Unusual Lung Infections, Bronchiectasis, and Cystic Fibrosis

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Faculty Disclosures

- PI for clinical trials with Insmed/Aradigm/Novartis/Chiltern (all bronchiectasis/NTM related)
- Consultant (ended 9/2018)
  - AIT Therapeutics
  - Insmed
Learning Objectives

- After this session, learners will be able to:
  1. Recall the classic presentations and radiographic findings of nocardiosis and actinomycosis infections of the lung
  2. Discuss the treatment of nocardiosis and actinomycosis infection in the lung
  3. List the causes of bronchiectasis
  4. Describe the genetic defects underlying CF
  5. List therapeutic approaches to the treatment of pulmonary disease in patients with CF
  6. Discuss the therapeutic options for the treatment of non-CF bronchiectasis
Question 1

- A 54 year old man with diabetes complains of increased facial pain, fevers, and chills. He developed an infection around his neck a few weeks ago. Despite over the counter medications and warm compresses, the area has now started to drain. He has been diabetic for 15 years and is managed with oral hypoglycemic agents. His blood sugars have been under good control. He denies trauma, sick exposures or recent travel. On exam, there is an area at the base of the right neck that is warm and erythematous with a central area draining sero-sanguinous fluid. Gram stain of the discharge reveals gram positive branching organisms. The most appropriate initial treatment is to begin intravenous....?
Question 1
1. Amphotericin
2. Penicillin
3. Clindamycin
4. Trimethoprim/sulfamethoxazole
Question 1
1. Amphotericin
2. Penicillin
3. Clindamycin
4. Trimethoprim/sulfamethoxazole
Question 2

- A 63 year old man with COPD presents with a 3 day history of headache, fever, and generalized weakness. He was treated 3 weeks ago with a 5 day course of azithromycin for a COPD exacerbation thought to be secondary to community acquired pneumonia. On exam, he is confused and incoherent. Lung exam reveals decreased breath sounds and egophony at the right base. Cranial nerves are normal. Neurologic exam reveals an inability to overcome minimal resistance more prominent on the right. Deep tendon reflexes are exaggerated. CXR reveals RLL consolidation with cavitation. MRI of the brain with gadolinium shows multiple enhancing lesions in both hemispheres. Lumbar puncture reveals neutrophilic pleocytosis and an elevated protein. Bronchoscopy with BAL and biopsy is performed. A smear of the lung tissue is shown:
Question 2
Question 2

- The next step in the management of this patient is to begin therapy with:

1. Isoniazid, rifampin, ethambutol, and pyrazinamide
2. Penicillin
3. Trimethoprim/sulfamethoxazole
4. Pyrimethamine and sulfadiazine
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Question 3

- Nocardiosis most commonly occurs in patients transplanted with which of the following solid organs?

1. Kidney
2. Pancreas
3. Lung
4. Liver
Question 3

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1. Kidney
2. Pancreas
3. Lung
4. Liver
Nocardia and Actinomyces Infections

