Therapies for Non-CF Bronchiectasis: Where is the Evidence?

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Disclosures

• Consultant
  – Insmed
  – Aradigm

• Clinical Trial Investigator
  – Aradigm
  – Insmed
Question

How many therapies are currently FDA approved for the treatment of non-CF bronchiectasis?

1. 0
2. 1-2
3. 3-5
4. More than 5
How many therapies are FDA approved for the treatment of non-CF bronchiectasis?

1. 0
2. 1-2
3. 3-5
4. More than 5
Summary

• There are no current therapies for non-CF bronchiectasis

• Questions?
Issues to consider

• Bronchiectasis is not Cystic Fibrosis
• What works for CF may not work for bronchiectasis
• Our highest quality data for therapies we frequently use in non-CF bronchiectasis comes from CF studies
Issues to consider

• We don’t know what outcomes to measure in bronchiectasis
  – Therapies that we think have benefit usually don’t improve FEV1 in this disease
  – Frequency of exacerbations is a tough endpoint for unfunded studies
  – QOL may be one of the most important endpoints
  – FDA has not generally accepted QOL as the primary outcome
<table>
<thead>
<tr>
<th>Therapies</th>
<th>800 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled bronchodilator</td>
<td>498 (62%)</td>
</tr>
<tr>
<td>Airway clearance</td>
<td>383 (48%)</td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>336 (42%)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>239 (30%)</td>
</tr>
<tr>
<td>Mucolytic</td>
<td>178 (22%)</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>111 (14%)</td>
</tr>
<tr>
<td>oxygen</td>
<td>82 (10%)</td>
</tr>
</tbody>
</table>
Treatment

- Mucus clearance regimens
- Mucoactive agents
- Anti-inflammatory agents
  - Macrolides
  - Inhaled Corticosteroids
- Inhaled Antibiotics
Mucus clearance-Vicious cycle hypothesis
Mucus clearance

- Chest physical therapy
- Devices
  - Positive pressure/vibratory
    - Acapella
    - Aerobika
    - Flutter
  - High Frequency Chest Wall Oscillation
Airway clearance devices

• Cochrane review
  – 7 studies, total of 105 patients
    • Only 2 studies 6 months or greater
  – Conclusions
    • They are safe
    • HFCWO may improve lung function short term
    • The devices probably increase volume of mucus clearance
    • May improved perceived ease of mucus clearance
    • No evidence of effect on exacerbations or long term prognosis
HFCWO vs PEP/vibratory

• If we assume that some method of airway clearance is important, this is probably the most important question, given cost and treatment burden
  – Limited data
  – In a 2 week crossover pediatric study, improved spirometry, no difference between HFCWO and traditional chest physiotherapy

Gokdemir, Pediatr Pulmonol, 2014
3-Way HFCWO study
Changes in lung function after 15 days of therapy

Nicolini, BMC Pulmonary Medicine, 2013
Mucoactive agents

- Theory is that by decreasing viscosity of the mucus, can be cleared more easily
  - Decreased inflammation
  - Improved quality of life
- It works for CF
Mucoactive agents

- Mucolytics
  - Dnase

- Hyperosmolar agents
  - Mannitol
  - Hypertonic saline
rhDNase in non-CF bronchiectasis

Table 3—Pulmonary Exacerbations: Rates and Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo Rate</th>
<th>rhDNase Rate</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDEs</td>
<td>0.56</td>
<td>0.66</td>
<td>1.17</td>
<td>0.85, 1.65</td>
</tr>
<tr>
<td>NPDEs</td>
<td>0.14</td>
<td>0.29</td>
<td>2.01</td>
<td>1.15, 3.50</td>
</tr>
<tr>
<td>PDEs and NPDEs</td>
<td>0.71</td>
<td>0.95</td>
<td>1.35</td>
<td>1.01, 1.79</td>
</tr>
</tbody>
</table>

O’Donnell, Chest, 1998
Hyperosmolar Agents

- Hypertonic saline (7%)
- Mannitol
Hypertonic Saline

- One small study, blinded to NS vs HS
- Cross over design
- Four single day interventions
  - Active cycle breathing (ACB)
  - Nebulised terbutaline, ACB
  - Nebulised terbutaline, then NS, then ACB
  - Nebulised terbutaline, then 7% saline, then ACB
Hypertonic Saline

