Overview of non-cystic fibrosis bronchiectasis

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Financial Disclosure

• Advisory Board and Consultant for Insmed
Epidemiology

• Average annual prevalence of bronchiectasis in the U.S during 2012-2014 was 701 per 100,000 people (Henckle, 2018).

• The prevalence increases with age, with an 8 to 10 fold difference in prevalence after the age of 60 (300 to 500/100,000) as compared to ages <40.

• Bronchiectasis is more common in women.
Cost of bronchiectasis

• Economic burden is high.

• In 2001, it was estimated that the annual medical cost of care for persons in the US with bronchiectasis was $13,244.

• This is more than other chronic diseases such as heart disease ($12,000) and chronic obstructive pulmonary disease ($11,000 to $13,000) (O'donnell, 2008).

• Expenditures for medical care are estimated to be greater than $1.4 billion annually (Aksamit, 2010).
**Significant impairment**

- Chronic nature; can require frequent medical and hospital visits, long hospital stays, antibiotics, chest physiotherapy.

- Mortality rate ranged from 10-16% over an approximate 4-year observation period.

- Can cause significant respiratory impairment and affect quality of life.
Heterogeneity in bronchiectasis

- 51% had dual diagnosis of COPD
- Newly diagnosed bronchiectasis patients with COPD had significantly different characteristics than those bronchiectasis patients without COPD
- More likely to be hospitalized for respiratory infections during the baseline period (16% vs 7%) and have a smoking history (46% vs 17%) compared to those without a dual diagnosis of COPD

Henckle, et al. CHEST, 2018
Pathogenesis- The vicious cycle hypothesis

Chronic bronchial infection
Long-term inhaled or oral antibiotic therapy
Eradication of new pathogenic microorganisms
Antibiotic treatment of exacerbations

Structural lung disease
Long-term bronchodilator therapy
Surgery
Pulmonary rehabilitation

Inflammation
Long-term anti-inflammatory therapies

Impaired mucociliary clearance
Long-term mucoactive treatments
Airway clearance

Polverino, et. al. Eur Resp J 2017
Pathogenesis
Etiology

**Autoimmune disease**
- Rheumatoid arthritis
- Sjogren’s Syndrome

**Cilia abnormalities**
- Primary ciliary dyskinesia

**Connective Tissue Disease**
- Tracheobronchomegaly (Mounier Kuhn)
- Marfan’s Syndrome
- Cartilage Deficiency (Williams Campbell)

**Hypersensitivity**
- Allergic Bronchopulmonary Aspergillosis (ABPA)

**Immune Deficiency**
- Immunoglobulin deficiency
- HIV
- Job’s Syndrome
Etiology

Inflammatory Bowel Disease
- Ulcerative colitis
- Crohn’s Disease

Injury
- Pneumonia
- Aspiration/smoke inhalation

Malignancy
- Chronic Lymphocytic Leukemia
- Stem cell transplant, GVD

Obstruction
- Tumor
- Foreign Body
- Lymphadenopathy

Other
- Yellow nail syndrome
- Alpha one antitrypsin deficiency
- Young’s syndrome
- Cystic Fibrosis
Diagnosis

- Chronic cough
- Sputum
- Repeated pneumonias (Pseudomonas, MRSA, NTM)
- Rhinosinusitis
- Hemoptysis
- Fatigue
- Weight loss
**Figure 3.** Radiographic signs of bronchiectasis. **A** = Bronchus terminating in a cyst; **B** = lack of bronchial tapering as it travels to the periphery of the lung; **C** = signet ring sign (bronchus is larger than the accompanying vessel); **D** = mucus plug (mucus completely filling the airway lumen).

Am J Respir Crit Care Med, 2013

Published in: Pamela J. McShane; Edward T. Naureckas; Gregory Tino; Mary E. Strek; Am J Respir Crit Care Med  188, 647-656.
DOI: 10.1164/rccm.201303-0411CI
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Question 1

Which of the following laboratory tests would you send as part of your work-up for bronchiectasis?

