Non-CF bronchiectasis:

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Pioneer of Respiratory Medicine

2016 marked 200th anniversary of his invention of the stethoscope

Correlated abnormalities found on physical examinations with autopsy findings

Anatomical description of bronchiectasis resulting from tuberculosis and pertussis

René Théophile Hyacinthe Laënnec (1781–1826)
The following conditions are associated with development of bronchiectasis except:

A) Common variable immunodeficiency
B) Non-tuberculous mycobacterial lung infection
C) Asthma
D) Rheumatoid arthritis
E) Obstructive sleep apnea
The following statements regarding bronchiectasis are true except:

A) The prevalence of non-CF bronchiectasis in the US is increasing

B) In the US, non-tuberculous mycobacterial lung infections are more common than those caused by tuberculosis

C) Fatigue and dyspnea occur at least in half of patients

D) Normal pulmonary function testing excludes a diagnosis of bronchiectasis
The following statements regarding non-CF bronchiectasis are true except:

A) Bronchiectasis is distinguished by other chronic airway diseases with use of chest imaging studies

B) The cause of bronchiectasis is identified in 75 % of patients

C) More than half of patients experience at least one exacerbation per year

D) Exacerbations are associated with a decline in lung function, physical activity and perceived quality of life
Which of the following statements regarding management of non-CF bronchiectasis are false?

A) Long term antibiotic therapy is associated with improved patient survival

B) Daily inhaled recombinant DNase is associated with a reduction in exacerbation rates

C) Inhaled corticosteroid therapy is associated with a reduction in exacerbation rates

D) Nebulized hypertonic (7 %) saline is superior to nebulized normal (0.9 %) saline as an airway clearance modality
Case

45 year old male nonsmoking reports persistent cough and wheezing diagnosed as asthma.

Treated with albuterol and inhaled corticosteroids that are intermittently effective.

Antibiotics prescribed for worsening bouts of productive cough.

Adopted and not aware of siblings with lung disease.

Since adolescence he has reported frequent colds and episodes of bronchitis.

No nasal polyps or GI symptoms
Case

Exam: Thin gentleman with intermittent cough
Ht 5' 7", Wt 180 lb, BP 140/70, Pulse 76, SpO2 93% (RA)
HEENT: No sinus tenderness, nasal mucosa without erythema
Lungs: Coarse breath sounds anterior & posterior
Heart: RRR, nml s1 and s2
Abd: Soft, nontender
Extr: No edema, 2 + pulses, no clubbing
Chest imaging
What is bronchiectasis

Bronkos = Bronchi
Ectasia = Dilatation

Bronchial dilation caused by structural defect of the wall of the airway
Bronchiectasis arising from chronic tuberculosis
Radiographic features

Bronchiectasis is diagnosed on axial images of chest CT based on:

Internal diameter of the bronchus being larger than the accompanying vessel or

bronchus fails to taper in the periphery of the chest.
Proposed mechanisms leading to development of bronchiectasis

- Neutrophil Inflammation (Proteases)
- Bacterial Colonization
- Airway Destruction and Distortion (Bronchiectasis)
- Abnormal Mucus Clearance

Normal Lung
Bronchiectasis
How common is bronchiectasis

Prevalence is increasing in the United States and Europe

In the UK, from 2004 to 2013, the incidence and prevalence increased annually across all age groups.

In the US, from 2002 to 2007, Medicare beneficiaries were noted to have annual increase in the prevalence of bronchiectasis defined on Part B outpatient databases.

The annual prevalence increased by 8% each year

Women were more often diagnosed with bronchiectasis


Bronchiectasis registry: 2008-2014
Bronchiectasis registry: 2008-2014

1,826 patients with non-CF bronchiectasis
Mean age 64 ± 14 years
Predominantly women (79 %), white (89%), never smokers (60 %)
NTM disease or NTM isolation in 63 % at registry entry
Bronchiectasis noted in 77 % of occurring between the ages of 50 and 79 years

Most common symptoms:
cough (73 %), productive (53 %),
dyspnea (64 %), fatigue (50 %)
Spirometry: Obstruction (51 %),
Normal (26 %)
Chest CT: Dilated airway involvement in more than 2 lung regions: 89 %.
RML most often involved.
Tree in bud infiltrates observed in 60 % with multiple lobe involvement