• Most common clinically relevant filamentous bacteria
• Means of infection, disease courses and medical management differ
• Nocardia ubiquitous in soil, action endogenous mucus membrane colonizers who take advantage of damaged epithelial barriers
• Cause disease in immunocompetent and immunocompromised patients, but actino is more common in the former and nocardia in the latter
• Appear similar to fungal organisms but are much thinner in diameter and lack septations
  • Nocardia more delicate and has a right angle branching compared to actinomyces (more acute angle branching)
<table>
<thead>
<tr>
<th>Nocardiosis</th>
<th>Actinomycosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive Aerobic; weakly AFB positive</strong></td>
<td><strong>Incidence increasing</strong></td>
</tr>
<tr>
<td><strong>Incidence increasing</strong></td>
<td><strong>Male 3:1 predominance</strong></td>
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<tr>
<td><strong>Male 3:1 predominance</strong></td>
<td><strong>Male 3:1 predominance</strong></td>
</tr>
<tr>
<td><strong>Occurs primarily in immunocompromised hosts; incidence in immunocompetent hosts is increasing</strong></td>
<td><strong>Occurs primarily in immunocompetent hosts; alcoholism and poor dental hygiene a risk</strong></td>
</tr>
<tr>
<td><strong>Pulmonary manifestations predominate</strong></td>
<td><strong>Pulmonary manifestations in minority (approximately 15%)</strong></td>
</tr>
<tr>
<td><strong>Chest wall involvement uncommon</strong></td>
<td><strong>Chest wall involvement and bony erosion common</strong></td>
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<tr>
<td><strong>Metastatic spread (esp. to brain) common</strong></td>
<td><strong>Metastatic spread uncommon; spread by direct contiguous invasion</strong></td>
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<tr>
<td><strong>Granuloma formation and fibrosis rare</strong></td>
<td><strong>Granuloma and intense fibrosis common; form the characteristic sulfur granule</strong></td>
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<tr>
<td>Diagnosis can usually be made on sputum, BAL or pleural fluid culture</td>
<td>Diagnosis often requires cytologic or histologic examination</td>
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<tr>
<td>Treatment with sulfonamides; Increasing resistance reported</td>
<td>Treatment with penicillin</td>
</tr>
<tr>
<td>Surgical drainage often needed</td>
<td>Often treated successfully with antibiotics alone</td>
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</tbody>
</table>
Nocardia

- Aerobic, non-mobile, non-spore forming organisms live as soil saprophytes
- Branching, filamentous forms that are gram + and usually acid fast
- Romanowsky staining is preferred
- May form small grains of eosinophilic matrix with branching filaments that fragment at the periphery
- Seven species associated with human disease
  - N. asteroides most common
  - N. brasiliensis most commonly associated with mycetoma
Actinomycosis

- Anaerobic or microaerophilic gram positive bacilli
  - Easily visualized using Papanicolaou stain
  - Classic feature is macroscopically visible sulfur granule comprised of bacteria and proteinaceous material
  - If granule not present, must suspect contamination
- Colonize mouth, colon, vagina
- Infection most commonly caused by A. israelii
- Actinomycotic infection in the lung usually polymicrobial
Nocardia

- Historically recognized as an opportunistic disease
- More recent reports detail disease in otherwise healthy adults

- Cell mediated immune deficiencies
  - Solid organ transplant (especially lung)
  - HIV (CD4 <100)
  - Lymphoma
  - Anti-TNF therapy (monoclonal > soluble)
  - Long-term corticosteroid use

- Chronic lung disease identified as risk
  - COPD, non-cf bronchiectasis, PAP, granulomatous diseases
## Nocardia

<table>
<thead>
<tr>
<th>Nocardia</th>
<th>Immunosuppressed</th>
<th>Immunocompetent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>Acute</td>
<td>Subacute</td>
</tr>
<tr>
<td><strong>Symptoms/site</strong></td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Species</strong></td>
<td><em>N. Nova</em> common</td>
<td>Varied; ? Higher rate of co-infection (esp with NTM)</td>
</tr>
<tr>
<td><strong>Underlying Conditions</strong></td>
<td>Cell-mediated disorders, HIV, organ transplant, corticosteroids</td>
<td>Non-cf bronchiectasis, COPD, NTM, PAP</td>
</tr>
<tr>
<td><strong>Radiography</strong></td>
<td>Nodules, masses and cavitation prominent</td>
<td>Bronchiectasis and centrilobular nodular opacities</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Similar mortality; longer duration of treatment</td>
<td></td>
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</tbody>
</table>
Clinical Presentation

- Subacute pneumonia most common
- Mediastinitis, pericarditis reported from direct spread
- Extrapulmonary dissemination common
  - Brain most common, especially in alcoholics
  - Skin, bone, muscle
  - Dissemination more common in patients with HIV and alcoholism
Nocardia Diagnosis

