NON-CF BRONCHIECTASIS IN ADULTS

Dr Robert Wilson
Royal Brompton Hospital, London, UK
A VICIOUS CYCLE OF INFECTION AND INFLAMMATION

- Inflammation
- Microbial Infection
- Impaired Lung Defences
- Tissue Damage
## Aetiology of bronchiectasis

<table>
<thead>
<tr>
<th>Cause</th>
<th>n (%) of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post infection</td>
<td>51 (32)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>42 (26)</td>
</tr>
<tr>
<td>PCD</td>
<td>17 (11)</td>
</tr>
<tr>
<td>ABPA</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Immune deficiency</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Young’s syndrome</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Pan bronchiolitis</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Yellow nail syndrome</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Mycobacterium infection</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>2 (1)</td>
</tr>
<tr>
<td>CF variant</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>161</strong></td>
</tr>
</tbody>
</table>

ABPA = Allergic bronchopulmonary aspergillosis, PCD = Primary ciliary dyskinesia, CF = Cystic fibrosis
Treatable Causes of Bronchiectasis

Immune Deficiency (CVID)
ABPA
Mycobacterial infection (MAC)
Airway obstruction
Inflammatory Bowel Disease
Rheumatoid Arthritis
Aspiration
### Comparison of patients with idiopathic and post infective bronchiectasis

<table>
<thead>
<tr>
<th></th>
<th>Idiopathic group</th>
<th>Post infection group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>42</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Gender - No. males (%)</td>
<td>15(36)</td>
<td>18 (35)</td>
<td>ns</td>
</tr>
<tr>
<td>Age at onset (SD)</td>
<td>42 (15)</td>
<td>7 (12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at referral to Royal Brompton Hospital (SD)</td>
<td>50 (14)</td>
<td>49 (17)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean number of lobes involved (SD)</td>
<td>4.1 (1.7)</td>
<td>4.4 (1.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Bilateral bronchiectasis (%)</td>
<td>41 (98)</td>
<td>48 (94)</td>
<td>ns</td>
</tr>
<tr>
<td>Predominantly lower lobe bronchiectasis (%)</td>
<td>34 (81)</td>
<td>25 (49)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chronic rhinosinusitis (%)</td>
<td>35 (83)</td>
<td>25 (49)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wheezy bronchitis in childhood (%)</td>
<td>11 (26)</td>
<td>11 (22)</td>
<td>ns</td>
</tr>
<tr>
<td>P. aeruginosa (%)</td>
<td>14 (33)</td>
<td>17 (33)</td>
<td>ns</td>
</tr>
<tr>
<td>Symptoms chronic since onset</td>
<td>38 (83)</td>
<td>25 (49)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>13 (31)</td>
<td>17 (33)</td>
<td>ns</td>
</tr>
<tr>
<td>Lobectomy (%)</td>
<td>1 (2)</td>
<td>5 (10)</td>
<td>ns</td>
</tr>
</tbody>
</table>
Genetic studies implicate altered regulation of natural killer (NK) cells in idiopathic bronchiectasis

- HLA-Cw*03 and HLA-C group 1 homozygosity associated with idiopathic bronchiectasis
- Analysis of relationship between HLA-C and KIR genes suggest a shift to activated NK cell activity

HLA-C and killer cell immunoglobulin-like receptor genes in idiopathic bronchiectasis. Boyton et al 2006 Am J Respir Crit Care Med 173, 327-333
Changes in lung function minor in most patients

FEV1 correlated with decreased attenuation (mosaic perfusion) of parenchyma \((r=0.55)\); also extent of bx and degree of bronchial wall thickening

Change in FEV1 correlated with changes in mucus plugging \(r=0.46\) (small and large airways)

Mosaic perfusion rarely regressed (cf plugging and thickening)

Changes in severity of bx, bronchial wall thickening and mucus plugging go together
A VICIOUS CYCLE OF INFECTION AND INFLAMMATION

- Inflammation
- Microbial Infection
- Impaired Lung Defences
- Tissue Damage
Bronchiectasis exacerbations bacteriology

Common
Haemophilus influenzae
Haemophilus parainfluenzae
Pseudomonas aeruginosa

Less Common
Streptococcus pneumoniae
Moraxella catarrhalis
Staphylococcus aureus
Stenotrophomonas maltophilia
GNEB
“Classic” CT of M.avium-intracellulare
Benefits from beta lactam plus aminoglycoside combination