Aksamit TR et al. Chest 2017;151:982-992
Microbiological Results for Patients With Bronchiectasis

Bacterial culture: n = 1,406

- Oropharyngeal flora: 1,307 (74 %)
- Haemophilus influenzae: 116 (8 %)
- Streptococcus pneumoniae: 49 (3 %)
- Staphylococcus aureus: 170 (12 %)
- Pseudomonas aeruginosa: 470 (33 %)
- Stenotrophomonas maltophilia: 76 (5 %)

Acid Fast Smear Positive: 319/1,314 (24 %)

- Mycobacterium avium complex: 484 (37 %)
- Mycobacterium abscessus: 130 (10 %)

Aksamit TR et al. Chest 2017;151:982-992
Non-tuberculous mycobacterial lung disease

Nontuberculous mycobacteria (NTM) are frequent cause of morbidity

Often detected in soil and water samples

> 140 NTM species identified and MAC is most common pulmonary pathogen

Annual average prevalence for NTM from 1997 to 2007 was 31 cases/100,000 persons

Prevalence higher in women

From 1997-2007, rising prevalence and more frequent than TB

Adjemian J et al. AJRCCM 2012;185:881-886
US prevalence of NTM lung infections

Adjemian J et al. AJRCCM 2012;185:881-886
# Etiology of bronchiectasis

<table>
<thead>
<tr>
<th>Etiology among three large cohorts</th>
<th>Percent patients (418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>48 %</td>
</tr>
<tr>
<td>Post-infectious</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>Rheumatoid arthritis</td>
<td>3 %</td>
</tr>
<tr>
<td>Young syndrome</td>
<td>2 %</td>
</tr>
<tr>
<td>Aspiration/GER reflux</td>
<td>2 %</td>
</tr>
<tr>
<td>Yellow nail syndrome</td>
<td>2 %</td>
</tr>
<tr>
<td>Nontuberculous mycobacterial infxn</td>
<td>1 %</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1 %</td>
</tr>
</tbody>
</table>

Clinical features

• Age of symptom onset
• Character of symptoms: Amount & character of sputum
• Symptoms associated with comorbidities
  • Arthralgias – Rheumatoid arthritis
  • Infertility – Cystic fibrosis, Primary ciliary dyskinesia (PCD)
  • Sinusitis – Cystic fibrosis, Primary ciliary dyskinesia, Immune deficit
  • Diarrhea – Ulcerative colitis
  • Nasal polyps - Cystic fibrosis, Primary ciliary dyskinesia
• Family history to identify genetic causes such as PCD
Initial evaluation of suspected patient with bronchiectasis

- Pulmonary function testing with bronchodilator responsiveness
- Chest radiograph (Posterior-lateral)
- High resolution chest tomography
- Sputum culture (bacterial, acid fast bacilli, fungi)
- Complete blood count with differential
- Quantitative immunoglobulins (IgG, IgM, IgA, IgE)
- Alpha-1 antitrypsin level
- Sweat chloride test or genetic testing for CFTR
Pulmonary ciliary dyskinesia with dextrocardia and situs inversus
Genetic causes

Congenital defects of airways

- Tracheobronchomegaly (Mounier-Kuhn syndrome)
- Familial Congenital Bronchiectasis (Williams-Campbell Syndrome)

Impaired mucociliary clearance

- Cystic Fibrosis
- Primary ciliary dyskinesia
- Young syndrome

Disorders of humoral immunity

- X-linked agammaglobulinemia
- Common variable immune deficiency
- Hyperimmunoglobulin E syndrome
## Differences between CF and non-CF bronchiectasis

<table>
<thead>
<tr>
<th>Cystic Fibrosis</th>
<th>Non-Cystic Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>More common in older age</td>
</tr>
<tr>
<td>No gender difference</td>
<td>More common in elderly women</td>
</tr>
<tr>
<td>More common in upper lobes</td>
<td>More common in lower lobes</td>
</tr>
<tr>
<td>CFTR genetic mutation</td>
<td>Generally post-infectious</td>
</tr>
<tr>
<td>Prevalence is uncommon</td>
<td>3-4 times higher prevalence than CF; prevalence rises with age</td>
</tr>
<tr>
<td>Comorbidities: pancreatic insufficiency, sinusitis,</td>
<td>Comorbidities: cardiovascular disease, COPD</td>
</tr>
</tbody>
</table>
Features of adult onset cystic fibrosis