- Can often culture, but bronchoscopy may be needed for adequate specimen
- Cultures incubated aerobically for up to 4 weeks
- + smear/culture in immunocompromised patient = disease
- Advances in DNA extraction and PCR speed diagnosis
Actinomycosis

- Most infections occur in normal hosts; patients with alcoholism or poor dental hygiene at increased risk
- 3:1 male predominance
- Respiratory infection typically follows aspiration, but extension of dz from abdominal cavity or neck can occur
- Grow in microcolonies or granules (sulfur granules)
- Chest wall invasion not uncommon
Clinical Presentation

- Cervicofacial infection following dental work
- Pulmonary disease usually indolent, subacute presentation; often not suspected
- Bronchocutaneous fistula highly suggestive
- Often confused with lung CA and tuberculosis
Actinomycosis Diagnosis

- Dx often not made without histologic examination

- Isolation of organism in sputum or bronchial washings not significant without sulfur granules
Radiographic Manifestations

• Airspace consolidation most common for both
• Tend to be in periphery and lower lung fields with actino
• Most common feature is cavitation
• Nodules also seen frequently in nocardia
• Adenopathy, bronchiectasis, pleural disease should alert you to actino
  • Lung abscess---empyema---osteomyelitis of ribs---- chest wall sinus tract formation
Nocardia Treatment

- DOC are sulfonamide agents, but resistance is increasingly being reported
  - In some reports, resistance is more common in patients with underlying lung disease (though not consistent)
  - Recommend two drugs up front until susceptibility known
- Minocycline can be used in sulfa allergic patients
- Linezolid high in vitro activity; cost and toxicity limit use to refractory cases
- 6-12 months of therapy
- Consider surgical drainage of abscesses
Mortality Risk in Nocardiosis

• Independent risk factors:
  • Age > 68 (HR 4.7; 1.6-14)
  • Pulmonary aspergillosis (HR 8.8; 2.4-33)
  • TMP/SMZ resistance (HR 4.3; 1.6-11)
Actinomycosis Treatment

- Untreated, disease is ultimately fatal
- Penicillin is drug of choice
- Tetracyclines, erythromycin, clinda in allergic patients
- Prolonged therapy usually needed; adjuvant surgical debulking may allow shorter course
Bronchiectasis
Etiology – Focal Bronchiectasis

- Mechanical obstruction
  - Foreign body aspiration
  - External compression
  - Stenosis
- Congenital bronchial atresia
- Necrotizing pneumonia
- Classic NTM disease (RML/Lingula)
Etiology - Diffuse

CF, Sarcoid, Post Radiation
Post Radiation
Immotile cilia syndromes
Idiopathic, post-infectious Chronic aspiration
ABPA
Cartilage Syndromes
NTM/MAC
CTDs
Post-transplant
HIV
Diagnostic Testing

- In most patients
  - CBC, IgG, IgA, IgM, spirometry, HRCT

- As directed by history
  - RF, ANA, IgE, aspergillus precipitans, alpha-1 antitrypsin, sputum cultures for mycobacteria and fungi, sweat chloride testing
  - Ciliary testing (eNO //genetic//ciliary biopsy) if hx of frequent upper respiratory infections or otitis, infertility
  - Bronchoscopy as needed (r/o obstruction; cultures in on-productive patient)
High-Resolution Computed Tomographic Images of Lungs with Bronchiectasis
Question 4

Which of the following about Cystic Fibrosis is true:

- Most common genetic dz in the US (1 in 3,000 births in Asian population)
- Autosomal recessive with variable penetrance
- CF gene is on the long arm of chromosome 17
- Most common CF transmembrane regulator protein (CFTR) mutation is ΔF506.
Which of the following about Cystic Fibrosis is true:

- Most common genetic dz in the US (1 in 3,000 births in Caucasian population)
- Autosomal recessive with variable penetrance
- CF gene is on the long arm of chromosome 7
- Most common CF transmembrane regulator protein (CFTR) mutation is ΔF508.
Age at Diagnosis of All Individuals with CF Seen in 2016

- Number of Individuals
- Cumulative Percentage

**Graph Details:**
- **X-axis:** Months (0-1, 1-3, 4-6, 7-11, 12, 13, 14, 15, 16-20, 21-30, 31-40, over 40)
- **Y-axis:** Number of Individuals and Cumulative Percentage
- **Legend:**
  - Blue bars: Number of Individuals
  - Orange line: Cumulative Percentage
• Located at cell surface
• Ion channel that regulates liquid volume on epithelial surfaces
  • Chloride secretion and inhibition of sodium absorption
  • May regulate other cell proteins
• Over 1600 mutations identified
• ΔF508 most common; accounts for 90% of cases of European descent
  Due to deletion of single phenylalanine at position 508
• Expressed in all epithelial cells (lung, pancreas, sweat glands, liver, intestine, testes)
CFTR Mutations

**Normal**
- CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water.

**Class I**
- No functional CFTR created.

**Class II**
- CFTR protein is created, but misfolded, keeping it from reaching the cell surface.

**Class III**
- CFTR protein is created and reaches cell surface, but does not function properly.

**Class IV**
- The opening in the CFTR protein ion channel is faulty.

**Class V**
- CFTR is created in insufficient quantities.

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS42X</td>
<td>No functional CFTR created.</td>
</tr>
<tr>
<td>W1282X</td>
<td>CFTR protein is created, but misfolded, keeping it from reaching the cell surface.</td>
</tr>
<tr>
<td>R553X</td>
<td>CFTR protein is created and reaches cell surface, but does not function properly.</td>
</tr>
<tr>
<td>G551D</td>
<td>The opening in the CFTR protein ion channel is faulty.</td>
</tr>
<tr>
<td>S549N</td>
<td>CFTR is created in insufficient quantities.</td>
</tr>
<tr>
<td>V520F</td>
<td></td>
</tr>
<tr>
<td>R117H</td>
<td></td>
</tr>
<tr>
<td>D1152H</td>
<td></td>
</tr>
<tr>
<td>R347F</td>
<td></td>
</tr>
<tr>
<td>3849+10delC&gt;T</td>
<td></td>
</tr>
<tr>
<td>2789+5G&gt;A</td>
<td></td>
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<tr>
<td>A4555E</td>
<td></td>
</tr>
</tbody>
</table>
Pathogenesis

- The defective CFTR protein leads to defective transport of ions
  - Alteration in composition of secretions in respiratory tract, pancreas, GI tract, sweat glands
    - Low water volume
    - High salt concentration
    - Airway acidification
    - Reduced bicarbonate secretion—mucin crosslinking
    - Dysregulation of inflammatory response
      - Increased intrinsic cellular inflammation
      - Primary pre-disposition to infection
• In lung, changes properties of the mucus layer lining the airways
  Impaired mucociliary clearance
  Persistent bacterial infection
  Increased inflammation (accumulation of cellular debris, including DNA and elastase)
  Airway obstruction
  Progressive lung dysfunction
Fahy JV, Dickey BF. NEJM 2010; 363:2233-47
### Diagnostic Criteria

<table>
<thead>
<tr>
<th>Elevated sweat chloride level on two occasions</th>
<th>-OR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of mutations known to cause CF in both CFTR genes</td>
<td>-OR-</td>
</tr>
<tr>
<td>In vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium</td>
<td>-PLUS-</td>
</tr>
<tr>
<td>One or more phenotypical features of CF</td>
<td>-OR-</td>
</tr>
<tr>
<td>Sino-pulmonary disease</td>
<td>-OR-</td>
</tr>
<tr>
<td>Characteristic GI or nutritional disorders</td>
<td>-OR-</td>
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<tr>
<td>Obstructive azoospermia</td>
<td>-OR-</td>
</tr>
<tr>
<td>Salt loss syndrome</td>
<td>-OR-</td>
</tr>
<tr>
<td>Sibling with CF</td>
<td>-OR-</td>
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<tr>
<td>Positive newborn screening</td>
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</table>
Diagnosis: CF in the Adult

