# Heterogeneous Nature of non-CF Bronchiectasis

## Aetiology

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Post-infectious, e.g. pneumonia, pertussis, measles, mycobacterial infections and tuberculosis</td>
<td>29–42%</td>
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<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>1–8%</td>
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<tr>
<td>Immunodeficiency</td>
<td>1–8%</td>
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<tr>
<td>Connective tissue diseases, e.g. rheumatoid arthritis, systemic lupus erythematosis, ankylosing spondylitis, Sjogren's syndrome and relapsing polychondritis</td>
<td>3–6%</td>
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<tr>
<td>Bowel disorders, e.g. inflammatory bowel disease and coeliac disease</td>
<td>1–5%</td>
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<tr>
<td>Aspiration/gastro-oesophageal reflux disease</td>
<td>1–4%</td>
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<tr>
<td>Chronic respiratory disease, e.g. asthma, COPD and alpha-1 antitrypsin deficiency</td>
<td>1–23%</td>
</tr>
<tr>
<td>Congenital disorders, e.g. primary ciliary dyskinesia</td>
<td>1–10%</td>
</tr>
<tr>
<td>CF</td>
<td>1–4%</td>
</tr>
<tr>
<td>Miscellaneous, e.g. endometriosis, amyloidosis, yellow nail syndrome and Young's syndrome</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>26–74%</td>
</tr>
</tbody>
</table>
Heterogeneous Nature of non-CF Bronchiectasis Trial Endpoint

- CF Bronchiectasis Trial – Will a baseball bat consistently hit a baseball past the infield.

- Non-CF Bronchiectasis Trial – Will a baseball bat consistently hit every other style of ball past the infield.
Heterogeneous Nature of non-CF Bronchiectasis Participants

- **CF Bronchiectasis Trial Participants**

- **Non-CF Bronchiectasis Trial Participants**
The clinical features of Bronchiectasis associated with Alpha-1 Antitrypsin Deficiency, Common Variable Immunodeficiency, and Primary Ciliary Dyskinesia

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Background

Bronchiectasis is associated with rare conditions including Alpha-1 antitrypsin deficiency (AATD), Common Variable Immunodeficiency (CVID) and Primary Ciliary Dyskinesia (PCD). These three rare but important conditions have different pathogenesis and important management considerations.

Objectives

The objectives of this study are to compare and contrast the clinical characteristics of bronchiectasis associated with these rare conditions: AATD, CVID, and PCD.

Materials and Methods

Study inclusion criteria:
- Adult patients (18 years or older) within the Bronchiectasis Research Registry (BRR)
- Physician established diagnosis of non-cystic fibrosis bronchiectasis
- Presence of AATD, CVID, PCD, or tests negative for the above conditions (Idiopathic)

Flow Diagram of the study participants

The group with PCD showed a significantly lower mean pre-bronchodilator FEV1/FVC (% predicted) as well as FEV1/FVC ratio than the other groups.

Results

A diagnosis of bronchiectasis was made at a much younger age in those with PCD than in the other groups (p<0.001). Significantly greater proportion of patients with PCD reported pulmonary exacerbations and hospitalizations in the past 2 years compared to AATD, CVID, and idiopathic groups (p=0.002 and p<0.001, respectively).

Select baseline demographic and clinical characteristics of the patients in the study sample, n=513

<table>
<thead>
<tr>
<th>Association</th>
<th>Idiopathic</th>
<th>AATD</th>
<th>CVID</th>
<th>PCD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment, mean (SD)</td>
<td>66.0 (13.0)</td>
<td>66.9 (10.7)</td>
<td>65.6 (11.1)</td>
<td>41.9 (14.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at bronchograms diagnosis, mean (SD)</td>
<td>60.8 (15.8)</td>
<td>66.2 (14.9)</td>
<td>94.0 (12.5)</td>
<td>22.9 (12.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulmonary exacerbations in the past 2 years, n (%)</td>
<td>31 (62.2)</td>
<td>24 (61.0)</td>
<td>11 (61.1)</td>
<td>59 (61.2)</td>
<td>0.502</td>
</tr>
<tr>
<td>Hospitalizations in the past 2 years, n (%)</td>
<td>83 (14.2)</td>
<td>11 (19.3)</td>
<td>11 (61.5)</td>
<td>5 (61.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Daily hours of exacerbations, n (%)</td>
<td>59 (61.2)</td>
<td>50 (61.2)</td>
<td>50 (61.2)</td>
<td>50 (61.2)</td>
<td>0.615</td>
</tr>
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</table>

Conclusions

Overall, Pseudomonas aeruginosa and Staphylococcus aureus were the most commonly reported bacterial isolates from sputum. The percentage of patients with PCD reported to be growing Pseudomonas in one or more sputum cultures (63.5%) was significantly greater compared to other groups (AATD: 33.3%, CVID: 29.3%, and idiopathic: 28.9%) (p<0.001).

The most prevalent bacterial isolate from sputum at baseline (%)

- Pseudomonas Aeruginosa: 30.2%
- Staphylococcus aureus: 25.8%
- Idiopathic: 9.2%

Our study found that patients with PCD within the BRR are significantly younger, more often report having respiratory symptoms, exacerbations and hospitalizations compared to other groups; their bacterial cultures more frequently show presence of Pseudomonas aeruginosa.

Acknowledgements


References

Barker A, Gombar AV. An update on the sputum bacteria and impact of bronchiectasis symptom.
Quality of Life Using the QOL-B Instrument
Measured every 28 Days, with 7 Day Recall

From Aradigm FDA hearing January 11, 2018.
Prespecified Quality of Life Endpoint

• Secondary Endpoint
  • QOL-B comparing baseline (before medication taken) to Week 48 (28 days after the last treatment)

From Aradigm FDA hearing January 11, 2018.
Placebo: Visit to Visit Changes in QOL-B Appear to Be Random as Are Small Changes in Colony Forming Units of *Pseudomonas aeruginosa*

- Minimal changes in CFUs during ON and OFF periods
- OFF Periods just as likely as ON Periods to have positive changes in QOL-B

Each data point represents the mean delta QOL-B for all patients during that treatment cycle. There are 6 on-treatment periods and 6-off treatment periods per study. From Aradigm FDA hearing January 11, 2018.
Linhaliq: Visit to Visit Changes in QOL-B are Correlated with Visit to Visit Changes in CFUs of *Pseudomonas aeruginosa*

Each data point represents the mean delta QOL-B for all patients during that treatment cycle. There are 6 on-treatment periods and 6 off-treatment periods per study.

Large reduction in QOL-B observed around the time of a pulmonary exacerbation.

From Aradigm FDA hearing January 11, 2018.
QOL Summary from Aradigm Trial

• The prespecified endpoint compared QOL-B at two time points when the patients were not on the trial medication

• Compared to each previous visit, patients treated with Linhaliq reported
  • Improvement in QOL-B at the end of each on-treatment period and worsening of the QOL-B at the end of each off-treatment period, consistent with the changes of the load of *P. aeruginosa* in their sputum

• Compared to each previous visit, patients treated with Placebo reported
  • Changes in QOL-B that appeared random
  • Occurrence of a pulmonary exacerbation was associated with a big drop in QOL-B, consistent with the report from the bronchiectasis trial with Cayston (Quittner et al., 2015)