CFTR mutations producing less severe functional abnormal may present be recognized in adults

Extrapulmonary findings may be lacking or mild

Pancreatic insufficiency may be absent

Less GI symptoms

Sweat chloride test interpreted as normal or indeterminate more likely with older age

Pseudomonas aeruginosa, mucoid variant, increases in prevalence as age at diagnosis increases
Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

To exclude cystic fibrosis:

Two sweat chloride measurements > 60 mmol/L are diagnostic

Measurements < 60 mmol/L require genetic testing

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Keating CL. Chest 2010;137:1157

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Table 4—Cystic Fibrosis Transmembrane Conductance Regulator Mutation Frequency

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Diagnosis ≤ 18 y</th>
<th>Diagnosis ≥ 18 y</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 7,723)</td>
<td>(n = 655)</td>
<td></td>
</tr>
<tr>
<td>ΔF508</td>
<td>88.7 (6,849)</td>
<td>74.1 (485)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>R117H</td>
<td>2.6 (199)</td>
<td>15.6 (102)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3849 + 10kbC→T</td>
<td>1.6 (127)</td>
<td>7.8 (51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>D1152H</td>
<td>0.2 (18)</td>
<td>6.0 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>W1282X</td>
<td>2.2 (168)</td>
<td>4.6 (30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2789 + 5G→A</td>
<td>0.9 (66)</td>
<td>3.5 (23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>R334W</td>
<td>0.4 (32)</td>
<td>3.2 (21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>A455E</td>
<td>0.5 (37)</td>
<td>2.4 (16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>L206W</td>
<td>0.2 (12)</td>
<td>1.1 (7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>H148T</td>
<td>2.6 (20)</td>
<td>0.9 (6)</td>
<td>.013</td>
</tr>
<tr>
<td>R347H</td>
<td>0.2 (12)</td>
<td>0.9 (6)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Data in first two columns given as % (No.).
### Diagnostic criteria for adult onset cystic fibrosis

<table>
<thead>
<tr>
<th>Chronic sinopulmonary disease with chronic cough, abnormal CXR, persistent colonization/infection with Burkholderia, S maltophilia, nonmucoid Pseudomonas.</th>
<th>Presence of symptoms or family history and 1 of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent acute or chronic pancreatitis</td>
<td>Sweat chloride value $\geq 60$ mmol/L</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>Two identified CF-causing mutations</td>
</tr>
<tr>
<td>Obstructive azoospermia</td>
<td>Sweat chloride 40-59 mmol/L with no or 1 CF-causing mutation but with family history and/or ancillary testing and clinical presentation strongly suggestive of CF</td>
</tr>
</tbody>
</table>

Does identifying the etiology of bronchiectasis influence outcomes?

For adults with newly diagnosed bronchiectasis standardized testing is recommended that includes:

- CBC with differential
- Quantitative immunoglobulins (IgG, IgM, IgA, IgE)

The Spanish, British and European Respiratory Societies have published guidelines to support the routine tests to identify the cause for bronchiectasis.

Observational studies identified adult patients (7-37 %) that had a change in management once a specific etiology was identified.

_Pasteur MC. Am J Respir Crit Care Med 2000;162:1277-1284_
_Shoomark A. Respir Med 2007;107:1001-1007_
_Anwar GA. Respir Med 2013; 101:1163-1170_
Management and goals of therapy

Establish whether an underlying cause, such as immunoglobulin deficiency, is present.

Initiate an airway clearance regimen

Obtain a sputum sample for bacterial culture and susceptibility, including acid-fast bacteria.

