Understanding the heterogeneity of the disease

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Bronchiectasis
as a radiological diagnosis
Bronchiectasis as a DISEASE

Chronic cough
Haemoptysis
Purulent sputum
Wheeze
Recurrent LRTI
Tiredness

LRTI: low respiratory tract infections
The heterogeneity of bronchiectasis

Etiology

Pulmonary Function

Completely normal

FEV$_1$

50-80%

35-50%

< 35%

Signs Symptoms

Chronic Productive cough

Recurrent Exacerbations

Recurrent pneumonia

Haemoptysis

Wheeze

Very mild S/S

Radiology
Disorders predisposing to bronchiectasis

CTD: connective tissue diseases; IBD: inflammatory bowel disease; GORD: gastro-oesophageal reflux disease, ABPA: allergic bronchopulmonary aspergillosis
Disorders predisposing to bronchiectasis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dundee (UK)</th>
<th>Newcastle (UK)</th>
<th>Leuven (Belgium)</th>
<th>Galway (Ireland)</th>
<th>Monza (Italy)</th>
<th>Athens (Greece)</th>
<th>Barcelona (Spain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-infective</td>
<td>18%</td>
<td>5%</td>
<td>19%</td>
<td>20%</td>
<td>25%</td>
<td>43%</td>
<td>15%</td>
</tr>
<tr>
<td>COPD</td>
<td>2%</td>
<td>12%</td>
<td>16%</td>
<td>13%</td>
<td>15%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>CTD</td>
<td>9%</td>
<td>10%</td>
<td>13%</td>
<td>21%</td>
<td>2%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>6%</td>
<td>8%</td>
<td>7%</td>
<td>6%</td>
<td>4%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>7%</td>
<td>0</td>
<td>10%</td>
<td>2%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>ABPA</td>
<td>11%</td>
<td>1%</td>
<td>6%</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
<td>1%</td>
</tr>
<tr>
<td>Ciliary dysfunction</td>
<td>0.3%</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
<td>0.5%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>IBD</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aspiration/GORD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0.7%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>0.5%</td>
<td>0.9%</td>
<td>1%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>51%</td>
<td>54%</td>
<td>31%</td>
<td>18%</td>
<td>44%</td>
<td>37%</td>
<td>58%</td>
</tr>
</tbody>
</table>

CTD: connective tissue diseases; IBD: inflammatory bowel disease; GORD: gastro-oesophageal reflux disease, ABPA: allergic bronchopulmonary aspergillosis

Lonni S et al. Submitted
Disorders predisposing to bronchiectasis

Impact on outcomes

De Soyza A et al Submitted
Disorders predisposing to bronchiectasis

Concerns

1) Different definitions across literature and across centers

1) Long-term retrospective recall

1) Sometimes, more than one predisposing factor may be identified

1) Even where the underlying cause is identified, the reasons why certain individuals develop bronchiectasis in association with these disorders are largely unknown
The heterogeneity of bronchiectasis

**Radiology**

**Signs Symptoms**

- Chronic Productive cough
- Recurrent Exacerbations
- Recurrent pneumonia
- Haemoptysis
- Wheeze
- Very mild S/S

**Pulmonary Function**

- Completely normal
- FEV₁ 50-80%
- FEV₁ 35-50%
- FEV₁ < 35%

**Etiology**

**Microbiology**
Chronic infection

What we know

- *H. influenzae* (14-52%), *P. aeruginosa*(12-58%) *S. pneumoniae* (7-37%),
  *M. catarrhalis* (8-27%)
- Despite the presence of purulent sputum, 18–40% of specimens will fail to grow any pathogens

McShane PJ et al Am J Respir Crit Care Med 2013; 188:647

**Mortality**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Pseudomonas</th>
<th>Non-Pseudomonas</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliberti 2014</td>
<td>3</td>
<td>0</td>
<td>162</td>
<td>31.16 [1.58, 616.55]</td>
</tr>
<tr>
<td>Chalmers 2014</td>
<td>15</td>
<td>47</td>
<td>538</td>
<td>2.85 [1.50, 5.43]</td>
</tr>
<tr>
<td>Chalmers 2015</td>
<td>6</td>
<td>17</td>
<td>242</td>
<td>2.09 [0.77, 5.64]</td>
</tr>
<tr>
<td>Goeminne 2014</td>
<td>10</td>
<td>20</td>
<td>225</td>
<td>10.25 [3.81, 27.57]</td>
</tr>
<tr>
<td>Loebinger 2009</td>
<td>8</td>
<td>19</td>
<td>71</td>
<td>1.82 [0.65, 5.15]</td>
</tr>
<tr>
<td>Martinez-Garcia 2014</td>
<td>38</td>
<td>41</td>
<td>271</td>
<td>2.42 [1.46, 4.01]</td>
</tr>
<tr>
<td>McDonnell 2014</td>
<td>9</td>
<td>13</td>
<td>108</td>
<td>1.73 [0.68, 4.38]</td>
</tr>
<tr>
<td>McDonnell 2015</td>
<td>13</td>
<td>27</td>
<td>178</td>
<td>3.46 [1.55, 7.73]</td>
</tr>
</tbody>
</table>

