The management of bronchiectasis in Europe

Data from the European Bronchiectasis Registry

James Chalmers
University of Dundee, UK
Presenter disclosures

Clinical Trials
AstraZeneca, Aradigm corporation, Bayer Healthcare, GSK

Research Grant Support
Wellcome Trust, Chief Scientist Office, Medical Research Council, AstraZeneca, EU Innovative Medicines Initiative, European Respiratory Society, Tenovus Scotland, Bayer Healthcare, Aradigm Corporation, Griffols, Pfizer inc

Consultancy
Bayer Healthcare, Griffols, AstraZeneca, Basilea, Napp
Why do we need a European Bronchiectasis registry?

- To answer key questions about the epidemiology of bronchiectasis
- A series of unsuccessful clinical trials suggests the need for better outcome measures and greater research co-ordination
- To contribute to the generation of evidence-based recommendations on the management of patients with BE
- To encourage young investigators to become involved in this emerging field
- To disseminate knowledge and communicate results at international conferences and in peer reviewed publications
What is the EMBARC?

- European Bronchiectasis Registry
- ERS Bronchiectasis task force – European BE guidelines due 2016
- European Bronchiectasis patient advisory group
- ERS clinical research collaboration
- European Bronchiectasis Clinical Trials Network
Challenges in forming a European registry

Variable definitions

Inclusion/exclusion criteria

Variable quality control

Huge cost of administering registries in every country

Solution:
Alignment of data fields and definitions at set-up

Single data collection platform

Shared administrative set-up = sustainability
Sharing expertise and research protocols around Europe. Help to build a wider
network and grow clinical research capacity for bronchiectasis in Europe.

EMBARC is a pan-European network committed to promoting clinical research and education in bronchiectasis, through sharing of protocols, research idea 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
Support Healthy Lungs for Life at ERS 2015
Sep 14 2015 8:39 PM
At Congress, the Healthy Lungs for Life campaign will launch its new theme: Take the Active Option. We think this campaign offers a great opportunity to raise awareness of the role of physical ...

The EMBARC registry receives funding from EU Innovative Medicines Initiative
Sep 7 2015 2:28 PM
EMBARC is contributing to a €50 million

Latest Research
Secreted mucins and airway bacterial colonization in non-CF bronchiectasis.

Non-cystic fibrosis bronchiectasis: clinical presentation, diagnosis and treatment, illustrated by data from a Dutch Teaching Hospital.

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

Follow EMBARC on Facebook!
Embarc Database CRF Case J2071

Basic case information Complete
Co-morbidities - Demographics and Background Complete
Bronchiectasis background information Draft
Aetiology and laboratory testing Draft
Microbiology Draft
Radiology Draft
Respiratory Treatments Draft
Additional information Draft
Registry study design

- Prospective observational study
- Patient consent and enrolment as baseline
- Follow-up annually for up to 5 years

Support
- Central administrative office/help desk
- Project management
- Support for statistics and dissemination
- Compensation to sites for enrolment

Baseline data collection → Follow-up form → Follow-up form

Recruitment started February 2015
Participants from 40 countries

TARGET:
• 1000 patients by April 2016
• 10,000 patients by March 2020

232 registered centres
The first results of the EMBARC Bronchiectasis registry
Results at 23/9/15

1283 patients enrolled

Demographics
57% female
Average age= 61 years
Most common aetiology-
post-infective= 35%
Never smoked =60.3%
Ex smoker= 28.7%
Disease impact- exacerbations

Outpatient exacerbations

Severe exacerbations

Nb of exacerbations breakdown

Nb of hospital admissions breakdown

29.9%
16%
21.3%
13.1%
7.1%
23.4%
9.3%
62.2%
Bronchiectasis severity index

Bronchiectasis Severity Index
Predicting Mortality and Exacerbation Rates in Non-CF Bronchiectasis

Online Calculation Tool
Enter your patient's information below to calculate the Bronchiectasis Severity Index.

