Mark Metersky, MD, FCCP, FACP is a Professor of Medicine at the University of Connecticut school of Medicine in the Division of Pulmonary and Critical Care and is Director of UCONN Center for Bronchiectasis Care. Dr. Metersky has long standing interest in pulmonary infections, including pneumonia and bronchiectasis and has published and presented extensively on diagnosis, treatment and prevention of pneumonia and bronchiectasis. He served on the Technical Expert Panel for the CMS National Pneumonia Project and was the American Thoracic Society Co-Chair of the writing panel for the “Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society” and is a member of the Community-Acquired Pneumonia Guideline panel. In his spare time, he enjoys fencing and skiing. He is not a wine connoisseur, but plans to make up for that deficiency during this meeting.

OBJECTIVES:
Participants should be better able to:

1. At the conclusion of the talk, the participant will be able to list common etiologies of bronchiectasis;

2. At the conclusion of the talk, the participant will be able to describe clinical characteristics of bronchiectasis related to specific underlying etiologies;

3. At the conclusion of the talk, the participant will understand the treatment options available treatments for bronchiecctasis and some of their limitations.
Dr. Metersky has received research grants from Aradigm and Bayer and serves as a consultant for Insmed, but these do not create a conflict related to the following presentation.

Bronchiectasis—A Case-Based Interactive Session

Mark L. Metersky, MD
Director, Center for Bronchiectasis Care,
Chief, Division of Pulmonary, Critical Care and Sleep Medicine, University of Connecticut
Disclosures

- Clinical trial participant
  - Gilead
  - Bayer
  - Aradigm
- Consultant
  - Grifols
  - Insmed

Diagnosis

- There are many recommended diagnostic protocols
- Most assume that all patients are alike
- The longer the list of tests recommended for all patients, the more skeptical one should be
  - Evaluation may vary depending upon
    - Patient age
    - Severity/character of disease
    - Resource availability
    - Distance
Reported etiologies of bronchiectasis pooled from three cohort studies

<table>
<thead>
<tr>
<th>Etiologies Among Three Large Cohorts</th>
<th>Percent of Patients (n = 418 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>48</td>
</tr>
<tr>
<td>Postinfectious</td>
<td>25</td>
</tr>
<tr>
<td>Immunodeficiency (various)</td>
<td>8</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>7</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>5</td>
</tr>
<tr>
<td>Young syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>2</td>
</tr>
<tr>
<td>Aspiration or gastroesophageal reflux</td>
<td>2</td>
</tr>
<tr>
<td>Yellow nail syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Non-tuberculous mycobacterial infection</td>
<td>1</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>Diffuse panbronchiolitis</td>
<td>1</td>
</tr>
<tr>
<td>Congenital</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Quast, Dis Mon, 2008
Pasteur, AJRCCM, 2000
Nicotra, Chest, 1995
Other Reported Etiologies

Acquired immunodeficiency
Lymphoma HIV-related
Organ or bone marrow transplant
Autoimmune
Relapsing polychondritis
Ankylosing spondylitis
Sjogren’s Syndrome
Chronic obstructive pulmonary disease
Congenital or genetic
α1-Antitrypsin deficiency
Job syndrome (hyper immunoglobulin E syndrome)
Marfan syndrome
Mounier-Kuhn syndrome (tracheobronchomegaly)
Williams-Campbell syndrome
Endobronchial obstruction
Neoplasm
Foreign body
Extrinsic compression by lymph nodes
Inhalational exposure
Smoke
Ammonia
Chlorine
Traction
Pulmonary fibrosis
Sarcoidosis


What causes idiopathic bronchiectasis?

- Unrecalled prior infection?
- Double hit hypothesis?
  - 1 CFTR mutation
    - Bienvenu, AJRCCM, 2010
  - Heterozygote alpha–1 antitrypsin deficiency
  - Mannose binding lectin deficiency
  - IgG subclass deficiency
  - Epithelial sodium channel (ENaC) mutations
    - Fajac, Respir Research, 2008
Is it important to determine etiology?

- Patients want to know
- Genetic counseling
- In two cohort studies, patients received a diagnosis that either resulted in a change in therapy (15%) or potentially would (37%)
  - ABPA
  - CF
  - GERD
  - CVID

Pasteur, AJRCCM, 2000
Shoemark, Respir Med, 2007

Diagnoses at UConn

Among patients who were being cared for by either a pulmonologist or ID specialist and did not have a specific diagnosis
N=44

- ABPA 1
- M. avium complex 2
- Alpha-1-PI-ZZ 2
- Hyper IgE syndrome 1
- Cystic fibrosis 1
- Total 7 (16%)*

*Two additional probable CF (sweat Chloride >60)
One recent confirmation of IgM deficiency with qualitative immunoglobulin defect
Ashraf, AJRCCM, 2013 (Abstract)
Patient Characteristics

