Bronchiectasis Treatment

*Antibiotics*

Charles Haworth
• Educational talks and / or consultancy for:
  – Aradigm, Chiesi, Gilead, Insmed, Novartis, Horizon, TEVA, Zambon, Vertex.
Development of bronchiectasis - vicious cycle

Problems with muco-ciliary clearance

Problems with Immune response

Inflammatory Insult
Problems with muco-ciliary clearance

Problems with Immune response

Inflammatory Insult

Bronchial wall inflammation

Development of bronchiectasis - vicious cycle
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Problems with muco-ciliary clearance

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Inflammatory
Insult

Bronchial wall inflammation

Disordered mucociliary clearance / obstruction
Development of bronchiectasis - vicious cycle

Problems with muco-ciliary clearance

Problems with Immune response

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Bronchial wall inflammation

Chronic / recurrent infection

Disordered mucociliary clearance / obstruction
Development of bronchiectasis - vicious cycle

Problems with muco-ciliary clearance
- Bronchial wall inflammation
- Bronchial wall damage

Problems with Immune response
- Inflammatory Insult
- Disordered mucociliary clearance / obstruction

Chronic / recurrent infection
Development of bronchiectasis - vicious cycle

Problems with muco-ciliary clearance

Problems with Immune response

Inflammatory Insult

[Diagram showing the development of bronchiectasis with a vicious cycle involving problems with muco-ciliary clearance and immune response.]
Development of bronchiectasis - vicious cycle

Bacterial load (CFU/ml)

Chalmers AJRCCM 2012
Common bacteria in people with bronchiectasis

**NTM**
Current: 1.7%
Previous: 3.1%
76% received treatment

**Pseudomonas aeruginosa**
Current: 18.5%
Previous: 10.2%
69% received eradication treatment

22.5% of patients did not provide sputum samples (similar to previous work)
Antibiotic use in bronchiectasis

- Exacerbation treatment
- Chronic suppression
- Eradication
Antibiotic use in bronchiectasis

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Exacerbations

• Essential to distinguish between steady state and exacerbation

• Acute exacerbations
  – Deterioration in symptoms over days
    • ↑ cough frequency
    • ↑ sputum volume / purulence / viscosity
    • ↑ chest tightness / wheeze / breathlessness

• Chest ache, streaky haemoptysis, temperatures
Exacerbation Treatment

- Important management principals:
  - Higher doses of an antibiotic are often more effective than lower doses of the same antibiotic

Hill SL Thorax 1986
• Important management principals:

- Expert consensus is that bronchiectasis exacerbations should be treated with 14 days of antibiotics.
Antibiotic treatment choices should be guided by previous sputum culture results.
Exacerbation Treatment

- **Oral antibiotics:**
  - *H. influenzae, S. pneumoniae*
    - Amoxicillin or Doxycycline
  - β-lactamase producing strains
    - Co-Amoxiclav
  - *P. aeruginosa*
    - Ciprofloxacin
  - MRSA
    - Rifampicin and Fucidic acid
Exacerbation Treatment

• Intravenous antibiotics:
  – *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*
    • Piperacillin/Tazobactam
    • Cefuroxime
    • Ertapenem
• Intravenous antibiotics for *P. aeruginosa*:

- Dual therapy
  - Reduce development of resistance
  - Potential for synergy
- Synergy with β-lactams & aminoglycosides in CF
- Individuals with chronic *P. aeruginosa*
- IV azlocillin + tobramycin or placebo
- Initial outcomes comparable...

- *P. aeruginosa* density decreased
- Time to next hospitalisation increased
Exacerbation Treatment

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Smith AL J Pediatr 1999
Intravenous antibiotics for *P. aeruginosa*:

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Exacerbation Treatment

• **Intravenous antibiotics for* P. aeruginosa:***

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Smith AL J Pediatr 1999
Antibiotic use in Bronchiectasis

- Exacerbation treatment
- Chronic suppression
- Eradication
• **Commonly prescribed to:**
  – Improve symptoms
  – Reduce exacerbation frequency
  – Optimise quality of life
Concerns regarding:

– Antibiotic resistance
– Creating a niche for other bacteria / fungi
– Antibiotic related diarrhoea (*C. difficile*)
– Toxicity
Chronic bacterial suppression – macrolides

141 patients
≥ 1 exacerbation
Azith 500mg MWF 6/12 then 6/12 no Rx

83 patients
≥ 3 exacerbation
Azith 250mg qid 12/12, 90/7 run out

117 patients
≥ 2 exacerbation
Erythro 400mg bid 11/12, 1/12 wash out

Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial
Conroy, Wong, Letaijaron, Noel Karakos, Tom Eaton, Cecilia Tong, Hans Hockey, David Milne, Wendy Ferguson, Christine Tuffery, Paul Sexton, Leanne Steney, Tami Ashton

Effect of Azithromycin Maintenance Treatment on Infectious Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis
The BAT Randomized Controlled Trial