• HS associated with
  – Increased mucus clearance
  – Improved subjective ease in expectoration
  – Decreased sputum viscosity
  – Marginal improvement in FEV1

Kellett, Resp Med, 2005
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Number of exacerbations over 12 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IS (0.9%)</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>1.0 (0–4)</td>
</tr>
<tr>
<td>Exacerbations requiring antibiotics</td>
<td>0.5 (0–3)</td>
</tr>
<tr>
<td>Exacerbation days</td>
<td>2.0 (0–26)</td>
</tr>
<tr>
<td>Exacerbation days requiring antibiotics</td>
<td>1.0 (0–19.5)</td>
</tr>
</tbody>
</table>

Data are median (IQR). IS: isotonic saline, HTS: hypertonic saline. p value for comparison of isotonic saline and hypertonic saline over 12 months.
SGRQ

![Graph showing changes in SGRQ scores over time. The graph compares Isotonic and Hypertonic groups with data points at baseline, 3 months, 6 months, and 12 months.]
Inhaled Mannitol

Time to exacerbation reduced

Annual exacerbation rate not reduced
SGRQ improved more than control
Antibiotic days reduced (26 vs 20 days)

Bilton, Thorax, 2014
Anti-Inflammatory Therapy

- Macrolides
- Inhaled corticosteroids
Why macrolides?

- **Effect on pathogens?**
  - Inhibit exotoxin production
  - Inhibit quorum sensing
  - Inhibit bio-film production

- **Direct immunomodulatory/anti-inflammatory effects**
  - Decreased neutrophil recruitment
  - Decreased mucus secretion
  - Decreased cytokine production
Wong, Lancet, 2012
**Macrolide effect on SGRQ**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Macrolides</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Altenburg 2013</td>
<td>-6.09</td>
<td>13</td>
<td>43</td>
<td>-2.06</td>
</tr>
<tr>
<td>de Diego 2013</td>
<td>-7.9</td>
<td>3.1</td>
<td>16</td>
<td>4.1</td>
</tr>
<tr>
<td>Liu 2012</td>
<td>-14</td>
<td>9</td>
<td>24</td>
<td>-10</td>
</tr>
<tr>
<td>Serisier 2013</td>
<td>-3.9</td>
<td>10</td>
<td>59</td>
<td>-1.3</td>
</tr>
<tr>
<td>Wong 2012</td>
<td>-5.17</td>
<td>12</td>
<td>71</td>
<td>-1.92</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>213</td>
<td>204</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 21.70$; $\chi^2 = 24.99$, df = 4 ($P < 0.0001$); $I^2 = 84$%

Test for overall effect: $Z = 2.34$ ($P = 0.02$)

**Figure 3** Forest plots showing a significant reduction in the St George’s Respiratory Questionnaire total scores in the macrolides group compared with control group. CI, confidence interval; IV, inverse variance; SD, standard deviation.
## Macrolide effect on exacerbations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altenburg 2013</td>
<td>0.84</td>
<td>1.1</td>
<td>43</td>
<td>2.05</td>
<td>1.6</td>
<td>40</td>
<td>32.4%</td>
<td>-1.21 (-1.80 to -0.62)</td>
</tr>
<tr>
<td>de Diego 2013</td>
<td>0.1</td>
<td>0.6</td>
<td>16</td>
<td>1.2</td>
<td>0.9</td>
<td>14</td>
<td>37.2%</td>
<td>-1.10 (-1.66 to -0.54)</td>
</tr>
<tr>
<td>Serisier 2013</td>
<td>1.29</td>
<td>1.38</td>
<td>59</td>
<td>1.97</td>
<td>1.96</td>
<td>58</td>
<td>30.3%</td>
<td>-0.68 (-1.30 to -0.06)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>118</td>
<td></td>
<td>112</td>
<td></td>
<td></td>
<td>100%</td>
<td>-1.01</td>
<td>(-1.35 to -0.67)</td>
</tr>
</tbody>
</table>

- **Heterogeneity:** Chi² = 1.64, df = 2 (P = 0.44); P = 0%

- **Test for overall effect:** Z = 5.83 (P < 0.00001)

Wu, Respirology, 2014
Potential Complications of Chronic Macrolide Therapy

- Macrolide resistant NTM
  - Must rule out NTM/ *M. avium* complex infection
  - Macrolide resistant *M. avium* complex extremely difficult to treat, with low cure rates

