BRONCHIECTASIS-
WHERE ARE WE?

Adam Hill
Royal Infirmary and University of Edinburgh
Plan

- Stable State
  - Aetiology
  - Treatable causes
  - Role of bacteria
  - Strategies

- Exacerbations
  - Viruses
  - When to give antibiotics
  - Role of IV antibiotics
What is bronchiectasis?

Symptoms and Pathology

- Permanently inflamed and damaged airways
- Leads to chronic colonisation
- Leads to daily cough + sputum production
- Leads to recurrent chest infections
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Colour</td>
<td>Mucoid</td>
<td>Mucopurulent</td>
<td>Purulent</td>
</tr>
<tr>
<td>24hr Sputum Volume</td>
<td>&lt;5mls</td>
<td>&gt;20mls</td>
<td></td>
</tr>
<tr>
<td>Exacerbation Frequency</td>
<td>&lt;2/yr</td>
<td></td>
<td>&gt;3/yr.</td>
</tr>
<tr>
<td>Exacerbation Severity</td>
<td>Oral Ab</td>
<td>IV Ab Hospital admission</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outpatient Tx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum bacteriology when stable</td>
<td>MNF</td>
<td>MNF/ Pathogens (HI, SPn, MC, SA)</td>
<td>PA, Enteric Gram-, MRSA</td>
</tr>
<tr>
<td>Affected lobes on CT scanning</td>
<td>&lt;3 Lobes</td>
<td></td>
<td>≥3</td>
</tr>
<tr>
<td>Degree of bronchial dilatation</td>
<td>Tubular</td>
<td>Varicose</td>
<td>Cystic</td>
</tr>
</tbody>
</table>
Sputum purulence

% Colonised

- Mucoid: 5%
- Mucopurulent: 43.5%
- Purulent: 86.4%

N=141

ERJ 2009;34:361-4
Case

- 51 female
- Cough, Thick Tenacious Sputum
- 6 exacs/yr
- PMH Asthma
- DH
  Seretide 250 2p bd
  Salbutamol prn
  Montelukast 10mg nocte
  Always well on steroids (6 courses past year)
- SH
  0 Pack Years
- Exam- Nil

Oct 2008
Case

- FEV₁ 2.0L 64% P
- O₂ sats air 98%

- Sputum microbiology
  01/09 MNF MP
  03/09 NTHI MP
  08/09 MNF MP
  12/09 NTHI MP
  03/10 MNF MP

- Eosinophils 1.1 (<0.4)
  IgE 2000 kU/L (<250)
What treatment did I give?

- A] DNase
- B] Omalizumab
- C] Oral steroids
- D] IV antibiotics
<table>
<thead>
<tr>
<th>Ref</th>
<th>N</th>
<th>INF</th>
<th>IMMUNE</th>
<th>CT</th>
<th>ABPA</th>
<th>CF</th>
<th>Ciliary</th>
<th>IBD</th>
<th>Aspiration</th>
<th>Cong</th>
<th>No cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>123</td>
<td>42%</td>
<td>4%</td>
<td></td>
<td></td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>2000</td>
<td>150</td>
<td>29%</td>
<td>8%</td>
<td>3%</td>
<td>7%</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td>4%</td>
<td>1%</td>
<td>53%</td>
</tr>
<tr>
<td>2003</td>
<td>100</td>
<td>33%</td>
<td>1%</td>
<td>6%</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41%</td>
</tr>
</tbody>
</table>

Pasteur et al Am J Respir Crit Care Med 2000; 162: 1277-84
Investigate treatable causes

- Exclude common variable immunodeficiency
- Exclude ABPA
- Exclude cystic fibrosis

Why?

- These all have treatments that differ from standard management

Case

- 61 male
- 6 exacs/yr
- PMH Hiatus Hernia
- DH
  Omeprazole 20mg od
- SH
  0 Pack Years
- Exam- BS in chest
Case

- CXR Hiatus Hernia
- HRCT HH + very mild bilat LL Bx
- FEV<sub>1</sub> 2.9L 88% P
- O<sub>2</sub> sats air 98%
- Sputum microbiology
  - 01/09 MNF MP
  - 03/09 SPn MP
  - 08/09 PA MP
  - 12/09 M Catt MP
  - 03/10 MNF MP

Management?