- Often results from CFTR mutations with residual function, resulting in delayed onset and lesser disease severity
- When to suspect:
  - Chronic infection with pseudomonas, S. aureus, NMTB
  - Recurrent/chronic idiopathic pancreatitis
    - Although pancreatic insufficiency is not commonly seen
  - Bilateral absence of vas deferens
  - Nasal polyposis/chronic sinusitis
  - Unexplained bronchiectasis
Diagnostic Criteria in Adulthood

- Presence of CF symptoms as just outlined
- And 1 of the following
  - Sweat chloride >60 mmol/L
  - Two identified CF-causing mutations
  - Sweat chloride 40-59 mmol/L with no or 1 CF causing mutation and strong clinical presentation (or family history)
- Diagnosis of CF is very unlikely with sweat chloride <30 mmol/L
Sweat Chloride Value (mmol/L), by Mutation Class Group

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>Median</th>
<th>5th Percentile</th>
<th>95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation Class I-III</td>
<td></td>
<td></td>
<td></td>
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<td>102.0</td>
<td>77.0</td>
<td>127.0</td>
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<td>N=17,562</td>
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<tr>
<td>Mutation Class IV-V</td>
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<td></td>
<td>70.0</td>
<td>25.0</td>
<td>113.0</td>
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<tr>
<td>N=2,633</td>
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<tr>
<td>Genotyped But Not Identified in Mutation Classes I-III or IV-V</td>
<td></td>
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<td></td>
<td></td>
<td>92.0</td>
<td>36.0</td>
<td>122.0</td>
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<td>N=4,807</td>
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<tr>
<td>All Individuals</td>
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<td></td>
<td></td>
<td>99.0</td>
<td>50.0</td>
<td>125.0</td>
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<tr>
<td>N=25,002</td>
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</table>
Pulmonary Manifestations

- Lungs normal at birth
- Infection occurs early and is persistent
  - *H. influenzae*, *S. aureus* early; pseudomonas later
  - Pseudomonas independent prognostic factor
  - MRSA incidence increasing and also associated with reduced lung function and survival
  - *Burkholderia cepacia* complex even worse prognosis
- Persistent cough
- AHR
- Bronchiectasis and obstructive lung disease; progress to respiratory failure and death

- S. aureus
- P. aeruginosa
- MRSA
- H. influenzae
- S. maltophilia
- MDR-PA
- Achromobacter
- B. cepacia complex

Percentage of Individuals

Year

90 92 94 96 98 00 02 04 06 08 10 12 14 16
Question 5
Medical therapy for all patients with CF who are older than 6 years includes:

A. Corticosteroids
B. Ivacaftor
C. High-dose ibuprofen
D. rhDNase (dornase alpha)
Question 5
Medical therapy for all patients with CF who are older than 6 years includes:

A. Corticosteroids  
B. Ivacaftor  
C. High-dose ibuprofen  
D. rhDNase (dornase alpha)
Management of CF

- Currently focused primarily on mitigation of downstream effects in respiratory and other organ systems
- Rapid progress is being made in actual disease modifiers
- Currently no cure
Management

- Clearance of airway secretions recommended for all patients with cystic fibrosis for clearance of sputum, maintenance of lung function, and improved quality of life
  - Chest physiotherapy
    - Forced expiratory techniques
    - Mechanical vests
    - Flutter valves
  - None proven superior to others
  - Aerobic exercise recommended as an adjunct
Management