A) AFB, bacterial and fungal sputum cultures
B) Quantitative immunoglobulin levels and autoimmune serologies
C) Sweat chloride testing
D) Both A and B
E) All of the above
Laboratory evaluation

- AFB, bacterial and fungal sputum cultures
- Quantitative immunoglobulins (IgA, IgG, IgE, IgM) and IgG subclasses
- ANA, rheumatoid factor
- Alpha one antitrypsin
- Aspergillus IgE
- Screen for comorbidities (reflux, aspiration, sinus disease)
- Vitamin D level
- CF sweat test and gene mutation panel
- Primary ciliary dyskinesia testing
Vitamin-D has been shown to reduce the production of pro-inflammatory cytokines. (van etten, 2005), and treatment enhanced killing of *P. aeruginosa*. (Wang, 2004)

Unknown whether this association reflects an effect of vitamin D on innate immunity or reduced outdoor physical activity due to more severe disease.
Microbiology

• Gram negative bacteria are the most frequently identified (H.influenzae, P.aeruginosa).

• NTM is commonly associated.

• Gram positive less common but can be present (MRSA, S.pneumoniae)

• A review of observational studies showed P.aeruginosa is associated with:
  1. A 3-fold increase in mortality risk
  2. A 7-fold increase in risk of hospital admission
  3. An average of one additional exacerbation per patient per year (Finch, 2015)
• Acquiring NTM does not always lead to pulmonary disease. It is unclear what factors lead to the development of disease.

• Oral and sputum sampled were collected in 106 participants. 20 lower airway samples from bronchoscopy were collected.

• Half of sputum samples had NTM.

• Lower airway samples frequently revealed enrichment with bacteria commonly considered oral commensals, and was associated with increase in inflammatory biomarkers.

• This suggests that aspiration of oral commensals in the lower airway may be associated with increased inflammation and development of NTM disease.

Myobiome was determined in 238 patients in a multi-centered, cross-sectional cohort of matched Asian and European bronchiectasis patients.

The bronchiectasis mycobiome is distinct, and characterized by specific fungal genera, including Aspergillus, Cryptococcus, and Clavispora.

Aspergillus fumigatus and Aspergillus terreus dominated profiles, the latter associated with increased exacerbations.

Those that were colonized and sensitized with aspergillus, and those with ABPA, had increased continuum of disease severity, respectively.

Screening for fungal disease, specifically Aspergillus, should be considered even in apparently stable patients.

A 62 year old female comes into your office with mild productive cough for 3 years. She has no weight loss, no hemoptysis. She has noticed a mild reduction in her exercise tolerance over the last 3 months. You check 3 induced sputum cultures for AFB, 2 of them return positive for MAC.
Question 2
Question 2

What is the next best step in management?

A) Start 3 drug therapy for MAC
B) Initiate airway clearance
C) Enroll in pulmonary rehabilitation
D) Both B and C
E) All of the above
Figure 4. Overview of a comprehensive approach to bronchiectasis management

- AAT = alpha 1 antitrypsin; IgG = immunoglobulin G; HRCT = high resolution computed tomography; NTM = nontuberculous mycobacteria
- *A two week course is suggested
Treatment aims

• Reduce symptoms

• Prevent further airway damage

• Prevent exacerbations

• Improve quality of life
Exacerbations can have effect on lung function decline, symptoms, quality of life, mortality, and may lead to future exacerbations.

Airway clearance

**Chest physiotherapy**
High frequency chest wall oscillation (HFCWO)
Positive expiratory pressure (PEP)
Postural drainage
Manual chest therapy
Active cycle breathing

**Inhaled Agents**
Hypertonic Saline
Mannitol
Airway clearance

• Improvement in exercise capacity and quality of life (QOL) in patients using an oscillatory device vs. management without chest therapy (Murray, 2009).

• Improved symptoms, pulmonary function, and reduced CRP and sputum neutrophils in HFCWO vs. PEP device (Nicolini, 2013).

• Improvements QOL and Leicester cough questionnaires, and fewer exacerbations, in those that performed ELTGOL (slow expiration with the glottis opened in the lateral position (Munoz, 2018)
• 1826 patients
• Non-pharmacologic measures were used in 56% of patients (48% using flutter or PEP device).
• Chest percussion and postural drainage were utilized in 15% and 16% of patients, respectively.
• Mucoactive agents were used in 24% of patients (of these, 76% used hypertonic saline)
• Those with NTM were more likely to use bronchial hygiene, chest percussion, flutter or PEP.
Pulmonary Rehabilitation

• Can help with mucociliary clearance.

• Short-term improvements in exercise capacity and QOL with a combination of endurance, strength and inspiratory muscle training (Newall, 2005).

