Bronchiectasis in 2016

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Presenter disclosures

Clinical Trials
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Consultancy
Bayer Healthcare, Griffols, AstraZeneca, Basilea, Napp, Raptor
An old disease re-emerging
What is bronchiectasis?

Radiological appearance
- Cyclindrical
- Varicose
- Cystic
- + additional features

Clinical syndrome
- Cough
- Sputum production
- Recurrent infections
- Chronic bacterial colonisation
## Radiological heterogeneity

### Lower lobes
- Idiopathic
- COPD associated
- Post-infectious
- Aspiration
- PCD

### Middles lobes
- NTM infection

### Upper lobes
- Cystic fibrosis

### Central
- ABPA
- Tracheobronchomegaly
UK prevalence data

UK Clinical Practice Research datalink (CPRD) 2004-2013

Headline prevalence
566/100,000 in women in 2013
485 per 100,000 in men
Comparing the prevalence of BE to COPD in Europe

Rate of bronchiectasis prevalence increasing in several European countries

COPD 7.6%

Bronchiectasis 0.07%-0.56%

Prevalence in > 65 years: 14.2%

Incidence >65 years 0.2%-0.87%

14-108 cases of COPD for each case of bronchiectasis

References
Bronchiectasis

“Bronchiectasis one of the most neglected diseases in respiratory medicine”
ERS White Book 2014

A disease characterised by recurrent respiratory tract infections and chronic bacterial “colonisation”

Neutrophil dominated lung inflammation

No licensed therapies but most treatments are antibiotic based and target airway infection
Neutrophils drive the disease

Sputum neutrophil elastase predicts exacerbations and mortality

N=381 stable patients with bronchiectasis, 36 month follow-up

Chalmers et al, Submitted 2016
Chalmers et al, Submitted 2016

Mature elastin

Cross-link

Elastase

Elastin fragments (with or without cross-links)
Bacteria and neutrophilic inflammation are linked

N=385, single centre UK study

Chalmers et al, AJRCCM 2012;186(7):657-65
Prognostic impact of airway infection

n=608 patients over 4 years in a single centre Scottish study

% hospitalization over 4 years

% mortality over 4 years

**Exacerbations**

### The Bronchiectasis Severity Index
An International Derivation and Validation Study

James D. Chalmers,1 Pieter Goeminne2 Stefano Alberti3 Melissa J. McDonnell4,9 Sara Lonne4 John Davidson4, Lucy Poppelwell1, Waleed Salih1, Alberto Pesco5, Lieven J. Dupont2, Thomas C. Fardon, Anthony De Soyza6, and Adam T. Hill3

1Tayside Respiratory Research Group, University of Dundee, Dundee, United Kingdom; 2Respiratory Medicine, University Hospital Gasthuisberg, Leuven, Belgium; 3Department of Health Sciences, University of Milan-Bicocca, Clinics Pneumologici, AO San Gerardo, Monza, Italy; 4Adult Bronchiectasis Service and Sir William Leech Centre for Lung Research, Freeman Hospital, Newcastle upon Tyne Hospitals, Heaton, Newcastle, United Kingdom; 5Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; and 6Department of Respiratory Medicine Royal Infirmary of Edinburgh and the University of Edinburgh, Edinburgh, United Kingdom

### A Comprehensive Analysis of the Impact of *Pseudomonas aeruginosa* Colonization on Prognosis in Adult Bronchiectasis

Simon Finch1, Melissa J. McDonnell2 Hani Abo-Leyah, Stefano Alberti3, and James D. Chalmers1

1Tayside Respiratory Research Group, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom; 2Department of Respiratory Medicine, Galway University Hospitals, Galway, Ireland; and 3Department of Health Sciences, University of Milan-Bicocca, Pneumology Clinic, San Gerardo Hospital, Monza, Italy.