• Bronchodilator therapy not recommended routinely
  • Patients with at least 10% improvement in FEV$_1$
  • Patients with asthma or ABPA
  • Prior to CPT and inhalational therapy
  • ?improve mucociliary clearance (salmeterol may restore chloride secretion)
Management

- Reduce viscosity of secretions
  - rhDNase I (dornase alpha)
    All patients >6
  - Inhaled hypertonic saline
    All patients >6
Antibiotic Therapy

- Four approaches/roles for antibiotics
  - Chronic prophylaxis to prevent specific infection
  - Conversion to culture negativity upon detection of new specific pathogens
  - Palliation of acutely elevated signs and symptoms of infection
  - Chronic suppression of established infections
Antibiotic Therapy

• Preventive or suppressive therapy for staph aureus NOT recommended

• Inhaled tobramycin or aztreonam strongly recommended for those with moderate to severe reductions in lung function; recommended for those with milder disease
  • Attempt to eradicate pseudomonas on detection (1 month inhaled tobramycin)
  • Chronic suppression of established gram negatives

• Insufficient evidence to recommend other inhaled antibiotics (gentamicin, colistin, fluoroquinolones, cephalosporins)
Anti-Inflammatory Therapy

- Azithromycin three times weekly strongly recommended in patients over 6 years of age colonized with pseudomonas. Should also be considered in patients >6 yrs without pseudomonas.

- High dose ibuprofen recommended for patients aged 6-17 yrs.

- Leukotriene modifiers NOT recommended.

- Systemic Steroids NOT recommended. Beneficial effects on lung function outweighed by adverse effects. Recommended only for asthma or ABPA.

- Lack of data on inhaled CS--- also recommended only for ABPA or asthma.
**New Therapies**

**Restore CFTR Function:**

- FDA approved:
  - Ivacaftor (Kalydeco) - helps facilitate opening of chloride channel
  - Lumacaftor + Ivacaftor (Orkambi) - corrects defective CFTR and improved function for chloride channel
  - Tezacaftor + Ivacaftor (Symdeko) - moves defective CFTR to proper place on cell surface and improves function of chloride channel


Other Clinical Trials

- **Mucociliary clearance:**
  - Phase III Trial Inhaled Mannitol (Bronchitol)
  - Phase II Trial BI125162 - blocks sodium channel

- **Anti-inflammatory:**
  - Phase II: Acebilustat (CTX-4430) - reduces Leukotriene B4 (LTB4) and Lenabasum (JBT-101) - promoted resolution of inflammation

- **Anti-infectives:**
  - Phase III: Inhaled Levofloxacin (Quinsair) and Inhaled Vancomycin (aeroVanc)
  - Phase II: Inhaled Molgramostim - (GMCSF) and Inhaled Nitric Oxide
Pulmonary Complications

- Hemoptysis
- Pneumothorax
- Non-tuberculous mycobacterial infection
- ABPA
- Respiratory failure; cor pulmonale
Transplantation in CF

• Generally good candidates; Transplanted lung does not develop defect
• Requires bilateral lung transplantation

• Indications
  Deterioration despite aggressive therapy; FEV1 <30% predicted; life-threatening complications (ICU stay); severe pulmonary hypertension; oxygen dependent hypoxemia; rapid decline, particularly in young female patients

• Contraindications
  Other organ failures; noncompliance; psychosocial instability, profound malnutrition, active aspergillus, NTM (*M. abscessus*) or *Burkholderia Cepacia* Complex (relative in some centers)
Proportion of 18-year-olds in the normal/mild category (FEV1 ≥70 percent predicted) has increased from 39.9 percent in 1990 to 72.1 percent in 2015.