Sputum culture dictate subsequent choice of antibiotics

Goals of therapy to 1) reduce symptoms, 2) improve quality of life, and 3) prevent exacerbations associated with worse outcomes.
Evolution of airway clearance techniques

Postural drainage

High-frequency chest wall oscillation
Airway clearance

Nebulized solution (7% hypertonic saline) & Chest physiotherapy (CPT)

- Oscillatory positive expiratory pressure (PEP) device
- High-frequency chest wall oscillation (HFCWO)
- Autogenic drainage
- Active cycle breathing with huff coughs
- Manual chest percussion
Mucolytic therapy

Inhaled mucolytics mannitol & hypertonic saline

Work by reducing sputum viscosity, which eases expectoration, potentially leading to reduced symptoms and exacerbation frequency.

*Daviskas E. J Aerosol Med 2002;15:331-341*

Nebulized hypertonic saline and mannitol inhaled as a dry powder improve clearance of mucus by reducing osmolality.

Comparison of nebulized 6 % saline and isotonic saline in pts with non-CF bronchiectasis found improvements in sputum bacteriology and quality of life in both groups.

Additional studies need to clarify if benefit is due to agent or clearance of airway secretions

*Nicolson CH. Respir Med. 2012;106:661-667*
DNase in non-CF bronchiectasis

Recombinant human DNase (rhDNase) is a commercially available mucolytic agent.

In patients with cystic fibrosis, reports demonstrated improvement in lung function and decreased frequency of exacerbations.

Randomized placebo control trial in subjects with idiopathic bronchiectasis (n = 349)

Nebulized rhDNase (2.5 mg) twice daily for 6 months

Subjects receiving rhDNase had more frequent exacerbations, hospitalizations, and antibiotic and corticosteroid prescriptions

rhDNase is not recommended for this population

Therapies for CF bronchiectasis may not be appropriate for non-CF bronchiectasis

O’Donell AE. Chest 1998;113:1329-1334
Pasteur MC. Thorax 2010;65:S1-S58.
Macrolide therapy

Macrolides exert immunomodulatory effects on host inflammatory responses without suppression of the immune system.

Effects of macrolides include modifying mucus production, inhibition of biofilm production, suppression of inflammatory mediators and moderating leukocyte recruitment and function.

Benefits of azithromycin observed in patients with CF and non-CF bronchiectasis.

Three large trials reported reduction in exacerbations in non-CF bronchiectasis.

Azithromycin 250 mg three times/week or 500 mg twice/week and erythromycin 250 mg bid reduced exacerbation frequency and improved quality of life in patients with non-CF bronchiectasis.

Wong C. Lancet 2012;380:660-667
Altenburg J. JAMA 2013;309:1251-1259
Serisier DJ. JAMA 2015;309:1260-1267
Controversy with chronic macrolides

Chronic macrolide therapy has potential for development of resistant bacterial strains.

Two clinical trials reported greater percentage of macrolide-resistant pathogens were identified in the azithromycin and erythromycin treated patients.

Chronic use of macrolides may foster growth of macrolide-resistant strains of NTM.

Important to rule out active NTM infection before initiating chronic macrolide therapy in patients with bronchiectasis.

Reports link fatal arrhythmias with prolonged QT interval, thus an initial ECG should be performed and drug interactions reviewed.

Wong C. Lancet 2012;380:660-667
Serisier DJ. JAMA 2015;309:1260-1267
Evolution of Pseudomonas aeruginosa infection in the lung from intermittent to chronic infection
Antibiotic use

Antibiotics are used to:

1) Attempt eradication of Pseudomonas and/or MRSA
2) Suppress the burden of chronic bacterial colonization
3) Treat exacerbations

Use of “rotating” antibiotics to minimize the development of resistance in colonizing bacteria has not been adequately studied and is not recommended.
Long-term treatment (> 3 months) should be offered for patients with three or more exacerbations per year.

Airway clearance should be optimized.

Recommendation to prescribe macrolides (azithromycin, erythromycin) for adults with bronchiectasis and chronic P. aeruginosa infection in which an inhaled antibiotic is not feasible or not tolerated.

Recommend long-term treatment with macrolides in addition to or in place of an inhaled antibiotic, for adults with bronchiectasis and chronic P. aeruginosa infection with frequent exacerbations despite taking an inhaled antibiotic.
Inhalation therapy-antibiotics

Inhaled drug therapy is appealing as direct drug delivery provides treatment to the site of infection and avoids systemic toxicity.