- **P. aeruginosa** colonization vs lack of **P. aeruginosa**
  - Mortality increased by ~3x*
  - Hospital admissions ~7x increased risk
  - Average of 1 additional exacerbation per patient per year
  - 15% lower FEV1 % predicted
  - Clinically significant impact on quality of life as measured by SGRQ

### Odds Ratio

<table>
<thead>
<tr>
<th>Study of Subgroup</th>
<th>M-H, Random, 95% CI</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliberti 2004</td>
<td>31.16 [1.58, 616.55]</td>
<td></td>
</tr>
<tr>
<td>Chalmers 2014</td>
<td>2.85 [1.50, 5.43]</td>
<td></td>
</tr>
<tr>
<td>Chalmers 2015</td>
<td>2.09 [0.77, 5.64]</td>
<td></td>
</tr>
<tr>
<td>Goeminne 2014</td>
<td>10.25 [3.81, 27.57]</td>
<td></td>
</tr>
<tr>
<td>Loebinger 2009</td>
<td>1.82 [0.65, 5.15]</td>
<td></td>
</tr>
<tr>
<td>Martinez-Garcia 2014</td>
<td>2.42 [1.46, 4.01]</td>
<td></td>
</tr>
<tr>
<td>McDonnell 2014</td>
<td>1.73 [0.68, 4.38]</td>
<td></td>
</tr>
<tr>
<td>McDonnell 2015</td>
<td>3.46 [1.55, 7.73]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2.95 [1.98, 4.40]*</td>
<td></td>
</tr>
</tbody>
</table>

### Heterogeneity:

- Tau² = 0.13
- Chi² = 11.72, df = 7 (P = 0.11)
- I² = 40%

### Test for overall effect:

- Z = 5.29 (P < 0.00001)
Components of the BSI - predictors of mortality and hospital admission

<table>
<thead>
<tr>
<th>Component</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0</td>
</tr>
<tr>
<td>50-69</td>
<td>2</td>
</tr>
<tr>
<td>70-79</td>
<td>4</td>
</tr>
<tr>
<td>80+</td>
<td>6</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>2</td>
</tr>
<tr>
<td>&gt;18.5</td>
<td>0</td>
</tr>
<tr>
<td><strong>FEV\textsubscript{1} % pred.</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;80%</td>
<td>0</td>
</tr>
<tr>
<td>50-80%</td>
<td>1</td>
</tr>
<tr>
<td>30-49%</td>
<td>2</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>3</td>
</tr>
<tr>
<td><strong>Exacerbation frequency</strong></td>
<td></td>
</tr>
<tr>
<td>3 or more per year</td>
<td>2</td>
</tr>
<tr>
<td>&lt;3 per year</td>
<td>0</td>
</tr>
<tr>
<td><strong>MRC dyspnoea score</strong></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Colonisation status</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Colonised</td>
<td>1</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>3</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
</tr>
<tr>
<td>3 or more lobes or cystic changes</td>
<td>1</td>
</tr>
<tr>
<td>&lt;3 lobes involved</td>
<td>0</td>
</tr>
</tbody>
</table>

Classification of the BSI
Mild = 0-4
Moderate = 4-8
Severe = 9+
(Range = 0-25)

*Chalmers et al, Am J Respir Crit Care Med. 2014;189(5):576-85*
Microbiome in bronchiectasis

Lung Microbiota and Bacterial Abundance in Patients with Bronchiectasis when Clinically Stable and during Exacerbation

Michael M. Tunney¹,²*, Gisli G. Einarsson¹,²*, Lan Wei¹,², Maire Drain³, Erich R. Klem⁴, Chris Cardwell⁵, Madeleine Ennis³, Richard C. Boucher⁴, Matthew C. Wolfgang⁴,⁶, and J. Stuart Elborn¹,²*

Remarkable stability over time
Effect of Long-term, Low-Dose Erythromycin on Pulmonary Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis: The BLESS Randomized Controlled Trial

Each point represents a separate protocol-defined pulmonary exacerbation (PDPE). Individual participants could account for more than 1 event each. P = .003 for the comparison with placebo for the rate of pulmonary exacerbations per patient per year.

