commonly used in cystic fibrosis) can be used in patients with greater mucus clearance needs. Airway clearance can also be facilitated pharmacologically, through the use of mucolytics such as dornase alpha, acetylcystine, or hypertonic saline. Small studies have shown improvements in a range of parameters including FEV1, quality of life, and health care utilization with use of hypertonic saline (Kellett, Respir Med 2011). Bronchodilators are commonly used as well prior to mucolytics, although there is no long-term data on efficacy in bronchiectasis (Cochrane Database Syst Rev 2003). Mucolytics such as DNase are not proven to be effective and may potentially harmful in non-CF patients, although it is important to remember that each non-CF cause of bronchiectasis is potentially distinct (O’Donnell et al, Chest 1998).
Figure 7. Chest physiotherapy interventions for bronchiectasis. (Polverino, Eur Resp Journal 2017; 50: 1)

Scenario 2 (cont.):
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, 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?

Acute exacerbations are characterized by:
- Increased cough
- Increased sputum volume
- Increased sputum purulence
- Increased dyspnea
- Fatigue/malaise
- Hemoptysis

U.S. Bronchiectasis Registry Data (2017):

<table>
<thead>
<tr>
<th>Bacterial culture findings, No. (%)</th>
<th>Data Available (No.)</th>
<th>Overall (N = 1,826)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No growth in any culture</td>
<td>1,406</td>
<td>93 (7)</td>
</tr>
<tr>
<td>Oropharyngeal flora</td>
<td>1,406</td>
<td>1,037 (74)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1,406</td>
<td>116 (8)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1,406</td>
<td>49 (3)</td>
</tr>
<tr>
<td>Staphylococcus aureus^b</td>
<td>1,406</td>
<td>170 (12)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa^c</td>
<td>1,406</td>
<td>470 (33)</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>1,406</td>
<td>76 (5)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>1,406</td>
<td>35 (2)</td>
</tr>
</tbody>
</table>

Figure 8. Microbiology data from U.S. Bronchiectasis Registry. (Aksamit, CHEST 2017; 151: 982)

For acute treatment ERS guidelines recommend a 14-day course of antibiotics (although optimal duration is not clear), tailored to antibiotic susceptibility profiles but typically an oral fluoroquinolone. The BTS guidelines suggest amoxicillin or clarithromycin for empiric treatment for mild-moderate exacerbations and oral respiratory quinolones in more severe patients and those with pseudomonas. In addition, if this is the first time that Pseudomonas has been isolated the European Respiratory Society guidelines recommend an attempt at eradication through one of three pathways outlined below.

Figure 9. Pseudomonas eradication therapy in bronchiectasis. (Polverino Eur Resp Journal 2017; 50: 1)
Scenario 2 (cont.):
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?

In this circumstance of a patient with recurrent exacerbation in the setting of pseudomonas infection, we recommend long term inhaled suppressive antibiotic therapy. Aerosolized antibiotics are generally safe and perform better than placebo in reducing bacterial load and risk of acute exacerbations (Brodt, et al ERJ 2014). Tobramycin is the most commonly used inhaled antibiotic, and has been shown in small trials to reduce exacerbations, admissions, and overall antibiotic use (Orriols, Respiration 2015). Available inhaled antibiotics are shown below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcomes</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>Reduction in exacerbations/admissions/abx use.                              Improved PSA clearance</td>
<td>Orriols, Respiration 2015 (90): 4, 299.</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1°: Reduced sputum bacterial load                                          Reduction in exacerbations, improved QOL Scores</td>
<td>Murray. AJRCCM 2011;183:491.</td>
</tr>
<tr>
<td>Colistin</td>
<td>Improved time to first exacerbation in pts taking &gt;80% doses</td>
<td>Haworth. AJRCCM 2014; 189(8):975.</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>No difference in QOL or time to first exacerbation</td>
<td>Barker. Lancet Resp Med 2014; 2(9): 738.</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Improved bacterial eradication rate in pts infected with PSA during exacerbations</td>
<td>Ailiyaer. Respiration 2018 (95): 5, 327.</td>
</tr>
</tbody>
</table>

Figure 10. Treatment of frequent exacerbations in bronchiectasis. (Polverino Eur Resp Journal 2017; 50: 1)

Figure 11. Inhaled antibiotics and efficacy in bronchiectasis.
Question 9: When should you consider the use of a macrolide antibiotic?

In addition to their antibacterial properties, macrolides have potent anti-inflammatory effects. ERS guidelines recommend macrolides for patients with more than 3 exacerbations per year. Macrolides have been shown to significantly reduce exacerbations (EMBRACE Lancet 2012; BAT JAMA 2013; and BLESS JAMA 2013 trials). A recent Cochrane review (Kelly C, et al Cochrane 2018) showed that the long term use of macrolide therapy may reduce the frequency of exacerbations and improve quality of life based on studies mainly using azithromycin. It’s important to counsel your patient regarding the cardiac risk, gastrointestinal symptoms, antibiotic resistance, and ototoxicity. We also recommend avoiding use in patients with known or suspected NTM infection.

<table>
<thead>
<tr>
<th></th>
<th>EMBRACE: New Zealand</th>
<th>BLESS: Australia</th>
<th>BAT: Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Azithromycin 500 mg three times per week</td>
<td>Placebo</td>
<td>Erythromycin 400 mg twice daily</td>
</tr>
<tr>
<td>Subjects n</td>
<td>70</td>
<td>58</td>
<td>40</td>
</tr>
<tr>
<td>Male %</td>
<td>29</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>Mean age years</td>
<td>59.0</td>
<td>63.5</td>
<td>64.6</td>
</tr>
<tr>
<td>FEV1 % predicted at baseline</td>
<td>67.3</td>
<td>70.1</td>
<td>82.7</td>
</tr>
<tr>
<td>Exacerbation rate pre-trial</td>
<td>3.93 (mean)</td>
<td>Not reported</td>
<td>4.0 (median)</td>
</tr>
<tr>
<td>SGRQ</td>
<td>36.6</td>
<td>38.1</td>
<td>40.2</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in FEV1 with treatment</td>
<td>-0.04</td>
<td>-4.0</td>
<td>-0.10</td>
</tr>
<tr>
<td>Change in SGRQ from baseline</td>
<td>-1.92</td>
<td>-1.3</td>
<td>-4.12</td>
</tr>
<tr>
<td>Total exacerbations in 12 months during trial n</td>
<td>178</td>
<td>114</td>
<td>78</td>
</tr>
<tr>
<td>Mean exacerbation rate during trial (per patient)</td>
<td>2.54</td>
<td>1.97</td>
<td>1.95</td>
</tr>
</tbody>
</table>

SGRQ: St. George's Respiratory Questionnaire. *: p<0.05 compared with placebo. #: p<0.001 compared with placebo group.

Figure 12. Trials of randomized controlled trials of macrolides for bronchiectasis. (Chalmers, ERJ 2015; 45: 1446)

Question 10: When should you consider lung transplant referral?

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

- 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

References:
17. Aksamit, T The RESPIRE trials: two randomized, multicenter, placebo controlled trial of Cipro for non-cf bronchiectasis ERJ 2014
18. Hayes and Meyer, Lung Transplantation for Advanced Bronchiectasis Seminars in Respiratory and Critical Care Medicine 2010
20. Darley et al. JAC 2000; 45
21. TSANZ Guidelines, MJA 2015
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32. Chalmers, ERJ 2015; 45: 1446
33. O’Donnell, NEJM 2022; 387:533
34. Chalmers, NEJM 2020; 383: 2127