- Antibiotic resistance
  - Oral Streptococci
    - Probably not often clinically significant

- Shift of microbiome towards GNs/Pseudomonas
Potential Roles for Inhaled corticosteroids

- Diminish progressive airway damage caused by chronic inflammation
- Decrease mucus hypersecretion
- Treat bronchial hyper-responsiveness
Inhaled corticosteroids

Randomized, blinded trial of inhaled fluticasone

Subjects: 24 patients, 50% female

Intervention: Fluticasone 500 ug BID vs placebo for 4 weeks

Endpoints: Spirometry, sputum volume, bacterial density, inflammatory mediators

Tsang, AJRCCM, 1998
Results

No improvement in FEV1 or PEFR
No improvement in 24 hour sputum volume or in sputum bacterial density

Improved sputum leukocyte density
Improved IL-1β, IL-8, LTB4

Quality of life not measured
Obviously not designed to assess affect on lung function loss
Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*

There was no difference in the incidence of ocular or bone side effects. The probability of having pneumonia reported as an adverse event was higher among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group and 18.3% in the fluticasone group) than in the placebo group (12.3%, P<0.001 for comparisons between these treatments and placebo).
<table>
<thead>
<tr>
<th>Chronic Antibiotic Therapies</th>
<th>800 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerosol antibiotic</td>
<td>94 (12%)</td>
</tr>
<tr>
<td>Rotating oral antibiotic</td>
<td>62 (8%)</td>
</tr>
<tr>
<td>Continuous po antibiotic</td>
<td>235 (29%)</td>
</tr>
</tbody>
</table>
Prolonged antibiotics

- Cochrane meta-analysis
- 9 studies
- Significant heterogeneity in treatment
  - 4 weeks-1 year
  - Inhaled and oral
  - Tobramycin, B-lactam, macrolide
- Significant heterogeneity in measured outcomes
Prolonged antibiotics

• Conclusion
  – Small benefit in symptoms
  – No benefit in frequency of exacerbation
  – Development of resistance not an obvious concern

Davis, Cochrane Database, 2011
Aerosolized aztreonam

$\log_{10}$ CFUs of *P. aeruginosa*
Change in QOL-B Respiratory Domain

Response at Day 28 (n = 83)

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>61</td>
<td>73.5%</td>
</tr>
<tr>
<td>Stable</td>
<td>6</td>
<td>7.2%</td>
</tr>
<tr>
<td>Worsened</td>
<td>16</td>
<td>19.3%</td>
</tr>
</tbody>
</table>

Barker et al, AJRCCM, 2010
Phase 3

• Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomized double-blind, placebo-controlled phase 3 trials
  – No clinically significant benefit
  – Increased treatment-related adverse events and discontinuations in aztreonam group

Lancet Respir Med, 2014
Open label gentamicin
% of patients improved SGRQ ≥4

Murray, Am J Respir Crit Care Med, 2011
Double-blind RCT of inhaled Colistin

• Patients with bronchiectasis and chronic Pseudomonas aeruginosa infection
  – Failed to reach primary endpoint (exacerbation rate), although significant decrease in the most compliant patients
  – Clinically significant improvement in SGRQ

Haworth, AJRCCM, 2014
Inhaled antibiotic trials

- Inhaled ciprofloxacin/liposomal ciprofloxacin
- Two Phase III studies for patients with *P. aeruginosa*
  - In only one was there a statistically significant increase in time to first exacerbation, or frequency of exacerbations
- Not approved by FDA in January, 2018
Dry powder Cipro

- Phase III studies
- 14 day and 28 day regimens
- Again, conflicting results with a positive and a negative result (positive for 14 days)
- Small increase in resistance noted
  - A potentially big problem for quinolones
    - The only oral Rx for Pseudomonas
- Turned down by FDA
Inhaled Antibiotics

• There is no doubt that some patients benefit
• “Life-changing”
• “Grandma, you’re not coughing today”
  – Not placebo effect
Inhaled antibiotics

• We do not know which are the right patients to treat
• We do not know the proper way to administer
  – 14 on/off
  – 28 on/off
  – Continuously
• We don’t know how long to administer
Summary

• We were in the golden age of bronchiectasis treatment investigation
  – May be over, with little to show for it
• Macrolides appear to be effective
• We think mucus clearance is important
  – Don’t ask for evidence
• Role of inhaled antibiotics for long term control remains to be seen