- A] Erythromycin
- B] Increase PPI
- C] Metoclopramide
- D] Fundoplication
- E] Long term nebulised
Case

- 51 female
- 6 exacs/yr
- PMH Nil
- DH Nil
- SH 0 Pack Years
- Exam- Nil
- CXR RML + Ling changes
- HRCT Nodular Bx RML + Ling
- FEV$_1$ see below
- O$_2$ sats air 98%
- Sputum microbiology
  - 01/09 MNF MP 2.7L
  - 03/09 MNF + MAC MP 2.6L
  - 08/09 MNF + MAC MP 2.6L
  - 12/09 MNF + MAC MP 2.3L
  - 03/10 MNF + MAC MP 2.3L
CT
Indications and Management

- Fibrocavitatory disease
- Nodular Bx with clinical deterioration

- What treatment?
  - A] RE
  - B] RECl
  - C] RECipro
  - D] RHZE
  - D] IV amikacin + IV tigecycline + moxifloxacin + rifampicin
Case

- 72 male
- 7 exacs/yr
- PMH COPD
- DH
  Tiotropium 18mcg od
  Seretide 250 2p bd
  Salbutamol prn
- SH
  60 pack years
  Current- 20cpd
- Exam- COPD
  + bibasal insp. crackles
Case

- CXR COPD
- HRCT Emphysema and bilat LL Bx
- FEV$_1$ 0.6L (28% Predicted)
- O$_2$ sats air 90%

Sputum microbiology:
- 04/09 NTHI  P
- 08/09 NTHI  P
- 12/09 MNF  MP
- 04/10 M Catt  MP

Chronically colonised

Severe COPD
Mild bilateral Bx
Excess Exacerbation History

Management?
Management

- A] Smoking Cessation Alone
- B] Smoking cessation + LT Oral Co-amoxiclav
- C] LT Oral Co-amoxiclav
- D] Smoking cessation and LT Nebulised Tobramycin
Are bacteria important

- Related to severity of bronchiectasis
- MNF Mild disease
- PA, enteric gram-ve, MRSA in severe disease
- Is bacterial load important?
Results - n=385

Median age 67 (IQR 56-74)

42.9% male

Predominantly post-infective/idiopathic bronchiectasis

Pathogenic microorganisms were isolated in 77.9% of patients.

- **H. Influenzae**: 37.4%
- **P. aeruginosa**: 13.2%
- **S. aureus**: 11.9%
- **S. pneumoniae**: 10.6%
- **M. catarrhalis**: 6.5%
- **Others**: 20.4%
Q1- Does bacterial load correlate with markers of airway and systemic inflammation?
Bacterial load drives neutrophil airways inflammation.
Bacterial load correlates with systemic markers of neutrophil recruitment
Q2- What is the clinical relevance?
Q3- Does antibiotic therapy reduce markers of airway inflammation?
## Role of long term oral antibiotics - Randomised trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Duration</th>
<th>Exacerbations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC 1957</td>
<td>122</td>
<td>Oral Penicillin 2G vs. Oral Tetracycline 2G vs. 2G Lactose</td>
<td>1 year 2 days per week</td>
<td>None recorded</td>
<td>↓ days confined to bed ↓ Less days off work</td>
</tr>
<tr>
<td>Currie et al 1990</td>
<td>38</td>
<td>3G bd oral amoxicillin vs. Placebo</td>
<td>32 weeks</td>
<td>24% had PA</td>
<td>↓ severe exacerbations but no effect on frequency</td>
</tr>
<tr>
<td>Tsang et al 1999</td>
<td>21</td>
<td>Oral Erythromycin 500mg BD vs. Placebo</td>
<td>8 weeks</td>
<td>76% PA 14% HI 5% KPn 5% E Coli</td>
<td>No effect</td>
</tr>
<tr>
<td>Lancet 2012 380 660-667</td>
<td>122</td>
<td>Azithromycin Vs. Placebo</td>
<td>6m</td>
<td>30% HI 11% PA 3% MC 3% SA 1% SP</td>
<td>Exacerbations (0.59/patient in Azi Gp. Vs. 1.57/pt in placebo gp) at 6m. (1.58/patient in Azi Gp. Vs. 2.73/pt in placebo gp) at 12m. Median time to exacerbation 239 vs. 85 days</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----</td>
<td>-------------------------</td>
<td>----</td>
<td>---------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>□ Azithromycin 500mg M,W, Fr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□ No change in FEV$_1$ or SGRQ (-5.17 vs. -1.92)</td>
</tr>
<tr>
<td>□ Entry criteria: 1 exac in last 1y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□ Decreased serum WCC and CRP but no effect on sputum differential cell ct.</td>
</tr>
<tr>
<td>□ Three primary endpoints: Exacs, FEV$_1$, SGRQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□ Baseline FEV$_1$ 67% predicted</td>
</tr>
<tr>
<td>□ 3.34-3.93 Exacerbations/year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□</td>
</tr>
</tbody>
</table>
EMBRACE study