- **Age**
  - Younger patients more likely to have a congenital cause
    - CF, primary ciliary dyskinesia, congenital immunodeficiency
- **Prior severe infection**
- **Autoimmune disease**
  - Sjogren’s, RA, ulcerative colitis
- **Paranasal sinus disease**
  - ABPA, CF, ciliary dyskinesia, immunodeficiency, Job syndrome (HIES)
- **Fertility problems**
  - CF, ciliary dyskinesia, Young’s syndrome

Imaging Studies

- Certain findings suggestive of specific diagnoses
  - Predominantly upper lobe disease– CF
  - Nodules, tree-in-bud, cavities– NTM
  - Middle lobe/lingula disease– NTM
  - Emphysema–α–1– antitrypsin deficiency
  - Focal disease– endobronchial obstruction
What is the most likely cause of bronchiectasis in this 26 year old female with a 3 year history of cough and sputum with recent hemoptysis?

1. Allergic bronchopulmonary aspergillosis
2. Severe combined immunodeficiency
3. Cystic fibrosis
4. Primary ciliary dyskinesia
5. Idiopathic
Predominant upper lobe disease
Young patient

CF must be considered
A mutation screen showed her to be heterozygote for ΔF508, with no other mutations
What is the next step?
What is the most likely cause of bronchiectasis in this 68 year old female?

1. M. avium
2. Idiopathic
3. Alpha-1–anti–trypsin deficiency
4. Cystic fibrosis
5. Common variable immunodeficiency
What is the most likely cause of bronchiectasis in this 68 year old female?

1. M. avium
2. Idiopathic
3. Alpha-1-anti-trypsin deficiency
4. Cystic fibrosis
5. Common variable immunodeficiency

<table>
<thead>
<tr>
<th>0%</th>
<th>0%</th>
<th>0%</th>
<th>0%</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2.</td>
<td>3.</td>
<td>4.</td>
<td>5.</td>
</tr>
</tbody>
</table>

- 90% of the patients had bronchiectasis
- High prevalence of CFTR mutations

<table>
<thead>
<tr>
<th>TABLE 7. MORPHOLOGIC FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Scoliosis</td>
</tr>
<tr>
<td>Pectus excavatum</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: PNTM = pulmonary nontuberculous mycobacterial.*

Kim RD, AJRCCM, 2008
Bronchiectasis in α –1– Antitrypsin Deficiency

- Has been controversial as to how common/clinically significant this is
- Some studies have shown no increased prevalence in large cohorts of patients with bronchiectasis
Bronchiectasis in $\alpha -1-$ Antitrypsin Deficiency

- A different picture emerges when one studies a large cohort of $\alpha -1-$anti-trypsin patients
- Among 74 Pi–ZZ patients
  - 70 had some bronchiectasis
  - 20 (27%) had at least 3 lung segments involved
  - A bronchiectasis predominant phenotype was identified
  - CT findings of bronchiectasis correlated with:
    - Increased sputum production
    - Increased frequency of exacerbations
    - Lower QOL
  
  Parr, AJRCCM, 2007

Recommended for all patients

- HRCT of chest
- PFTs
- Sputum for bacteria, AFB, fungus
- CBC with differential
- Quantitative Immunoglobulins IgG, IgA, IgM
- IgE level

Recommended for most patients without an identified etiology

- α-1-anti-trypsin level
- CF screening
  - Sweat chloride or
  - Nasal potential difference or
  - CF mutation screen


Recommended for selected patients without an identified etiology

- Aspergillus–specific IgG, IgE and/or skin testing
- Bronchoscopy (focal disease, NTM suspected)
- Ciliary biopsy, nasal nitric oxide
- Immunologic evaluation
- Serologies for autoimmune disease

Summary

- Determining etiology often leads to changes in therapy
- Systematic evaluation recommended
- Nonetheless, this evaluation should be tailored to the specific patient being evaluated

Treatment

- Therapeutic approach for bronchiectasis is not highly evidence-based
- BTS guidelines, largely expert opinion-based
- We will discuss potential treatment options
- I will then reveal what I did and the results (good and bad)
- I hope to prompt spirited discussion
A 58 year old female pediatrician is referred in 2012 for evaluation after a chest radiograph and subsequent CT are found to be abnormal.

- She has had a few respiratory tract infections over the years.
- Her only complaint is a bothersome dry cough, persistent over 10–15 years, but recently worse.
- She worries about its effect on her patients’ perception of her.
- She is very physically active and otherwise feels well.
- Nothing to suggest GERD.
Her physical examination is unrevealing
Her PFTs are supernormal
Laboratory testing for the “usual suspects” is unrevealing
She is unable to produce a sputum sample
Bronchoscopy reveals no secretions and the “corrugation” pattern associated with Mounier-Kuhn
No organisms of any type are cultured
Approach to Therapy

What would you provide her for treatment?