Microbiome - BLESS

Table 4. Significant correlations between the relative abundance of the dominant bacterial taxon and clinical measures of disease

<table>
<thead>
<tr>
<th>Clinical Measure</th>
<th>Spearman’s p</th>
<th>Significance (P Value)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-BD FEV₁</td>
<td>−0.225</td>
<td>0.027</td>
<td>96</td>
</tr>
<tr>
<td>Post-BD FEV₁</td>
<td>−0.223</td>
<td>0.029</td>
<td>96</td>
</tr>
<tr>
<td>Bronchiectasis duration, yr</td>
<td>0.221</td>
<td>0.031</td>
<td>96</td>
</tr>
<tr>
<td>CRP</td>
<td>0.306</td>
<td>&lt;0.001</td>
<td>96</td>
</tr>
<tr>
<td>Sputum IL-8</td>
<td>0.585</td>
<td>&lt;0.001</td>
<td>81</td>
</tr>
<tr>
<td>Sputum IL-18</td>
<td>0.626</td>
<td>&lt;0.001</td>
<td>81</td>
</tr>
<tr>
<td>Sputum neutrophils, absolute</td>
<td>0.240</td>
<td>0.031</td>
<td>81</td>
</tr>
<tr>
<td>Sputum neutrophils, %</td>
<td>0.347</td>
<td>0.001</td>
<td>81</td>
</tr>
<tr>
<td>Sputum macrophages, absolute</td>
<td>−0.340</td>
<td>0.002</td>
<td>81</td>
</tr>
<tr>
<td>Sputum macrophages, %</td>
<td>−0.389</td>
<td>&lt;0.001</td>
<td>81</td>
</tr>
<tr>
<td>24-h sputum volume, g</td>
<td>0.370</td>
<td>0.002</td>
<td>96</td>
</tr>
</tbody>
</table>

Definition of abbreviations: BD = bronchodilator; CRP = C-reactive protein.

Bronchiectasis microbiome

Dicker et al. Presented at ATS 2016
Exacerbations

Dicker et al. Presented at ATS 2016
Long-term nebulized gentamicin for BE

Objectives

- To assess efficacy of continuous nebulized gentamicin over 1 year in patients with NCFB chronically infected with a variety of pathogens
- To assess if treatment effects were sustained over a 3-month, treatment-free follow-up period

Primary endpoint

A ≥1 log unit reduction in sputum bacterial load (baseline pathogens: *P. aeruginosa*, *H. influenzae*, *S. aureus*, *S. pneumoniae*, *Moraxella catarrhalis* and other (coliforms)

Murray MP et al. Am J Respir Crit Care Med 2011;183:491
### Long-term nebulized gentamicin for NCFB: key results

<table>
<thead>
<tr>
<th>Exacerbation frequency</th>
<th>33.3% of patients treated with gentamicin experienced exacerbations during the 12 month treatment period (range 0–1) compared with 80% in the saline group (P=0.0005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function</td>
<td>No significant differences in FEV1 or FVC between the groups at any time point throughout the study</td>
</tr>
<tr>
<td>Bacterial burden</td>
<td>In the gentamicin group, 13/27 (48.1%) patients infected with <em>P. aeruginosa</em> at baseline. Four of these patients (30.8%) achieved eradication at 12 months</td>
</tr>
<tr>
<td>Daily symptoms</td>
<td>At end of month 12, the gentamicin group achieved a clinically significant improvement in LCQ vs saline (81.4% vs. 20%, p&lt;0.01) and also in SGRQ (87.5% vs. 19.2%, p&lt;0.004), respectively. Effect was only sustained at follow-up for the SGRQ score</td>
</tr>
<tr>
<td>Safety</td>
<td>Gentamicin: Two non-treatment-related deaths occurred; two patients discontinued owing to being unable to tolerate treatment; seven of 32 patients (21.9%) had bronchospasms and received adjunctive treatment</td>
</tr>
<tr>
<td></td>
<td>Saline: Two of 33 (6%) patients had bronchospasms and received adjunctive treatment. Both discontinued treatment</td>
</tr>
</tbody>
</table>