Total (95% CI): 400 / 1795 (100.0%) 2.95 [1.98, 4.40]

Total events: 102 / 184

Heterogeneity: Tau² = 0.13; Chi² = 11.72, df = 7 (P = 0.11); I² = 40%

Test for overall effect: Z = 5.29 (P < 0.00001)

Finch S et al. Ann Am Thorac Soc. 2015 Sep 10
Chronic infection

What we know: NTM

Overall prevalence of 9.3%

MAC (up to 53%), *M. abscessus* (39%), *M. kansasii* (3-28%), *M. fortuitum* (1-3%), *M. chelonae* (1%), *M. malmoense* (1%)

Co-infection with *P. aeruginosa* (up to 52%)

Usually, no frequent exacerbators

*Ad hoc* criteria for treatment in bronchiectasis

Chronic infection
What we are learning

- **Prevotella**
- **Veillonella**
- **Streptococcus**
- **Pseudomonas**
- **Haemophilus**
- Other

Relative Abundance (% OTUs)

Clinically Stable (n=10)

- Campylobacter
- Megasphaera
- Porphyromonas
- Lactobacillus
- Neisseria
- Susobacterium
- Serratia
- Kingella
- MoraxellaKingella

Tunney MM. Am J Respir Crit Care Med. 2013
The heterogeneity of bronchiectasis

### Microbiology
- **Pseudomonas** dominant
- **Haemophilus** dominant
- Other pathogens dominant
- Non-tuberculous mycobacteria
- Viruses? Fungi?

### Etiology
- Non-tuberculous mycobacteria
- Idiopathic
- Post-infective
- Immunodeficit

### Pulmonary Function
- Completely normal
- FEV$_1$ 50-80%
- FEV$_1$ 35-50%
- FEV$_1$ < 35%

### Signs Symptoms
- Chronic Productive cough
- Recurrent Exacerbations
- Recurrent pneumonia
- Haemoptysis
- Wheeze
- Very mild S/S

### Radiology

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The heterogeneity of bronchiectasis

Microbiology
- Pseudomonas dominant
- Haemophilus dominant
- Other pathogens dominant
- Non-tuberculous mycobacteria
- Viruses? Fungi?

Etiology
- Non-tuberculous mycobacteria
- Idiopathic
- Post-infective
- Immune deficiency

Pulmonary Function
- FEV1 50-80%
- FEV1 35-50%
- FEV1 < 35%
- Completely normal

Signs
- Chronic productive cough
- Recurrent exacerbations
- Recurrent pneumonia
- Haemoptysis
- Wheeze
- Very mild S/S

Radiology

Other pathogens dominant
1. Stratification according to severity

Radiology

Signs Symptoms

Chronic Productive cough
Recurrent Exacerbations
Recurrent pneumonia
Haemoptysis
Wheeze
Very mild S/S

Pulmonary Function

Completely normal
FEV$_1$ 50-80%
FEV$_1$ 35-50%
FEV$_1$ < 35%

Etiology

Microbiology

Pseudomonas dominant
Haemophillus dominant
Other pathogens dominant
Non-tuberculous mycobacteria
Viruses? Fungi?

Pulmonary Function

Chronic Productive cough
Recurrent Exacerbations
Recurrent pneumonia
Haemoptysis
Wheeze
Very mild S/S

Etiology

Microbiology

Pseudomonas dominant
Haemophillus dominant
Other pathogens dominant
Non-tuberculous mycobacteria
Viruses? Fungi?
1. Stratification according to severity

The Bronchiectasis Severity Index

5 European Centres
- Dundee
- Edinburgh
- Leuven
- Milan
- Newcastle

Total study population 1310
1. Stratification according to severity

The Bronchiectasis Severity Index

www.bronchiectasisseverity.com

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Exacerbations before the study</th>
<th>MRC dyspnea score</th>
<th>Pseudomonas colonization</th>
<th>Colonization with other organisms</th>
<th>Radiological severity: ≥3 lobes involved or cystic bronchiectasis</th>
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</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0</td>
<td>0</td>
<td>1–3</td>
<td>No</td>
<td>No</td>
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<tr>
<td>50–69</td>
<td>2</td>
<td>1–2</td>
<td>4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>70–79</td>
<td>4</td>
<td>3 or more</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>80+</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BMI</td>
<td></td>
<td></td>
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<tr>
<td>&lt;18.5</td>
<td>2</td>
<td></td>
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<td></td>
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<td>18.5–25</td>
<td>0</td>
<td></td>
<td></td>
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<td>26–29</td>
<td>0</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>30 or more</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV(_1) % predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;80</td>
<td>0</td>
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<td>50–80</td>
<td>1</td>
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<td>30–49</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission before study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BSI Risk Classes