- No effect on bacterial clearance
- No bacterial load measured
- 4% developed SPn resistance
- More GI side effects
  - 27% vs. 13%
  - (diarrhoea 18%, nausea or vomiting 13%, epigastric discomfort 7% and constipation 3%)
- No audiometry carried out
### Role of long term nebulised antibiotics-Randomised trials in PA

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Duration</th>
<th>Treatment</th>
<th>Effect on Exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker et al 2000</td>
<td>74</td>
<td>Nebulised Tobramycin 300mg BD vs. Placebo</td>
<td>4 weeks</td>
<td>100% PA</td>
<td>No Effect</td>
</tr>
</tbody>
</table>
| Drobnic et al 2005| 30          | Nebulised Tobramycin 300mg BD vs. Placebo         | 6 months | 100% PA   | ↓ number and days of hospital admission  
No differences in number of exacerbations                                               |
| Orriols et al 1999| 15          | Nebulised Ceftazidime plus Tobramycin vs. symptomatic treatment | 1 year   | 100% PA   | ↓ no. hospital admissions  
↓ no. days in hospital                                                                   |
Role of nebulised Gentamicin: a randomised controlled trial

**Randomised Controlled Trial**
- Nebulised Gentamicin 80mg BD for 12 months, n=27
  - Review and assessment at 0, 3, 6, 9, and 12 months
  - Follow-up 3 months after end of treatment
- Nebulised 0.9% Saline BD for 12 months, n=30
  - Review and assessment at 0, 3, 6, 9, and 12 months
  - Follow-up 3 months after end of treatment

Sputum Bacteriology

Gentamicin Group:

- 30.8% of those colonised with *Pseudomonas aeruginosa* achieved eradication.
- 92.8% of those colonised with pathogenic organisms other than *Pseudomonas aeruginosa* achieved eradication.
% Purulent sputum