Age
< 60
BMI
< 18.5
% FEV1 Predicted
> 80%

Previous Hospital Admission
No
has the patient been hospitalised with a severe exacerbation in the past 2 years?
Number of exacerbations in previous year
0
MRC Breathlessness Score
1 - 3
4 - 5
6 - 8
9 - 11
MRC Breathlessness Score
1 - Not troubled by breathlessness except on strenuous exercise
2 - Short of breath when hurrying or walking up a slight incline.
3 - Walks slower than companions on level ground because of breathlessness, or has to stop for breath when walking at own pace
4 - Stops due to breathlessness after walking 100m
5 - Housebound due to breathlessness, or breathlessness on dressing or undressing.

Pseudomonas Colonisation
No
Chronic colonization is defined by the isolation of pseudomonas aeruginosa in sputum culture in 2 or more occasions, at least 3 months apart in a 1 year period

BSI class
Mild
Moderate
Severe
% of patients
0 10 20 30 40

How are patients with bronchiectasis treated in Europe?
The image contains a flowchart explaining the treatment of respiratory conditions associated with bacterial colonisation and airway inflammation. The key points include:

**Bacterial colonisation**
- Drugs: Tobramycin, Amikacin, Aztreonam, Specific anti-pseudomonals, Colistin, Gentamicin, Ciprofloxacin, Macrolides

**Goals of treatment**
- Reduce exacerbations
- Improve quality of life
- Reduce symptoms
- Improve lung function
- Prevent hospital admissions/mortality

**Impaired mucociliary clearance**
- Inhaled mannitol
- Hypertonic saline
- rDNase
- N-acetylcysteine
- Physiotherapy and devices

**Airway inflammation**
- CXCR2 antagonists
- Elastase inhibitors
- PDE4 inhibitors
- Inhaled corticosteroids
- Macrolides

The flowchart illustrates the relationship between bacterial colonisation and impaired mucociliary clearance, as well as airway inflammation, and the associated treatment strategies and goals of treatment.
Inhaled and mucoactive therapies

Bronchodilators/anti-inflammatory agents:
- Inhaled corticosteroids
- Long acting bronchodilators
- Beta-agonists
- Anti-cholinergics
- Mucolytics
- Theophylline

Airway clearance:
- Hypertonic saline
- DNAse
- Nebulised normal saline
- Physiotherapy only

% of cohort
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 for *P. aeruginosa* and non-tuberculous *Mycobacteria*

**Key**

<table>
<thead>
<tr>
<th>Airway clearance techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term Antibiotic therapy</td>
</tr>
<tr>
<td>Anti-inflammatory therapy</td>
</tr>
<tr>
<td>Therapies In advanced disease</td>
</tr>
</tbody>
</table>

**Therapies In advanced disease**

- Long term oxygen therapy, Lung transplantation, Surgery,
- Inhaled corticosteroids in selected patients
- Macrolides for patients with frequent exacerbations*
  - Inhaled antibiotics particular with *P. aeruginosa* colonisation
- Regular physiotherapy +/- adjuncts (devices/hyperosmolar agents)

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

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

**Moderate severity or persistent symptoms despite standard care**

- Daily physiotherapy

**Mild severity**

Chalmers et al, ERJ 2015
Mild severity

Moderate severity or persistent symptoms despite standard care

Severe bronchiectasis or persistent symptoms despite standard care

Exacerbations per year

BSI score

Mild

Moderate

Severe
Pseudomonas aeruginosa is a key pathogen

**TABLE 3**
Multivariate Cox proportional hazard stepwise analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RR (95% CI)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.10 (1.06–1.15)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>PSA</td>
<td>3.61 (1.35–9.62)</td>
<td>0.010</td>
</tr>
<tr>
<td>Male sex</td>
<td>3.42 (1.34–8.77)</td>
<td>0.010</td>
</tr>
<tr>
<td>LF criteria % pred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV/TLC</td>
<td>1.03 (1.01–1.04)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>TLC</td>
<td>0.95 (0.93–0.98)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Kco</td>
<td>0.96 (0.94–0.98)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Health-related quality of life questionnaire scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGRQ activities</td>
<td>1.05 (1.02–1.08)</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Comprehensive analysis of *P. aeruginosa* impact