• Not clear if benefits persist long term.
The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis – a randomised controlled trial

Annemarie L. Lee¹,²,³*, Catherine J. Hill²,⁴, Nola Cecins⁵,⁶, Sue Jenkins⁵,⁶,⁷, Christine F. McDonald²,⁴, Angela T. Burge¹, Linda Rautela²,⁴, Robert G. Stirling¹,⁸, Philip J. Thompson⁵,⁶,⁷ and Anne E. Holland¹,²,⁹

- 42 patients in the exercise training group, which consisted of a twice weekly exercise program for 8 weeks
- 43 patients in the control group (usual exercise pattern)
The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis – a randomised controlled trial

Annemarie L Lee¹,²,³*, Catherine J Hill²,⁴, Nola Cecins⁵,⁶, Sue Jenkins⁵,⁶,⁷, Christine F McDonald²,⁴, Angela T Burge¹, Linda Rautela²,⁴, Robert G Stirling¹,⁸, Philip J Thompson⁵,⁶,⁷ and Anne E Holland¹,²,⁹

**Figure 4.**

Time to first exacerbation (months)

Cumulative exacerbation-free survival

Resolution: standard / high

Group

- control
- exercise
- control-censored
- exercise-censored

Time to first exacerbation, \( p = 0.047 \).

Download authors' original image
Inhaled corticosteroids for bronchiectasis

Nitin Kapur\textsuperscript{1,2}, Helen L Petsky\textsuperscript{3}, Scott Bell\textsuperscript{4}, John Kolbe\textsuperscript{5}, Anne B Chang\textsuperscript{6,7}

- During stable state in a short-term group (ICS for 6 months or less) based on two studies, there were no significant differences from baseline in FEV\textsubscript{1}, FVC, exacerbation frequency and health related quality of life, compared to non ICS users.

- One study on long term outcomes (over 6 months) showed no significant effect of ICS on lung function or other clinical outcomes.

- Conclusions could not be drawn on adverse effects due to limited data available.

- ERS guidelines suggest:
  
  1. Not offering treatment with inhaled corticosteroids to adults with bronchiectasis (\textit{conditional recommendation, low quality of evidence})

  2. The diagnosis of bronchiectasis should not affect the use of inhaled corticosteroids in patients with comorbid asthma or COPD (\textit{best practice advice, indirect evidence}).

Statins

- Statins have anti-inflammatory properties, but preliminary data do not support a role in bronchiectasis unless the patient has another indication for statin therapy.

- Adverse events including headache, leg pain, and diarrhea were more frequent in the atorvastatin group (Mandal, 2014).

- ERS guidelines recommend not offering statins for the treatment of bronchiectasis (strong recommendation, low quality of evidence).
Macrolide Therapy

- Has anti-microbial and anti-inflammatory effect

- Suppresses inflammatory mediators, and moderates leukocyte recruitment and function

- Modifies mucus production, and may reduce biofilm around organisms

- Promotes gastric emptying that may reduce the potential for acid reflux
Macrolide Trials

EMBRACE

• Azithromycin 500mg three times a week for 6 months increased proportion of patients free of exacerbations, sustained over 6 month follow-up. (Wong, 2012. Lancet)

BLESS

• Erythromycin succinate 400mg twice daily for 48 weeks decreased pulmonary exacerbations and sputum weight density(Serisier, 2013. JAMA)

BAT

• Azithromycin 250mg daily for 52 weeks decreased median number of exacerbations, improved FEV1 and QOL scores. (Altenberg, 2013. JAMA)

• Resistance is a concern
Hypertonic saline

- Directly stimulates coughing.
- Lowers sputum viscosity, leading to a higher weight of expectorated sputum.
- Helps to humidify airways and enhance ciliary function.
- Appears to be well-tolerated in bronchiectasis patients (Kelly, 2001).
Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis

Fiona Kellett a,*, Niven M. Robert b

- 30 patients with non-CF bronchiectasis
- Randomized to 7% hypertonic saline or placebo (0.9% normal saline) for 3 months
- Excluded patients with pseudomonas
- Improvement in SGRQ scores in 7% hypertonic saline vs 0.9% normal saline

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Changes in lung function over treatment periods (% change from pre-treatment baseline).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Active (HS)</td>
</tr>
<tr>
<td>FEV₁ % change (95% C.I.)</td>
<td>15.1 (8.2;22.0)</td>
</tr>
<tr>
<td>FVC % change (95% C.I.)</td>
<td>11.23 (8.6;13.9)</td>
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</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Outcome of exacerbations/health care utilization.</th>
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<tbody>
<tr>
<td></td>
<td>Baseline retrospective recall</td>
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<tr>
<td>Annualised antibiotic use n/year</td>
<td>2.11</td>
</tr>
<tr>
<td>Annualised exacerbations n/year</td>
<td>2.60</td>
</tr>
</tbody>
</table>

Kellet, et al. Respiratory medicine, 2011
The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis

Caroline H.H. Nicolson, Robert G. Stirling, Brigitte M. Borg, Brenda M. Button, John W. Wilson, Anne E. Holland

- 40 patients randomized to 6% hypertonic saline or 0.9% normal saline daily for 12 months
- Significant improvements in QoL, FEV$_1$, and reduction in sputum colonization in both groups, no difference between the groups.

