Care of the Bronchiectasis Patient: Current State

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  • Grifols
  • Aradigm
Bronchiectasis

- Characterized **pathologically** by airway inflammation and permanent bronchial dilatation, and **clinically** by productive cough
- Heterogeneous entity with multiple etiologies
- Prevalence is increasing
- Clinical course punctuated by exacerbations
- Associated with notable QOL impairment, and significant morbidity and mortality

- Seitz et al. *Chest* 2012; 142:432-439
- Chalmers et al. *AJRCCM* 2013; 189.
Bronchiectasis: Impact on Quality of Life

SGRQ total score

Goals of Treatment

- Control symptoms - cough, sputum characteristics
- Maintain lung function
- Improve quality of life
- Reduce exacerbations
- Reduce mortality
- Reduce cost of care
Challenges

• **Pulmonary function**  - FEV$_1$ generally does not improve with therapy
  - Aim is to stabilize lung function

• **Quality of life**  - No fully validated method of assessment

• **Exacerbations**  - Difficult to define
  - Some progress has been made

• **Mortality**  - Difficult to study in short term trials
Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research  

Eur Resp J; 49, 2017

Adam T. Hill¹,2,², Charles S. Haworth²,², Stefano Aliberti ³, Alan Barker⁴, Francesco Blasi³, Wim Boersma⁵, James D. Chalmers⁶, Anthony De Soyza⁷, Katerina Dimakou⁸, J. Stuart Elborn⁹, Charles Feldman¹⁰, Patrick Flume¹¹, Pieter C. Goeminne¹²,¹³, Michael R. Loebinger¹⁴, Rosario Menendez¹⁵, Lucy Morgan¹⁶, Marlene Murriss¹⁷, Eva Polverino¹⁸, Alexandra Quittner¹⁹, Felix C. Ringhsausen²⁰, Gregory Tino²¹, Antoni Torres²², Montserrat Vendrell²², Tobias Welte²², Rob Wilson¹⁴, Conroy Wong²³, Anne O’Donnell²⁴,²⁷ and Timothy Aksamit²⁵,²⁷ for the EMBARC/BRR definitions working group

Definition of a bronchiectasis pulmonary exacerbation for clinical trials

A person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h:

1) Cough
2) Sputum volume and/or consistency
3) Sputum purulence
4) Breathlessness and/or exercise tolerance
5) Fatigue and/or malaise
6) Haemoptysis

AND a clinician determines that a change in bronchiectasis treatment is required#
Current State

✓ There are no approved therapies

✓ Available guidelines regarding management are based on low quality of evidence

✓ Clinical trials for many of the pillars of treatment are lacking
77 y.o. African-American man:

☑ Diagnosed with bronchiectasis at age 12 after a pneumonia at 18 months of age
Clinical Course

✓ Did well for many years

✓ Managed with rotating antibiotics + airway clearance
Clinical Course

- Has quinolone-resistant chronic *Pseudomonas aeruginosa* infection
- 3-4 exacerbations per year often requiring IV antibiotics
- Daily sputum production - 40ml/day
- Perceives QOL as declining
Bronchiectasis: Treatment

Antibiotics
- Systemic
- Inhaled

Airway clearance

Treatment of underlying conditions

Surgery

- Macrolides
- Steroids

Neutrophil Inflammation (Proteases)

Airway Destruction and Distortion (Bronchiectasis)

Bacterial Colonization + Infection

Abnormal Mucus Clearance

Am J Resp Crit Care Med 2013;188:647-656
1826 patients with physician-established diagnosis of bronchiectasis enrolled between 2008 and 2014

- Airway clearance - 56%
- Antibiotics only for exacerbation - 41%
- Suppressive antibiotics - 39%: 10% aerosol, 7% rotating oral regimen
- Inhaled bronchodilators - 61%
- Inhaled steroids - 39%, systemic steroids - 13%
Airway Clearance Therapy
✓ Techniques designed to enhance mucociliary clearance
  • Considered mainstay of management
  • Little data
    Cochrane Review 2015

✓ Number of modalities in use:
  • Mechanical methods
  • Pharmacologic
Vibratory PEP Devices

PEP valve use most common in US Bronchiectasis Registry
High Frequency Chest Wall Oscillation
Airway Clearance: Pharmacologic agents

✓ Hyperosmolar agents
  • Inhaled mannitol
    ▪ Phase III trial: no significant reduction in exacerbation rates
  • Hypertonic saline
    ▪ Improved sputum rheology, SGRQ, annual antibiotic usage

• Daviskas et al. Respirology 2005: 10.
• Bilton, Tino et al. Thorax 2014; 69.
• Cochrane Database Review, 2009
• Tarrant et al. Respirology, 2017; 22.
Pharmacologic agents