- Only data from CF
- Smith et al J. Pediatr. 1999
  Azlocillin + tobramycin (n=43) v azlocillin + placebo (n=33).
  No difference in clinical response, lung function
  P.a. sputum density decreased more on combination (p<0.05)
  Longer time to readmission (p<0.001)
- Cochrane Review Elphick and Tan 2002 – 8 trials
  Many flawed and/or small numbers
  No difference in clinical response, lung function
  Monotherapy associated with ↑ P.a. resistance
Prolonged antibiotics for purulent bronchiectasis
Cochrane review
Evans, Bara, Greenstone 2005

- 6 randomised placebo controlled trials from 447 abstracts reviewed
- 4 weeks or more
- 2 nebulised, 4 oral
- Limited meta analysis
- “Response rate” significant for antibiotics
- Exacerbation rate and lung function NS
Antibiotic prophylaxis in bronchiectasis

Key messages

- Reduce exacerbation days
- Reduce sputum volume/purulence
- May ↑ lung function
- Side effects
- Emergence of resistance (oral)
Antibiotic prophylaxis in Bx

consider if
Management otherwise optimal
3 sputum samples negative for AFB
Frequent oral antibiotics $\geq$ 6/year
and rapid relapse after iv without an explanation
$\geq$ 2 hospital admissions per year
Antibiotic prophylaxis in Bx

Approaches
Nebulised (P. aeruginosa)
Long term oral
Rotating antibiotics
Pulsed iv
Macrolides
Figure 1. Comparison of baseline FEV1 with pseudomonas status.
Effect of Bacteriology on Quality of Life

SGRQ Activity score

Mean scores

*P<0.01 cf Hi, NG & Non-Pa
Figure 2. Comparison of baseline FEV1 with longitudinal behaviour, when analysed as decline or improvement of > 10% over time.
Mortality in Bronchiectasis
Loebinger et al ERJ In Press

• 91 patients with moderate to severe bx followed up for 13 yrs
• 29.7% died (70% directly due to bronchiectasis), median age 60 years
• Age, SGRQ activity score, Pseudomonas aeruginosa infection, TLC, RV/TLC and KCO all independently associated with mortality.
Mortality in Bronchiectasis
Loebinger et all ERJ In Press

CT features predicting mortality in multivariate analyses
• Increased wall thickness
• Emphysema
also in univariate analyses
• Bronchiectasis extent
• Dilation severity
• Small and Large airway plugging
• Mosaicism
Prognostic significance of CT signs of raised pulmonary artery pressure in bronchiectasis

Devaraj et al  Submitted 2009

- Average RMPA/LMPA diameter strongest predictor of mortality of all other CT features of bronchiectasis

- Diameter greater than 18 mm most strongly predicted mortality
A VICIOUS CYCLE OF INFECTION AND INFLAMMATION

- Inflammation
- Microbial Infection
- Impaired Lung Defences
- Tissue Damage
INHALED CORTICOSTEROIDS IN BRONCHIECTASIS

Tsang et al Thorax 2005
Fluticasone 500mg bd versus placebo
No effect on exacerbation frequency or FEV\textsubscript{1}
Reduced sputum volume in sub-groups
(Pseudomonas)

Martinez-Garcia et al Resp Med 2006
Fluticasone 500mg bd versus 250mg bd versus no treatment
No effect on exacerbation frequency or FEV\textsubscript{1}
Improved QOL with higher dose
9 months later
Symptoms

Figure 1. Box plot of symptom scores after Azm prophylaxis on 5 point score with 3 = no change. Median, 25% & 75% percentiles & SD shown.
Figure 2. Histogram of number of infections per month in the period prior to Azm prophylaxis and after for both oral & i.v. antibiotics.
Azithromycin prophylaxis

500mg 6 days, 250mg 6 days, 250mg Mon, Weds, Fri or alternate days

Side Effects
Liver function, check 2 weeks and 3 monthly
Reduced hearing
Tinnitus
Antibiotic holiday
A VICIOUS CYCLE OF INFECTION AND INFLAMMATION

- Microbial Infection
- Impaired Lung Defences
- Tissue Damage
- Inflammation