Figure 2 SGRQ Totals. No significant difference between groups at any time point.

Nicolson, et al. Respiratory Medicine, 2012
461 patients were randomized to either 400mg mannitol inhaled twice daily vs. low dose mannitol (50mg twice daily) for 52 weeks.

The annual rate of exacerbations between the groups was not significantly different (1.69 vs 1.84, p = 0.31).

There was an increase in time to net exacerbation and a small improvement in SGRQ with mannitol treatment.

Kaplan–Meier plot of the time to first graded pulmonary exacerbation.

Cochrane Database review inhaled saline and mannitol

- Eleven studies, 1021 participants
- Five studies (833 participants) compared inhaled mannitol with placebo.
- Four studies (N = 113) compared hypertonic saline versus isotonic saline.
- It is not possible to draw robust conclusions given limited data.
- An analysis of adverse events data revealed no difference between mannitol and placebo (OR 0.96; 95% CI 0.61 to 1.51).
- The data suggest that mannitol is unlikely to have benefit over isotonic saline in patients with mild disease.
- Future studies should test its use in those with more severe disease.

Hart, et al.

Cochrane Database Syst Rev, 2014
Antibiotics

• Attempt to eradicate *Pseudomonas* and/or MRSA

• Suppress the burden of chronic bacterial colonization

• Treat exacerbations

• Improve symptoms
Inhaled antibiotics

Liposomal Ciprofloxacin (ORBIT-3, ORBIT-4)

- Time to first exacerbation improved in ORBIT-4 in patients with *P. aeruginosa* and a history of at least two exacerbations; the primary endpoint was not met in ORBIT-3.
- Pooled data from 582 patients showed a significant reduction in frequency of exacerbations and time to first exacerbation.

Dry Power Ciprofloxacin (RESPIRE-1, RESPIRE-2)

- Reduced frequency of exacerbations and increased time to first exacerbation in the 14 day on/off regimen, no improvement in the 28 day on/off regimen (RESPIRE1)
- RESPIRE-2 did not show improvement in frequency of exacerbations and time to exacerbation in either arm.
Inhaled antibiotics

**Inhaled continuous gentamycin (Murray 2011)**

- Reduced sputum bacterial density, less sputum purulence
- Increase in exercise capacity, improvement in cough and QOL
- No improvement in pulmonary function and 24-hour sputum volume.

**Inhaled colistin (Haworth, 2014)**

- Did not meet primary endpoint in time to first exacerbation in all subjects
- Improvement in median time to exacerbation in adherent patients, with improvement in QOL and pseudomonas density.
• 12 trials, looking at inhaled amikacin, gentamycin, tobramycin, aztreonam, ciprofloxacin and colistin

• Inhaled antibiotics were more effective than placebo or symptomatic treatment in reducing sputum bacterial load, eradicating the bacteria from sputum, and reducing the risk of exacerbations.

• 10% developed bronchospasm in treatment groups, vs 2.3% in control.

• Safe and effective

• Each study included two 4-week courses of aztreonam of inhalation solution (AZLI) 75mg or placebo three times a day, followed by 4 weeks off treatment.

• AIR-BX1: 134 AZLI patients, 132 placebo

• AIR-BX2: 136 AZLI patients, 138 placebo

• Both studies showed an increase in adverse events in the AZLI group, mainly dyspnea, cough and increased sputum.

• Cannot pool studies shown to be successful in the CF population and apply it to non-CF bronchiectasis.

Barker A, et al.

Lancet Resp Med. 2014
Goals of Surgery

• Can be used for those not improving on or tolerating therapy

• Resolve complications such as recurrent infection, empyema, or hemoptysis

• Improve symptoms and quality of life
• 212 thoracoscopic lobectomies and segmentectomies

• Operative mortality was zero.

• Overall complication rate of 8.9%

• Complications included prolonged air leak, atrial fibrillation, bronchial injury, pneumonia, wound infection, atelectasis, and pleural effusion.