Saline

Gentamicin
Inflammation

- Airways Inflammation
- Systemic Inflammation

**Effect on Sputum Myeloperoxidase**

**Effect on CRP**

**Assessment Timepoint**

- Baseline
- End of treatment
- Follow-Up

**Assessment Timepoint**

- Baseline
- End of treatment
- Follow-Up
<table>
<thead>
<tr>
<th></th>
<th>Gentamicin n=27</th>
<th>Saline n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time point (months)</strong></td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td><strong>IL-8 ng/ml</strong></td>
<td>38.4 (34.8-44.1)</td>
<td>33.2 (25.0-37.5)*#</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39.1 (37.8-46.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42.9 (36.1-48.5)</td>
</tr>
<tr>
<td><strong>TNF-α pg/ml</strong></td>
<td>1346 (485.1-3581)</td>
<td>485.4 (115.1-1286)*#</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1281 (374.9-2874)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1421 (290-3074)</td>
</tr>
<tr>
<td><strong>IL-1β ng/ml</strong></td>
<td>2.2 (0.96-4.0)</td>
<td>0.99 (0.46-2.2)*#</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.1 (0.59-3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0 (0.68-3.0)</td>
</tr>
<tr>
<td><strong>ICAM-1 ng/ml</strong></td>
<td>304.7 (190.9-463.8)</td>
<td>245.3 (167.4-359.4)**#</td>
</tr>
<tr>
<td></td>
<td></td>
<td>278.8 (163.2-459.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>318.7 (177-458.3)</td>
</tr>
<tr>
<td><strong>E-selectin ng/ml</strong></td>
<td>72.7 (50.7-91.7)</td>
<td>54.4 (36.5-77.1)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65.6 (45.1-80.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63.1 (47.2-80.8)</td>
</tr>
<tr>
<td><strong>VCAM-1 ng/ml</strong></td>
<td>671.2 (473.4-869)</td>
<td>591.5 (362.7-836.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>671.6 (399.1-878.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>642 (447.1-862)</td>
</tr>
<tr>
<td><strong>% positive microbiology</strong></td>
<td>100%</td>
<td>33.3%**#</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96.7%</td>
</tr>
</tbody>
</table>
## Role of long term nebulised antibiotics - Randomised trials in PA + Other Pathogens

<table>
<thead>
<tr>
<th>Murray et al 2011</th>
<th>67; 57 finished study</th>
<th>Nebulised Gent 80mg bd vs. 0.9% saline</th>
<th>1 year</th>
<th>40-48% PA Other PPMs</th>
<th>Reduced exacerbations and increased time to first exacerbation</th>
</tr>
</thead>
</table>

### Exacerbations
- Gent 33% vs. Saline 80%
- Gent 0(0-1) vs. Saline 1.5(1-2)
- Gent 120d (87-162) vs. Saline 61.5d (20-7-122.7)
Other clinical endpoints

- Increased ETT 95m
- Increased frequency of improved HRQOL
- LCQ 81% vs. 20%
- SGRQ 82.5% vs. 19.2%

- No effect 24hr volume, FEV$_1$, FVC, FEF25/75
- 21.9% (7 of 32 patients) reported bronchospasm and received adjunctive nebulised β$_2$ agonist treatment.
- Despite this, two patients required withdrawal from the study (one at month 3 and one at month 6)

- Treatment needs to be continuous for its ongoing efficacy.
Other therapies
<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Type of study</th>
<th>Treatment</th>
<th>Number</th>
<th>Results</th>
</tr>
</thead>
</table>
| Tsang et al     | Thorax 2005 60:239       | Randomised    | Fluticasone 500mcg bd vs. Placebo 12/12| 86     | ↓ 24hr sp. vol  
°Δ sp. Purulence  
°Δ PFT  
°Δ Exacs  
Better in PA patients but small nos. |
| Martinez-Garcia et al | Resp Med 2006 100:1623 | Randomised    | Fluticasone 250mcg bd vs. 500mcg bd vs. Placebo 6/12 | 93     | 500mcg BD  
↓ cough+sputum  
↓ breathless  
↑ SGRQ (5U)  
°Δ micro  
°Δ PFT  
°Δ Exacs |
| Kapur et al     | Cochrane 2009 Jan 21;CD0009 96 | Cochrane review of RCTs |                                       | 303    | Insufficient evidence                                   |
Other therapies

**Oral Tx**

- Leukotriene B4 inhibitors – no randomised trials
- Elastase inhibitors - phase 2 trials ongoing
- Statins - ongoing RIE - will be reported next year

**Inhaled Tx**

- Inhaled mannitol improved mucociliary clearance
  Daviskas et al Blu J 1999:159:1843
  Daviskas et al Respirology 2005:10:46