✓ Bronchodilators
  - No long-term randomized controlled trial data to suggest efficacy

✓ Mucolytics
  - rh DNase not effective and potentially deleterious in non-CF patients

Airway Clearance Therapies

✓ Target:
  • Symptomatic patients: cough, sputum production
  • Difficulty expectorating sputum
  • Impaired quality of life
  • Frequent acute exacerbations

ERS Guideline. Polverino et al. *ERJ* 2017; 50
Weak recommendation

Recommend a modality that will maximize patient adherence
Systemic Antimicrobial Therapy for Exacerbations
Sputum analysis is critical

### Table 1
Bacteriology of bronchiectasis

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Nicotra et al, 1995 (n = 123)</th>
<th>Pasteur et al, 2000 (n = 150)</th>
<th>King et al, 2007 (n = 89)</th>
<th>Li et al, 2005 (n = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H influenza</td>
<td>30</td>
<td>35</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td>P aeruginosa</td>
<td>31</td>
<td>31</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>M catarrhalis</td>
<td>2</td>
<td>20</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>S pneumoniae</td>
<td>11</td>
<td>13</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>S aureus</td>
<td>7</td>
<td>14</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No organism</td>
<td>Not specified</td>
<td>23</td>
<td>21</td>
<td>Not specified</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>17</td>
<td>0</td>
<td>2</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

#### US BRR:
- **P. aeruginosa** - 33%
- **S. aureus** - 11.3%

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Antimicrobial Therapy

General Principles:

✓ *Pseudomonas aeruginosa* and *S. aureus* infections can be especially challenging

✓ Adjust/narrow antibiotic if specific pathogen isolated

✓ Optimal duration unknown:
  - 14 day course
  - Longer courses as dictated by clinical response

Inhaled Antibiotic Therapy
Bacterial Load: Impact on Pulmonary Exacerbations

☑ High bacterial load (CFUs) linked to:
  • Risk of future exacerbations
  • Future hospitalizations for exacerbations
  • Markers of lung inflammation

“Frequent Exacerbator” Phenotype

✓ 2572 patients from 10 sites in Europe and Israel

✓ About 40% of patients had 0-1 exacerbations, 37% had 3 or more

✓ Prior and frequent exacerbations were strongest predictor of future exacerbations

Chalmers et al. AJRCCM 2018; Epub.
“Frequent Exacerbator” Phenotype

✓ Other independent predictors:
  • *H. flu* and *P. aeruginosa* infection
  • Low FEV$_1$
  • Radiological severity
  • Co-existing COPD

✓ Frequent exacerbators also had worse QOL, high disease severity and increased mortality

Chalmers et al. *AJRCCM* 2018; *Epub.*
Impact of *Pseudomonas* Infection

7 × Higher Risk of Hospitalization

- P. aeruginosa: 88.6%
- Other GNR: 21.2%
- S. aureus: 0%
- M. catarrhalis: 5%
- H. influenzae: 10%
- S. pneumoniae: 15%
- Not colonized: 20%  

3 × Higher Mortality

- P. aeruginosa: 6%
- S. aureus: 12%
- M. catarrhalis: 18%
- H. influenzae: 24%
- S. pneumoniae: 30%
- Not colonized: 36%

Inhaled antibiotics have been standard of care in CF patients with *P. aeruginosa* infection

- **Tobramycin:** Ramsey et al. *NEJM*, 1999; 340
- **Aztreonam:** McCoy et al. *AJRCCM*, 2008; 178
Inhaled Antibiotics

Pros:

- High concentration in the airway
- Reduced systemic absorption
- Reduced systemic toxicity

Cons:

- Airway side effects
- Possible emergence of resistance
### US Bronchiectasis Registry

Cohort of patients with 2-year follow-up data (N=1049)

*information captured for events during the past 2 years


<table>
<thead>
<tr>
<th>Patients with ≥2 exacerbations/year (n=198 (18.9%))</th>
<th>Patients with &lt;2 exacerbations/year (n=851 (81.1%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> sputum isolation (% of patients)</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>35%</td>
</tr>
<tr>
<td><strong>Inhaled antibiotic (% of patients)</strong></td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>13%</td>
</tr>
<tr>
<td>History of hospitalization (% of patients)</td>
<td>29.7%</td>
</tr>
<tr>
<td>for exacerbation (% of patients)</td>
<td>17.2%</td>
</tr>
<tr>
<td></td>
<td>79.2%</td>
</tr>
<tr>
<td></td>
<td>56.0%</td>
</tr>
<tr>
<td><strong>During 2-year follow-up period:</strong></td>
<td></td>
</tr>
<tr>
<td>Average exacerbations (in 2 years) +/- SD</td>
<td>2.58 +/-0.97</td>
</tr>
<tr>
<td></td>
<td>0.32 +/-0.47</td>
</tr>
<tr>
<td>Hospital admissions per year (mean)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
</tr>
</tbody>
</table>
Inhaled Antibiotics: Guidelines