- Mild = 0-4
- Moderate = 4-8
- Severe = 9+

(Range = 0-25)
1. Stratification according to severity

- **Airway clearance techniques**
- **Long-term antibiotic therapy**
- **Anti-inflammatory therapy**
- **Therapies in advanced disease**

General management (applies at all stages of disease):
- Vaccination against influenza and pneumococcus
- Manage co-morbidities and underlying cause
- Pulmonary rehabilitation
- Prompt treatment of exacerbations
- Sputum surveillance of *Pseudomonas aeruginosa* and non-tuberculous *Mycobacteria*

- **Long-term oxygen therapy, lung transplantation, surgery**
- **Inhaled corticosteroids in selected patients**
- **Macrolides for patients with frequent exacerbations**
- **Inhaled antibiotics particular with *Pseudomonas aeruginosa* colonisation**
- **Regular physiotherapy±adjuncts (devices/hyperosmolar agents)**

**Inhaled corticosteroids in selected patients**
- Consider macrolides for patients with frequent exacerbations
- **Regular physiotherapy±adjuncts (devices/hyperosmolar agents)**

**Severe bronchiectasis or persistent symptoms despite standard care**

- **Daily physiotherapy**

**Mild severity**

Chalmers JD et al. Eur Respir J 2015;45:1446
The heterogeneity of bronchiectasis

**Radiology**

**Signs**
- Chronic Productive cough
- Recurrent Exacerbations
- Recurrent pneumonia
- Haemoptysis
- Wheeze
- Very mild S/S

**Symptoms**
- Completely normal
- FEV$_1$ 50-80%
- FEV$_1$ 35-50%
- FEV$_1$ < 35%

**Pulmonary Function**

**Etiology**
- Pseudomonas dominant
- Haemophilus dominant
- Other pathogens dominant
- Non-tuberculous mycobacteria
- Viruses? Fungi?

**Microbiology**

**Completely normal**

**FEV$_1$ 50-80%**

**FEV$_1$ 35-50%**

**FEV$_1$ < 35%**

**Microbiological**

**Immunodeficiency**

**Cystic Fibrosis**

**CFD**

**Cystic Fibrosis**

**CTD**

**BD**

**GRD**

**Asthma**

**AB**

**Psoriasis**

**Eosinophilia**

**Graft-versus-host Disease**

**HIV**

**Other**

**Radiology**

**Completely normal**

**FEV$_1$ 50-80%**

**FEV$_1$ 35-50%**

**FEV$_1$ < 35%**
2. Identification of clinical phenotypes

- **Pseudomonas** dominant
- **Haemophilus** dominant
- **Other pathogens** dominant
- **Non-tuberculous mycobacteria**
- **Idiopathic**
- **Post-Infective Immuno-deficit**
- **COPD**
- **CTD**
- **IBD**
- **GO**
- **RD**
- **Asthma**
- **AB**
- **PA**
- **Genetic/Congenital**
- **Other**

**Signs**
- Chronic productive cough
- Recurrent exacerbations
- Recurrent pneumonia
- Haemoptysis
- Wheeze
- Very mild S/S

**Pulmonary Function**
- Completely normal
- FEV\(_1\) 50-80%
- FEV\(_1\) 35-50%
- FEV\(_1\) < 35%

**Outcomes**
- Microbiology
- Pseudomonas dominant
- Haemophilus dominant
- Other pathogens dominant
- Non-tuberculous mycobacteria
- Viruses?
- Fungi?

**Treatment**
- Radiology
- Biology
- Pulmonary Function
- Etiology
- Microbiology
2. Clusters in bronchiectasis

1,145 adults with bronchiectasis

- Monza (Italy)
- Dundee (UK)
- Leuven (Belgium)
- Athens (Greece)
- Galway (Ireland)

1. Spearman correlation
2. Principal component analysis
3. Hierarchical analysis
4. Cluster analysis

1. Age
2. Radiological Severity (Reiff score)
3. Daily cough
4. Daily sputum
5. Dyspnea (Medical Research Council)
6. Long-term oxygen therapy
7. Exacerbations in the previous year
8. Hospitalization in the previous year
9. FEV$_1$
10. Chronic infection with *Pseudomonas aeruginosa*
11. Chronic infection with other pathogens
12. Charlson Comorbidity Index