Nebulizer systems provide higher flows, higher respirable fractions and smaller particles with a decreased treatment time and increased deposition.

Currently, inhaled antibiotics are used for suppressive treatment of chronic infection but not for active infection.

Tobramycin and aztreonam are approved in U.S. for patients with cystic fibrosis.
There are currently no drugs that are specifically approved for treatment of patients with non-CF bronchiectasis.

Inhaled tobramycin resulted in a statistically significant reduction in P. aeruginosa bacterial load.

Two large, randomized, double-blind, phase 3 trials evaluated aztreonam lysinate in 540 patients and reported no difference versus placebo in patient outcomes.

Recently, two phase-3 clinical trials examining dry powder inhaled ciprofloxacin provided different outcomes.

Additional research is needed to optimize benefits in specific groups of patients with non-CF bronchiectasis.
Pulmonary rehabilitation
Pulmonary rehabilitation for non-CF bronchiectasis

Pulmonary rehabilitation improves exercise tolerance and quality of life for patients with chronic lung disease

Retrospective study of 111 patients with non-CF bronchiectasis and exertional dyspnea

Patients participated in 6–8 weeks of twice-weekly supervised exercise sessions of walking, cycling, and strengthening exercises.

Significant improvement in 6-minute walk distance (mean change, 50.4 m; 95% CI, 40.9–60.0) and health-related quality of life scores

Ong HK. Chronic Respir Dis. 2011;8:21-30
Characteristics of clinical phenotype using cluster analysis

<table>
<thead>
<tr>
<th>Age</th>
<th>Young with Mild Disease</th>
<th>Phenotype 2: Elderly with Mild Disease</th>
<th>Phenotype 3: Elderly with Frequent Exacerbations</th>
<th>Phenotype 4: Elderly with Severe Disease, Few Exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Young</td>
<td>Elderly</td>
<td>Elderly</td>
<td>Elderly</td>
</tr>
<tr>
<td>BMI†</td>
<td>Low</td>
<td>Mild</td>
<td>Slightly low</td>
<td>Slightly high</td>
</tr>
<tr>
<td>Clinical severity‡</td>
<td>Mild</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Airflow obstruction</td>
<td>No</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Frequent exacerbations§</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chronic bronchial infection rate‖</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Etiology associated and respiratory comorbidities</td>
<td>Genetic/ID</td>
<td>Postinfectious</td>
<td>Postinfectious</td>
<td>Postinfectious</td>
</tr>
<tr>
<td>Respiratory comorbidities</td>
<td>Idiopathic</td>
<td>COPD</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Nonrespiratory comorbidities</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Death rate Cause</td>
<td>Low</td>
<td>High</td>
<td>Respiratory causes</td>
<td>Neoplasms</td>
</tr>
</tbody>
</table>

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; ID = immunodeficiencies.

*Elderly was defined as older than 65 years.
†Normal BMI is defined as 25 kg/m². Overweight is defined as a BMI between 25 and 30 kg/m².
‡Clinical severity was evaluated taking into account FACED score (FEV₁ percent predicted (F; cutoff, 50%; maximum value, 2 points), age (A; cutoff, 70 yr; maximum value, 2 points), chronic colonization by Pseudomonas aeruginosa (C; dichotomic; maximum value, 1 point), radiological extension (E; number of lobes affected; cutoff, two lobes; maximum value, 1 point), and dyspnea (D; cutoff, grade 2 on the Medical Research Council dyspnea scale; maximum value, 1 point).
§Frequent exacerbations was defined as three or more exacerbations in the previous year.
‖Chronic bronchial infection rate was defined as more or less than the average of the total cohort.
Characteristics of frequent exacerbator

> 2000 patients with bronchiectasis from 10 clinical centers across examined stability and outcomes of frequent exacerbating patients with non-CF bronchiectasis.

Increasing exacerbations at baseline were associated with higher rates of exacerbation during follow-up.

Additional independent predictors of future exacerbation frequency: *Haemophilus influenzae, Pseudomonas aeruginosa* infection, reduced FEV$_1$, radiological severity of disease and co-existing COPD.

Chalmers JD. Am J Respir Crit Care Med 2018; (in press)