✓ SEPAR: 2008
  • Chronic nebulized antibiotics when poor response +/- adverse effect of oral antibiotics, chronic PA infection

✓ BTS: 2010
  • Long term nebulized antibiotics should be considered for ≥3 AE, fewer but severe exacerbations, PA colonization

✓ TSANZ: 2015
  • Long term nebulized antibiotics should not be prescribed routinely; consider trial for frequent exacerbations +/- PA infection

• Vendrell et al. Arch Bronco 2008; 44.
• TSANZ Guidelines, MJA 2015.
Inhaled Antibiotics: Clinical Trials

✓ Tobramycin*
✓ Gentamicin
✓ Colistin*
✓ Aztreonam for inhalation solution
✓ Levofloxacin
✓ Dry powder ciprofloxacin (RESPIRE)*
✓ Liposomal ciprofloxacin (ORBIT)*
Inhaled Tobramycin

✓ Profound microbiologic impact on *P. aeruginosa*; no emergence of resistant organisms
✓ Improvement in symptoms and QOL suggested
✓ Efficacy as either maintenance therapy or treatment of acute exacerbations has not yet been established
✓ Adverse effects (cough, dyspnea, bronchospasm) well described

- Barker et al. *AJRCCM*; 162: 2000
- Scheinberg et al. *Chest*; 127: 2005
- Bilton et al. *Chest*; 130: 2006
Inhaled Colistin

✓ 144 patients with *Pseudomonas* infection: inhaled colistin vs placebo daily for up to 6 months
✓ Enrolled within 21 days of an acute exacerbation

✓ **Primary endpoint**: time to exacerbation
✓ **Secondary endpoints**: time to exacerbation based on adherence (I-neb), bacterial density, SQRG total score, safety parameters

Haworth et al. *AJRCCM* 2014; 189: 975.
Inhaled Colistin

✓ Primary exacerbation endpoint not met in ITT group
  • Significant reduction in *Pseudomonas* CFU after 4 and 12 weeks
  • Improvement in SGRQ after 26 weeks (10.5 units)
  • Well-tolerated; no emergence of colistin resistance

✓ In adherent patients (>80%)
  • Median time to exacerbation: 168 days in colistin group versus 103 days in placebo (p = 0.038)
  • Exacerbation rate: 50% in colistin group, 72% in placebo

Haworth et al. *AJRCCM* 2014; 189: 975.
Phase 3, PRDB trials: twice-daily ciprofloxacin DPI - 14 or 28 days on/off for 48 weeks

≥ 2 exacerbations in preceding 12 months; stringently defined

7 pre-specified pathogens

FEV$_1$: 30-90% predicted

Primary endpoints:

- Time to first exacerbation
- Number of exacerbation events
<table>
<thead>
<tr>
<th></th>
<th>Respire - 1 (n = 416)</th>
<th>Respire - 2 (n = 521)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first exacerbation</td>
<td>✓ 14 day on/off  ((336 \text{ vs } 186 \text{ days}))</td>
<td>NS</td>
</tr>
<tr>
<td>Frequency of exacerbations</td>
<td>✓ 14 day on/off ((39% \text{ reduction}))</td>
<td>NS</td>
</tr>
</tbody>
</table>
Phase 3, identical PRDB trials - once daily liposomal ciprofloxacin; 48 weeks, 6 cycles - 28 days on/off, then a 28-day open-label extension

Chronic *P. aeruginosa* infection with at least 2 exacerbations in preceding 12 months

Exacerbations and severity defined in protocol

**Primary endpoint**: increase in median time to first pulmonary exacerbation (PE)

**Secondary endpoint**: frequency of exacerbations over 48-week treatment period
### Haworth et al. ATS, 2017.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ORBIT-3 (n = 304)</th>
<th>ORBIT-4 (n = 278)</th>
<th>POOLED ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first exacerbation (all severities)</td>
<td>NS</td>
<td>✓</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(230 vs 136 days)</td>
<td></td>
</tr>
<tr>
<td>Frequency of exacerbations</td>
<td>NS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(37% reduction)</td>
<td>(33% reduction)</td>
</tr>
<tr>
<td>Median time to first PE requiring treatment with antibiotics</td>
<td>NS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Reduced sputum density of PA without attenuation of antibiotic activity during each treatment cycle over the 48-week trial</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Inhaled Antibiotics: Summary