Data from 4 published/unpublished cohorts in the European registry project

Systematic review of all published BE data

EMBARC
The European Bronchiectasis Registry
- Mortality increased by 3x
- Hospital admissions 7 x increased risk
- Average of 1 additional exacerbation per patient per year
- 15% lower FEV1 % predicted
- 18.2 points difference on the SGRQ quality of life score

**Table:**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Pseudomonas Events</th>
<th>Pseudomonas Total</th>
<th>Non-Pseudomonas Events</th>
<th>Non-Pseudomonas Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allbert 2014</td>
<td>3</td>
<td>39</td>
<td>0</td>
<td>182</td>
<td>1.7%</td>
<td>31.18 [1.58, 616.55]</td>
</tr>
<tr>
<td>Chalmers 2014</td>
<td>15</td>
<td>70</td>
<td>47</td>
<td>538</td>
<td>17.9%</td>
<td>2.85 [1.50, 5.43]</td>
</tr>
<tr>
<td>Chalmers 2015</td>
<td>6</td>
<td>44</td>
<td>17</td>
<td>242</td>
<td>11.0%</td>
<td>2.09 [0.77, 5.64]</td>
</tr>
<tr>
<td>Goeminne 2014</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>225</td>
<td>11.0%</td>
<td>10.25 [3.81, 27.57]</td>
</tr>
<tr>
<td>Lockinger 2009</td>
<td>8</td>
<td>20</td>
<td>19</td>
<td>71</td>
<td>10.3%</td>
<td>1.82 [0.65, 5.15]</td>
</tr>
<tr>
<td>Martinez-Garcia 2014</td>
<td>38</td>
<td>126</td>
<td>41</td>
<td>271</td>
<td>21.8%</td>
<td>2.42 [1.46, 4.01]</td>
</tr>
<tr>
<td>McDonnell 2014</td>
<td>9</td>
<td>47</td>
<td>13</td>
<td>109</td>
<td>12.0%</td>
<td>1.73 [0.60, 4.90]</td>
</tr>
<tr>
<td>McDonnell 2015</td>
<td>13</td>
<td>34</td>
<td>27</td>
<td>179</td>
<td>14.3%</td>
<td>3.46 [1.55, 7.73]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>400</td>
<td><strong>1705</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1000</strong></td>
<td><strong>2.05 [1.98, 4.40]</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect (PA vs non-PA):**

- Test statistic: Z = 5.29 (P < 0.00001)
- Heterogeneity: Tau² = 0.13, Chi² = 11.72, df = 7 (P = 0.11), I² = 40%
Treatment of *P. aeruginosa*

- 290 patients reported at least one isolation of *P. aeruginosa*
- 66% had at least one attempt at eradication
- Successful in 62% (defined as PA clear for at least 2 years)
How is this impacted by COPD?

N=3636
Bronchiectasis
20.8% associated with more exacerbations, worse FEV₁

Single centre studies
- 50-60% of patients with moderate to severe COPD
- More bacterial colonisation
- More P. aeruginosa
- Independent predictor of death

N=2164
Bronchiectasis
5% GOLD III, 7% GOLD IV

Stewart et al, AJRCCM 2012
Agusti et al, Respir Res 2012
Martinez et al AJRCCM 2013
Getheral et al COPD 2014
How is this impacted by COPD?

8.1% reported to have COPD
COPD

Non-smokers with airflow obstruction

Smokers/ex smokers with BE

Two or more conditions co-existing e.g RA/bronchiectasis and COPD

Non-smokers with airflow obstruction
Evidence gap

• Inhaled corticosteroids

• Recombinant DNAse

• Bronchodilators
Largest trial= 43 patients in each arm. Small improvement in sputum volume. No improvement in exacerbations or lung function.

No clinical benefits in long term and in placebo controlled studies.