Proportion in the severe category (FEV1<40 percent predicted) has decreased from 24.9 percent to 5.3 percent.
Median Predicted Survival Age, 1986–2016 In Five Year Increments
Question 6:
Similar to patients with CF, patients with non-CF bronchiectasis and frequent exacerbations should be treated with:

A. Corticosteroids  
B. Macrolide antibiotics  
C. High-dose ibuprofen  
D. rhDNase (dornase alpha)
Question 6:
Similar to patients with CF, patients with non-CF bronchiectasis and frequent exacerbations should be treated with:

A. Corticosteroids
B. Macrolide antibiotics
C. High-dose ibuprofen
D. rhDNase (dornase alpha)
Therapy

- Management often extrapolated from CF trials
- No specific therapies have been approved for NCFB
- **Treat underlying disease where possible**
- Bronchodilators/ICS for AHR
- Airway clearance techniques/rehab-exercise training----safe and improve QOL, symptoms
- Mucolytic agents
  - Dornase alpha NOT recommended in non-CF patients
  - Hypertonic saline may be of benefit
- Role of CFTR in NCFB uncertain
- Neutrophil elastase inhibitors being investigated

Koser U, Hill A. 6(F1000 Faculty Rev):527
• Risk stratification gaining importance—
  • Bronchiectasis severity index (BSI) and FACED
    • Predicts severity and mortality
      • Both include FEV1, dyspnea, pseudomonas colonization, and radiographic features
  • BSI also includes predictors for hospitalization
Therapy for Bronchiectasis

- Antibiotics
  - Acute exacerbations, prevent exacerbations, reduce bacterial burden
  - Maintenance or rotating oral antibiotics not recommended
  - Similar to patients with CF, chronic pseudomonas infection has been independently associated with mortality
    - Small trials/BTS Guidelines support regular inhaled aminoglycosides for pseudomonas
    - Most attempt eradication on first detection
  - No good evidence for chronic use with other pathogenic organisms
    - Effective in reducing bacterial load, but not other important endpoints and can be associated with bronchospasm and reductions in FEV1

Anti-Inflammatory Agents

- Inhaled corticosteroids
  - Especially in those with underlying bronchospasm
  - Improve symptoms, QOL, sputum volume
  - No effect on lung function
- Oral corticosteroids
  - Short course only for exacerbations
- No studies support routine use of NSAIDs or LRTAs in NCFB
- Statins being investigated

Macrolides in Non-CF Bronchiectasis

- 3 published trials in NCFB suggest benefit
- BLESS, BAT and EMBRACE (erythromycin, azithromycin)
  - Reduced exacerbations
  - Improved lung function in two of the trails
  - Trend towards improved QOL
  - No evidence of the emergence of new pathogens
  - Increased macrolide resistance for some organisms without clinical consequence
Macrolides in Non-CF Bronchiectasis

- All trials enrolled patients with frequent exacerbations, thus reasonable consideration in patients with frequent exacerbations (or those at risk for frequent exacerbations (BSI))
- May improve QOL
- Best evidence for azithromycin
- Need to check for NTM prior to treatment
- Monitor liver function, QTC and hearing

Serisier DJ. JAMA 2013; 309:1260-1267
Altenburg J. JAMA 2013; 309:1251-1259
Wong C. Lancet 2012; 380:660-667
Chochrane Database Syst Rev 2018 Mar
FIGURE 4 Summary of recommendations for long-term antibiotic treatment.
Advances in NCFB

- Characterizing and understanding the lung microbiome
- Phenotyping bronchiectasis based on clinical, radiological, and microbiological features
- Understanding co-morbidities, particularly asthma and COPD
- Screening and assessment tools (QOL-B, BSI and FACED)
- Bronchiectasis registries
- Newer inhaled antibiotics and formulations
Summary of Key Points

- Nocardia and actinomycosis share many features;
  - High index of suspicion in at-risk population
- Bronchiectasis common
- Systematic approach to exclude treatable conditions
- Patients with CF living longer
- Management of pulmonary disease paramount
- Medical management of NCFB similar to that of CF in some respects
  - Treat underlying disorder
Thank You