✓ Clear microbiologic impact
✓ Clinical efficacy has not been proven conclusively in clinical trials thus far
✓ None currently approved by regulatory agencies
✓ Emergence of resistant pathogens has not been observed

✓ Target population:
  • Chronic GNR infection
  • Frequent exacerbations - >3/year
  • Other therapy optimized
✓ ?daily versus on/off regimen
✓ Relationship to chronic macrolides has not been established
Chronic Macrolide Therapy
Macrolides & Bronchiectasis

✓ Scientific plausibility: myriad anti-inflammatory and immunomodulatory properties
  • Inhibit mucus hypersecretion
  • Reduce IL-8 and neutrophil elastase
  • Inhibit neutrophil adhesion to epithelial cells
  • Inhibit biofilm formation
  • Inhibit production of reactive oxygen species from neutrophils

✓ Precedent for their use in other airways diseases: CF, DPB, post-transplant OB, COPD

EMBRACE  
(Wong et al. Lancet 2012: 380)
- 141 patients
- At least 1 exacerbation in past year
- Azithromycin 500mg thrice weekly for 6 months
- Co-primary endpoints:
  - Event-based exacerbation frequency
  - FEV1
  - SGRQ

BAT  
(Altenburg et al. JAMA 309, 2013)
- 83 patients
- At least 3 exacerbations in past year
- Azithromycin thrice weekly for 12 months
- Primary endpoint:
  - # of infectious exacerbations

BLESS  
(Serisier et al. JAMA 309, 2013)
- 107 patients
- At least 2 exacerbations in past year
- Erythromycin 400mg twice daily for 48 weeks
- Primary endpoint:
  - Mean rate of exacerbations/year

All three studies reported decrement in exacerbations
Macrolides & Bronchiectasis: Concerns

- Bacterial antibiotic resistance
- NTM macrolide resistance
- Cardiac risk
- Other adverse effects
  - GI tract
  - Ototoxicity
Macrolides: Target Patients

- Frequent exacerbations (> 2-3 per year)
  - No subgroup data; role in other settings?
- No significant underlying cardiac disease and normal EKG/QTc
  - Avoid in patients with known or strongly suspected NTM infection.
  - Duration of therapy has not been established
Long-term Antibiotic Treatment


Conditional recommendations
Not Recommended

✓ Inhaled corticosteroids
  • No convincing data to support routine use
  • Possible increased risk of NTM infection

• Polverino et al . ERS Guideline. ERJ 2017; 50.
Not Recommended

✓ Chronic systemic antibiotics
  • No evidence-based data to support the use of systemic, non-macrolide, suppressive/maintenance therapy
    • Wurzel et al. *Cochrane Review* 2011
    • TSANZ Guidelines, *MJA* 2015

✓ Chronic systemic corticosteroids
Surgery

An option for:

- Localized disease, frequent exacerbations despite medical therapy
- As an adjunct to medical therapy for NTM infection
- Refractory, massive hemoptysis

Acceptable morbidity and mortality reported

Weak recommendation
Supportive Measures

- Specific therapy when appropriate
- Short-course systemic steroids for some exacerbations
- Exercise /pulmonary rehabilitation
- Supplemental oxygen
- Nutrition evaluation
- Lung transplantation
Proposed Treatment Algorithm

**BRONCHIECTASIS**
Confirmed by HRCT

Clinical History and Laboratory Evaluation to Identify Etiology

- Treat Underlying Cause eg.,
  - AAT Replacement
  - IgG Replacement

- Initiate Airway Clearance
  1. Nebulized Agent
  2. Chest Physiotherapy
  3. Postural Positioning

- Sputum Culture

- Exercise Program or Pulmonary Rehabilitation

- Consider Macrolide Therapy if Patient Experiences Frequent Exacerbations

- Normal Flora
  - Observe

- Non-Pseudomonas
  - Antibiotic targeted toward specific bacteria and local sensitivity patterns*

- Pseudomonas
  - Treat for acute exacerbation
  - Suppressive antibiotics (nebulized)

- Nontuberculous mycobacteria (NTM)
  - Monitor future cultures for NTM
  - If > 2 positive cultures consider treatment according to guidelines
  - Avoid macrolide monotherapy

*McShane et al. AJRCCM. 188 (6). 647–656. 2013
“The sobering reality is that patients with bronchiectasis suffer significant morbidity and mortality, and yet can be offered few proven, effective therapies.

Ultimately we need better characterization of our patients, more high-quality clinical trials to further define this entity, and, most crucially, better therapies - antimicrobial or otherwise.

The process of adoption of this orphan disease by clinicians and researchers needs be accelerated.”
Opportunities

- Better characterize the epidemiology and natural history
- Strengthen support for and expand patient registries
- Rethink endpoints for clinical trials and address regulatory challenges
- Identify new targets for treatment