1. Nothing, she is doing well
2. Airway clearance regimen, eg. with Acapella
3. Chronic macrolide therapy
4. Empiric treatment for GERD
5. Hypertonic saline nebulization
6. Other intervention
She began treatment with Azithromycin, 250 mg TIW
Returns 3 months later
Cough “50–75% improved”
Coworkers spontaneously note her improved cough, not knowing she was on therapy
Had to stop temporarily secondary to vaginal candidiasis, Sx worsened and improved with restart

Macrolide effect on SGRQ

Figure 3: Forest plots showing a significant reduction in the St George’s Respiratory Questionnaire total scores in the macrolides group compared with control group. CI, confidence interval; IV, inverse variance; SD, standard deviation.
A 53 year old female is referred for bronchiectasis in 2003
She has been coughing 1–2 teaspoons of variably colored sputum daily for several years
Exacerbations 1–2 times a year characterized by fever, chest pain and increased purulence
Each responds quickly to oral antibiotics
No systemic complaints
She is active, works full time
Physical examination, laboratory testing unrevealing
PFTs normal
She grows pan–sensitive Pseudomonas only
She is prescribed a flutter valve and uses it intermittently
What additional therapies would you have prescribed (2003, pre-macrolide era)?

1. Nothing, she is doing well
2. Inhaled tobramycin (2003, other options now)
3. Inhaled hypertonic saline
4. High frequency chest wall oscillation
5. Attempt at “eradication” of Pseudomonas
What additional therapies would you have prescribed (2003, pre-macrolide era)?

1. Nothing, she is doing well
2. Inhaled tobramycin (2003, other options now)
3. Inhaled hypertonic saline
4. High frequency chest wall oscillation
5. Attempt at “eradication” of Pseudomonas

She is now 66, happily retired

- We tried azithromycin, no benefit, so stopped
- Still coughs 1–2 teaspoons a day, usually green
- Still 1–2 exacerbations a year, quickly respond to levofloxacin (although now intermediate sensitivity in vitro)
- PFTs stable
- Grew MAC once, not subsequently
- Overall, no change in almost 12 years, essentially without therapy
- Would her QOL be better with inhaled antibiotics?
Aerosolized antibiotics

- Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomized double-blind, placebo-controlled phase 3 trials
  - No clinically significant benefit
  - Increased treatment-related adverse events and discontinuations in aztreonam group

  Lancet Respir Med, 2014

Aerosolized antibiotics

- Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection
  - Failed to reach primary endpoint (exacerbation rate), although significant decrease in the most compliant patients
  - Clinically significant improvement in SGRQ

  Haworth, AJRCCM, 2014
Inhaled fluoroquinolones

- Dry powder ciprofloxacin
  - Met primary endpoint of time to exacerbation in Phase 3 study in 14 day on and 14 day off arm, not 28 day arm
    - De Soyza, CHEST, 2016 (Abstract only)

- Liposomal ciprofloxacin preparation
  - Met time to exacerbation endpoint in one Phase 3 study, not the other.
    - Aradigm Press release

Case 3

- 69 year old male self-referred with long history of bronchiectasis

- Sputum grows MSSA and MAC
- Never grows MAC again
- Next seen 2 years later (he has a primary pulmonologist)
Sputum production has increased
Grows MSSA/Pseudomonas on multiple cultures over the next year.
About 3 exacerbations a year characterized by increased sputum without systemic complaints
Using Acapella BID
Respond well to levofloxacin
Condition is quite similar to patient in case 2 except:
His girlfriend wants to be more proactive
Enrolled in inhaled mannitol study
No obvious benefit
Grows Pseudomonas repeatedly

What would you do next?

1. Start TIW azithromycin (it has been 4 years since he grew MAC)
2. Switch from Acapella to HFCWO
3. Start inhaled antibiotic
4. Start inhaled hypertonic saline
What would you do next?

1. Start TIW azithromycin (it has been 4 years since he grew MAC)
2. Switch from Acapella to HFCWO
3. Start inhaled antibiotic
4. Start inhaled hypertonic saline

- Started on inhaled tobramycin
  - Chronic sputum production completely remits
  - “Life changing”
  - Creatinine increases from 0.9 to 1.4
- Switched to inhaled aztreonam
  - Develops diffuse papular rash within several days
- Try to enroll him in liposomal cipro study
  - Grows MSSA only, so is a screen failure
- Currently doing well on Augmentin 10 days each month
Unresolved therapeutic issues that continue to give me anxiety

- When to escalate to high frequency chest wall oscillation from Acapella/Flutter, etc?
- When to start nebulized antibiotics?
- When to consider hypertonic saline?
- When to STOP azithromycin in patients who do not appear to have responded?