Unpublished data from the EMBARC Network
## 2. Clusters in bronchiectasis

Unpublished data from the EMBARC Network

<table>
<thead>
<tr>
<th>Variables</th>
<th>Severe Pseudomonas 19%</th>
<th>Others Chronic Infections 24%</th>
<th>Daily Sputum 33%</th>
<th>Mild-to-Moderate 24%</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>median (IQR)</td>
<td>67 (56-75)</td>
<td>65 (56-73)</td>
<td>67 (57-74)</td>
<td>66 (55-74)</td>
</tr>
<tr>
<td>Male n.(%</td>
<td>81 (45)</td>
<td>112 (41)</td>
<td>148 (40)</td>
<td>109 (36)</td>
<td>0.19</td>
</tr>
<tr>
<td>Body Mass Index median (IQR)</td>
<td>25 (21-27)</td>
<td>25 (22-28)</td>
<td>25 (22-28)</td>
<td>25 (21-28)</td>
<td>0.47</td>
</tr>
<tr>
<td>Smoker or ex n.(%</td>
<td>56 (31)</td>
<td>90 (33)</td>
<td>165 (44)</td>
<td>121 (39)</td>
<td>0.005</td>
</tr>
<tr>
<td>Charlson Comorbidities Index&gt;1 n.(%)</td>
<td>53 (30)</td>
<td>101 (37)</td>
<td>113 (30)</td>
<td>106 (35)</td>
<td>0.20</td>
</tr>
<tr>
<td>Reiff score median (IQR)</td>
<td>6 (4-9)</td>
<td>4 (2-6)</td>
<td>3 (2-6)</td>
<td>3 (2-6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Daily cough n.(%</td>
<td>170 (95)</td>
<td>241 (88)</td>
<td>322 (86)</td>
<td>154 (50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Daily sputum n.(%</td>
<td>166 (93)</td>
<td>204 (75)</td>
<td>362 (97)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Haemoptysis n.(%</td>
<td>42 (24)</td>
<td>36 (13)</td>
<td>80 (22)</td>
<td>43 (14)</td>
<td>0.002</td>
</tr>
<tr>
<td>MRC median (IQR)</td>
<td>3 (2-5)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>1 (1-2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Exacerbations in the previous year median (IQR)</td>
<td>3 (2-4)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>FEV1 (% predicted) median (IQR)</td>
<td>59 (46-78)</td>
<td>71 (55-93)</td>
<td>77 (57-95)</td>
<td>84 (68-101)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pseudomonas n.(%</td>
<td>179 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other pathogens n.(%</td>
<td>0 (0)</td>
<td>273 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP, mg/L median (IQR)</td>
<td>10.7 (4.0-36.0)</td>
<td>5.0 (3.7-9.0)</td>
<td>4.5 (2.0-7.7)</td>
<td>3.0 (1.2-7.2)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

MRC: Medical Research Council; CRP: C-reactive protein

Unpublished data from the EMBARC Network
## 2. Clinical phenotypes in bronchiectasis

<table>
<thead>
<tr>
<th>Quality of life</th>
<th>Severe Pseudomonas 19%</th>
<th>Others Chronic Infections 24%</th>
<th>Daily Sputum 33%</th>
<th>Mild-to-Moderate 24%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGRQ</td>
<td>median (IQR)</td>
<td>58 (34-72)</td>
<td>43 (27-61)</td>
<td>39 (27-55)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>median (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-2)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>during one-year follow-up</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

SGRQ: St. George’s Respiratory Questionnaire

Unpublished data from the EMBARC Network
The heterogeneity in research
2000-2015; adults; original papers on bronchiectasis
The heterogeneity in research
2000-2015; original papers on bronchiectasis
The burden of bronchiectasis

Prevalence data
- 67/100,000 Germany
- 52/100,000 USA

- Mild-to-moderate patients with bronchiectasis (Secondary Care and Primary Care)
- Patients with Signs / Symptoms without a radiological diagnosis of bronchiectasis (COPD)
- Asymptomatic patients with a radiological diagnosis
Conclusions

The Bronchiectasis Severity Index
www.bronchiectasisseverity.com

BSI Risk Classes
- Mild = 0-4
- Moderate = 4-8
- Severe = 9+

(Range = 0-25)
Acknowledgements

**Executive committee**
James Chalmers
Eva Polverino

**Scientific Committee**
Anthony De Soyza
Felix Ringshausen
Marlene Murris
Montserrat Vendrell
Wim Boersma
Stefano Aliberti

**Steering Committee**
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Antoni Torres
Tobias Welte
Diana Bilton
Robert Wilson
Charles Haworth
Gernot Rohde
Michael Loebinger
Katerina Dimakou
Stuart Elborn

www.bronchiectasis.eu