*Multicentred studies ongoing and results awaited*

- DNAse harmful
  Cochrane review 2000
<table>
<thead>
<tr>
<th>Author</th>
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<th>Type of study</th>
<th>Treatment</th>
<th>Number</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kellett et al</td>
<td>Resp Med 2011</td>
<td>Randomised 3m crossover study</td>
<td>0.9% Saline vs. 7% Saline for 1yr.</td>
<td>28</td>
<td>• HS improvement %FEV$_1$, SGRQ better + reduced antibiotic use</td>
</tr>
<tr>
<td></td>
<td>105:1831</td>
<td>Single blinded</td>
<td></td>
<td></td>
<td>• No data on microbiology or other therapies</td>
</tr>
<tr>
<td>Nicolson et al</td>
<td>Resp Med 2012</td>
<td>Randomised</td>
<td>0.9% Saline vs. 6% Saline for 1yr.</td>
<td>40</td>
<td>• FEV$_1$ slightly better (20ml IS vs. 90 ml)</td>
</tr>
<tr>
<td></td>
<td>106:661</td>
<td></td>
<td></td>
<td></td>
<td>• Improvement in HRQOL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 55-60% colonisation reduced to 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>

Conflicting results- further studies are needed
Case

- 74 year old man with known bronchiectasis presents to GP feeling unwell with 2/7 history of cough, myalgia, headaches and fevers.
- No change in sputum volume or purulence

Is this an exacerbation requiring antibiotics?

- Vote for antibiotics
Case

- 69 year old lady with known tubular bronchiectasis RLL presents feeling less well for 5 days and there is increased sputum volume and purulence

- Investigations?

- Is this an exacerbation requiring antibiotics?
Antibiotics recommended if deteriorating symptoms + change of sputum volume + purulence

Prior to antibiotics being commenced send sputum C+S

Empirical Abs based on previous microbiology.

Treat 14 days but there is a lack of RCTs

Di Bilton + colleagues
Chest 2006;130(5):1503

UK+US study in PA

14/7 ciprofloxacin 750mg bd +/- inh tobramycin 300mg bd

No change in clinical outcomes at days 14 or 21

Increased wheeze with tobramycin 50% vs. 15%
Case- Known case attending GP

- 61 male
- 5 exacs/yr
- PMH Bx
- DH
  - Omeprazole 20mg od
  - Fluticasone 500mcg bd
  - Salbutamol prn
- SH
  - 0 Pack Years
- Exam- Bilateral course inspir crackles
Case

- FEV₁ 1.9L 61% P
- O₂ sats air 94%

- Sputum microbiology
  01/10 PA P
  03/10 NTHI + Mccatt P
  08/10 PA P
  12/10 PA P
  03/11 PA MP

Management?
Went to GP with a further chest infection
GP Gave Ciproxin 500mg bd for 14d but patient still felt ill. What action?
IV Antibiotics

- Dual agents to reduce drug resistance
  - Ceftazidime + Ciproxin/Gentamicin
  - Tazocin + Ciproxin/Gentamicin
  - Meropenum + Ciproxin/Gentamicin
  - Meropenum + Colomycin
  - Aztreonam + Colomycin

- In Vitro Resistance does it matter?
  - Yes
    - Risk of lack of response if given in vivo
    - Risk of polymicrobial resistance

- How do you assess treatment response?
  - Often patients respond even when in vitro resistance - try and assess response
Assessing Response to Treatment

- Few evidence based endpoints
- Studies to date use various markers
- Sputum colour + volume; Sputum bacterial clearance; CRP; SGRQ were the best markers

Murray et al Eur Respir J. 2009 Feb;33(2):312-8
Case

- 45 year old lady
- Bilateral cystic bx
- $FEV_1$ 63% predicted
- Chronically colonised with PA resistant to Cipro + Tazocin
- 8 Chest infections in the past year
- On Seretide 500 1 accule bd
- Salbutamol prn
- Neb Colomycin
- What action?
Treatments strategy

- Ensure complying with treatment
- Ensure complying with chest physiotherapy
- 8 Weekly IV Antibiotics
- May make patients feel better and more control of the Bx

QJM. 2012 Sep 27.
Acknowledgements

- Maeve Murray
- James Chalmers
- Pallavi Mandal
- Colleagues in CIR and CF Microbiology Unit
- CSO
- MRC
- CHSS