Limited data (6 trials, 303 patients)

*Should be limited to patients with overlapping COPD and asthma and not used routinely in bronchiectasis*
349 patients randomized (173 DNAse, 176 placebo) 
30% vs 19% $P. aeruginosa$ colonisation

**Results**

Reduced FEV1 with DNAse (-3.6% vs --1.7%, p<0.05)

Increase in exacerbations RR 1.35 (1.01-1.79)

British Thoracic Society Guidelines 2010- 
Grade A recommendation against DNAs
Inhaled bronchodilators

Long-acting beta2-agonists for bronchiectasis (Review)
Sheikh A, Nolan D, Greenstone M

Anticholinergic therapy for bronchiectasis (Review)
Lasserson TJ, Holt K, Evans DJ, Milan SJ, Greenstone M

No valid randomized controlled trials identified
Working towards better evidence

• Bronchiectasis trials are challenging
• Recruitment
• Feasibility
• Endpoints

How can EMBARC help with trials?

• Feasibility- identification of patients and sites

• End-point validation

• Obtain funding from EU and national sources

• Patient input into trials through the ELF patient advisory group

• Identification of research priorities

• Standardisation of procedures and end-points.

• Identification of subgroups and phenotypes
EMBARC promotes awareness and clinical excellence in bronchiectasis care through educational events, courses and online resources.

EMBARC is a pan-European network committed to promoting clinical research and education in bronchiectasis, through sharing of protocols, research idea 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
Call for participation- the Bronchiectasis research roadmap
Jul 9 2014 1:03 PM
The European Bronchiectasis Network (EMBARC) seeks to promote clinical research in bronchiectasis and to build research capacity in Europe. A key task in this will be identifying the areas of ...

Latest Research
Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial.

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

Follow EMBARC on Facebook!
Data access

Sites have unrestricted access to their own data for analysis.

Analysis to the full dataset is open to anyone – apply online at www.bronchiectasis.eu

Applications to use the data are screened by the registry scientific committee

Members

• Anthony De Soyza (UK)
• Felix Ringshausen (Germany)
• Stefano Aliberti (Italy)
• Charlie Haworth (UK)
• Pieter Goeminne (Belgium)
• Marlene Murris (France)
• Montserrat Vendrell (Spain)
• Wim Boersma (Netherlands)
Why bronchiectasis research?

- Common
- Disabling
- Neglected
- Tractable
Summary

- The first data from the European Bronchiectasis registry suggest *P. aeruginosa* and *H. influenzae* are the most common pathogens.

- The treatment burden in *P. aeruginosa* infection is high and prognosis is poor, suggesting a key unmet need.

- The most frequently used therapies are inhaled corticosteroids and bronchodilators, for which we lack robust evidence.

- The majority of bronchiectasis patients, therefore, are managed with therapies for which there is no evidence.
The future

• Recruit 10,000 patients from across Europe with high quality data and consistent follow-up

• Disseminate and publish epidemiological data that can increase knowledge of bronchiectasis and lead to improvements in care

• Make a registry that is sustainable beyond the life of the project

• Inform high quality randomized controlled trials, providing the evidence base for current and future therapies.
Acknowledgements

Executive group
Eva Polverino
Stefano Aliberti

iABC co-ordinator
Stuart Elborn

Steering committee
Francesco Blasi
Diana Bilton
Wim Boerma
Anthony De Soyza
Katerina Dimakou
Michael Loebinger
Charlie Haworth
Adam Hill
Rosario Menendez
Marlene Murris
Felix Ringshausen
Antoni Torres
Montserrat Vendrell
Tobias Welte
Robert Wilson

ELF
Sarah Masefield
Pippa Powell
Patient advisory grp.

Advisory group
Tim Aksamit
Anne O’Donnell
Charles Feldman
Oscar Rizzo
Lucy Morgan

National leads
Ian Clifton
Michal Schteinberg
Victor Botnaru
Charlotte Ulrik
Menno van Eerden
Gernot Rohde
Branislava Milenkovic
Perluigi Paggiaro

Study co-ordinator
Megan Crichton
Come and visit us in the World Village (desk 1)