In the pipeline for bronchiectasis

<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial design</th>
<th>Primary outcome or objective</th>
<th>Duration</th>
<th>Participants (n)</th>
<th>Single centre or multicentre</th>
<th>Location</th>
<th>Current status</th>
<th>Trial registration number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Single-ascending dose and multiple-ascending dose in healthy people</td>
<td>Safety</td>
<td>28 days</td>
<td>42</td>
<td>Single centre</td>
<td>UK</td>
<td>Completed</td>
<td>NCT02468908</td>
</tr>
<tr>
<td>1</td>
<td>Non-randomised safety assessment</td>
<td>Safety</td>
<td></td>
<td>6</td>
<td>Single centre</td>
<td>Miami, FL, USA</td>
<td>Recruiting</td>
<td>NCT02625246</td>
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<tr>
<td>1</td>
<td>Single-ascending dose and multiple-ascending dose in healthy people</td>
<td>Safety</td>
<td>15 days</td>
<td>72</td>
<td>Single centre</td>
<td>Belgium</td>
<td>Completed</td>
<td>NCT03056326</td>
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<td>1</td>
<td>Single-ascending dose and multiple-ascending dose in healthy people</td>
<td>Safety</td>
<td>18 days</td>
<td>33</td>
<td>Single centre</td>
<td>UK</td>
<td>Terminated because of adverse events</td>
<td>NCT02058407</td>
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<td>2</td>
<td>Double-blind, randomised, placebo-controlled</td>
<td>Time to first exacerbation</td>
<td>24 weeks</td>
<td>240</td>
<td>Multicentre</td>
<td>Worldwide</td>
<td>Not yet recruiting</td>
<td>NCT03218917</td>
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<td>2</td>
<td>Open-label</td>
<td>Change in CASA-Q</td>
<td>16 weeks</td>
<td>25</td>
<td>Single centre</td>
<td>South Korea</td>
<td>Unknown</td>
<td>NCT01580748</td>
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<td>3</td>
<td>Randomised open-label</td>
<td>Frequency of acute exacerbations</td>
<td>12 months</td>
<td>150</td>
<td>Single centre</td>
<td>China</td>
<td>Recruiting</td>
<td>NCT02088216</td>
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<tr>
<td>3</td>
<td>Randomised crossover</td>
<td>Change in FEV₁, and safety</td>
<td>28 days</td>
<td>150</td>
<td>Multicentre</td>
<td>Worldwide</td>
<td>Recruiting</td>
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<td>Randomised, blinded, placebo-controlled</td>
<td>SGRQ</td>
<td>24 weeks</td>
<td>100</td>
<td>Single centre</td>
<td>China</td>
<td>Completed</td>
<td>NCT01684683</td>
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<td>3</td>
<td>Randomised, blinded, placebo-controlled</td>
<td>Time to first exacerbation</td>
<td>1 year</td>
<td>200</td>
<td>Single centre</td>
<td>China</td>
<td>Unknown</td>
<td>NCT02507843 (registered retrospectively)</td>
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<td>Safety</td>
<td>56 days</td>
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<tr>
<td>3</td>
<td>Randomised, placebo-controlled</td>
<td>Percentage of patients free from exacerbations</td>
<td>1 year</td>
<td>244</td>
<td>Multicentre</td>
<td>China</td>
<td>Recruiting</td>
<td>NCT01968421</td>
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</table>

The selected trials are registered in public databases and are either active, recruiting, or completed, but not yet published. We included studies that either did not assess antibiotics and enrolled patients with stable bronchiectasis, or assessed novel drugs in healthy people when the term “bronchiectasis” was included in the registration, indicating these patients as the target population. CASA-Q=cough and sputum assessment questionnaire. ENaC-epithelial sodium channel. GM-CSF=granulocyte-macrophage colony-stimulating factor. SGRQ=St George’s Respiratory Questionnaire. *Specific for patients due to primary ciliary dyskinesia.
Summary

• Bronchiectasis is becoming increasingly common with significant patient and economic burden.

• Research is increasing. The microbiome is of particular interest.

• Non-pharmacologic therapies are important and should be utilized.

• Inhaled antibiotics and surgery are options.
THANK YOU!
References


References


References


References


Shapiro at al. Diagnosis of primary ciliary dyskinesia. Am J Respir Crit Care Med Vol 197, Iss 12, pp e24–e39, Jun 15, 2018


References