LCQ: Leicester Cough Questionnaire; SGRQ: St George’s Respiratory Questionnaire

Additional trials for Colistin, Tobramycin and aztreonam inconclusive

Trials with inhaled ciprofloxacin, tobramycin and colistin ongoing
Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomized, double-blind placebo controlled trial

Dose= 500mg three time per week

Graph showing participants remaining exacerbation-free during the 6 month treatment period and the follow-up period.
The European Bronchiectasis Registry is supported by the European Union Innovative Medicines Initiative under the "New Drugs for Bad Bugs" programme, to help facilitate the development of new antibiotics against Gram-negative infections.

EMBARC is a pan-European network committed to promoting clinical research and education in bronchiectasis, through sharing of protocols, research ideas and expertise. Central to this project is the creation of the European Bronchiectasis Registry, a collaboration open to all investigators around Europe caring for patients with bronchiectasis.

Latest News
EMBARC passes 2000 patients enrolled! February Newsletter is online
Feb 26 2016 9:00 AM
Congratulations to EMBARC investigators and members from 23 countries who have contributed to achieving the 2000th patient enrolled. This greatly exceeds our targets for the first year of recruitment. ...

January EMBARC newsletter is online
Jan 28 2016 10:04 AM

Latest Research
Quality standards for the management of bronchiectasis in Italy: a national audit

Telomere Dysfunction and Senescence-associated Pathways in Bronchiectasis

Join EMBARC
EMBARC is an open group and free to join.
For more information contact info@bronchiectasis.eu
Sign up at the registration page

Talk to us on Twitter!
Participants from 40 countries

232 registered centres

TARGET:

• 1000 patients by April 2016
• 10,000 patients by March 2020
Results at end of May 2016

4115 patients consented

3377 patients data entered

Demographics
59% female
Average age= 65 years

Most common aetiology-
• Idiopathic= 36%
• post-infective= 29%

Never smoked =55.7%
Ex smoker= 35.3%
Disease impact - exacerbations

Outpatient exacerbations

- 0 exacerbations: 8.3%
- 1 exacerbation: 26.4%
- 2 exacerbations: 12.5%
- 3 exacerbations: 18.1%
- 4 exacerbations: 21.9%

Severe exacerbations

- 0 exacerbations: 8.4%
- 1 exacerbation: 22.2%
- 2 exacerbations: 64.1%
Inhaled and mucoactive therapies

Bronchodilators/anti-inflammatories
- Inhaled corticosteroids
- Long acting bronchodilators
  - Beta-agonists
  - Anti-cholinergics
- Mucolytic
- Theophylline

Airway clearance
- Hypertonic saline
- Nebulised normal saline
- DNAse
- Sodium hyaluronate
- Physiotherapy

% of cohort
Summary

• Bronchiectasis is driven by neutrophilic inflammation and bacterial infection

• The most effective therapies are chest clearance and prophylactic oral and inhaled antibiotics for severe patients.

• Current data suggests in much of Europe bronchiectasis is treated “like COPD” and there remains are high burden of disease
Acknowledgements

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www.bronchiectasis.eu

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EROS - European Respiratory Society
www.ersnet.org

Wellcome Trust
www.wellcome.ac.uk

IMI - Innovative Medicines Initiative
www.imi.europa.eu

NHS National Institute for Health Research
www.nihr.ac.uk

PROGNOSIS
www.prognosis.org.uk

UNIVERSITY OF DUNDEE
www.dundee.ac.uk

SIRM
www.sirm.org

ECFS
www.ecfs.net

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www.bronchiectasisresearchregistry.org

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