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

Wong Lancet 2012
Altenberg JAMA 2013
Serisier JAMA 2013
• MRC trial 1957

n=122

Oxytetracycline vs Penicillin vs Placebo

• 2 days / week for one year

↓ sputum volume / purulence

↓ time off work / days confined to bed
Chronic bacterial suppression – inhaled antibiotics

• **Benefits**
  – Very high drug concentrations within the airways
  – Reduced systemic adverse effects
  – Reduced risk of *C. difficile*
  – Easy to administer
Chronic bacterial suppression – inhaled antibiotics

- Predominantly for patients chronically infected with *P. aeruginosa*
Chronic bacterial suppression – inhaled antibiotics

- Impact of *Pseudomonas*
  - Increased exacerbation frequency
  - Increased hospitalisation
  - Worse quality of life
  - Faster rate of FEV$_1$ decline
  - More severe disease
  - Increased mortality

Evans SA ERJ 1996
Wilson CB ERJ 1997
Miszkiel KA Thorax 1997
Ho-PL Chest 1998
Martinez-Garcia Chest 2007
Loebinger MR ERJ 2009
Chalmers AJRCCM 2014
Chronic bacterial suppression – inhaled antibiotics

- **Colistin: I-neb**
  
  *(Haworth et al ARJCCM 2014)*
Chronic bacterial suppression – inhaled antibiotics

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<th>Placebo</th>
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<td>Sex, n (%)</td>
<td></td>
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<td>27 (37)</td>
<td>34 (48)</td>
<td>61 (42)</td>
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<td>Female</td>
<td>46 (63)</td>
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Chronic bacterial suppression – inhaled antibiotics

• Colistin: I-neb
  (Haworth et al ARJCCM 2014)

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![Graph showing exacerbation rate and time to exacerbation with Promixin and Placebo groups.]

**Exacerbation Rate (%)**

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<td>0-20</td>
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**Median time to exacerbation (days)**

- Promixin: 168
- Placebo: 103

**p=0.028**

- Gentamicin - ↓bacterial, exacerbations, ↑QoL
  (Murray et al 2011 AJRCCM)
Chronic bacterial suppression – inhaled antibiotics

• Colistin: I-neb
  (Haworth et al ARJCCM 2014)

![Graph showing SGRQ QoL score over time with error bars.]

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Chronic bacterial suppression – inhaled antibiotics

- **Colistin: I-neb**
  
  \[(Haworth et al ARJCCM 2014)\]

- **Nebulized Aztreonam**
  - No change in QoL-B
  - Adverse events ++

\[(Barker et al Lancet Resp Med 2014)\]
Chronic bacterial suppression – inhaled antibiotics

- **Colistin: I-neb**
  
  *(Haworth et al ARJCCM 2014)*

- **Nebulized Aztreonam**
  - No change in QoL-B
  - Adverse events ++
  
  *(Barker et al Lancet Resp Med 2014)*

- **Nebulized Gentamicin**
  - ↓ bacterial load, ↓ exacerbations, improved quality of life
  
  *(Murray et al 2011 AJRCCM)*
Chronic bacterial suppression – inhaled antibiotics

- **Ciprofloxacin Dry Powder Inhaler**
  
  \(\text{(Wilson ERJ 2013)}\)
Chronic bacterial suppression – inhaled antibiotics

- **Ciprofloxacin Dry Powder Inhaler**
  
  *(Wilson ERJ 2013)*

- **Nebulized Ciprofloxacin**
  - Dual Release Liposomal preparation
  
  *(Serisier Thorax2013)*
Current trials of inhaled antibiotics
Chronic bacterial suppression – ERS guidelines

> 3 exacerbations per year

Optimise airway clearance
Treat underlying causes

P. aeruginosa Infection
Non- P. aeruginosa Infection

Long term inhaled antibiotic treatment

Lack of response or intolerance

Inadequate response

Combined oral and inhaled antibiotic treatment

Long term macrolide treatment

Lack of response or intolerance

Long term targeted oral antibiotic

Figure 4. Summary of recommendations for long-term antibiotic treatment.
Antibiotic use in Bronchiectasis

- Exacerbation treatment
- Chronic suppression
- Eradication
Randomised controlled trial
- 35 patients with new growths of *Pseudomonas aeruginosa*

- All patients received:
  - Ceftazidime + Tobramycin for 2 weeks

- Randomised to:
  - Neb TOBI 300mg or Placebo placebo 3 months

*Orriols Respiration 2015*
Pseudomonas aeruginosa eradication

• Free of *P. aeruginosa* after 1 month:
  – TOBI 91%
  – Placebo 77%

• Free of *P. aeruginosa* after 12 months:
  – TOBI 55%  p=0.048
  – Placebo 29%
Summary

• Antibiotic use in bronchiectasis
  – Exacerbation treatment
  – Chronic suppression
  – Eradication
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