Use of antimicrobials to treat acute exacerbations of chronic bronchitis, asthma and COPD

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Presenter Disclosures

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Antibiotics in airways diseases

Proposed effects

Risk factor for childhood allergies? **No**


Improve control of asthma?

Inflammatory mechanisms and treatment of OLD with neutrophilic inflammation

- Similar amplification of innate immune activation in asthma, COPD and bronchiectasis
- Inflammatory mediator release
- Toll-like receptor 2 expression
- Neutrophil persistence through
  - Impaired apoptosis
  - Efferocytosis
  - Mucus hypersecretion
- Impaired neutrophil clearance
- Reduced ability to respond to bacterial infection
- Neutrophil-induced airway damage

Inflammatory mechanisms and treatment of OLD with neutrophilic inflammation

- Few treatments reduce neutrophil accumulation
  - Theophylline,
  - Statins
  - Antagonists of pro-inflammatory cytokines
  - Macrolide antibiotics

- Macrolides reduce airway
  - Neutrophils
  - Levels of CXCL8
  - Neutrophil proteases in the airway epithelium

Macrolides in Asthma

   Troleadomycin
   Itkin IH & Menzel ML. J Allergy 1970; 45: 146-62

1. Immune modulation in diffuse panbronchiolitis and cystic fibrosis

2. Immunomodulation with 14-member (erythromycin, clarithromycin and roxithromycin) and 15-member, but not with 16-member macrolides (josamycin)

Crosbie PAJ & Woodhead MA. ERJ 2009:33:171-81
Does macrolide treatment improve asthma control?

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment</th>
<th>Dose</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richeldi [44]</td>
<td>Meta-analysis</td>
<td>Clarithromycin</td>
<td>500 mg b.i.d.</td>
<td>8 weeks</td>
<td>Insufficient evidence for a conclusion</td>
</tr>
<tr>
<td>Simpson [45]</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>Clarithromycin</td>
<td>500 mg b.i.d.</td>
<td>8 weeks</td>
<td>↑ QoL; ↓ wheeze; FEV1 unchanged; BHR unchanged</td>
</tr>
<tr>
<td>Johnston [46]</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>Telithromycin 800 mg daily for 10 days</td>
<td>278/0</td>
<td>6 weeks</td>
<td>↓ Symptom score; home PEF unchanged</td>
</tr>
<tr>
<td>Kostadima [47]</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>Clarithromycin</td>
<td>63/0</td>
<td>8 weeks</td>
<td>↓ BHR; FEV1 unchanged</td>
</tr>
<tr>
<td>Kraft [48]</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>Clarithromycin</td>
<td>500 mg b.i.d. (32% ICS)</td>
<td>6 weeks</td>
<td>↑ FEV1 in PCR+ subjects</td>
</tr>
<tr>
<td>Black [49]</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>Roxithromycin</td>
<td>150 mg b.i.d. (&gt;75% ICS)</td>
<td>6 weeks (6 month follow-up)</td>
<td>Morning PEF unchanged; ↑ evening PEF; symptom score unchanged</td>
</tr>
<tr>
<td>Amayasu [50]</td>
<td>Randomised, double-blind, placebo-controlled, crossover</td>
<td>Clarithromycin</td>
<td>17/0</td>
<td>8 weeks</td>
<td>FEV1 unchanged; ↓ BHR; ↓ symptom score</td>
</tr>
<tr>
<td>Shoji [51]</td>
<td>Randomised, double-blind, placebo-controlled, crossover</td>
<td>Roxithromycin</td>
<td>150 mg b.i.d. (no ICS)</td>
<td>14/0</td>
<td>Two blocks; FEV1 unchanged; BHR unchanged; ↓ symptom score</td>
</tr>
<tr>
<td>Kamada [52]</td>
<td>Randomised, double-blind, parallel treatment arms</td>
<td>Troleandomycin + methylprednisolone; troleandomycin + prednisone; methylprednisolone</td>
<td>0/19 (all ICS)</td>
<td>12 weeks</td>
<td>All ↓ steroid dose; ↓ symptom score; pulmonary function unchanged</td>
</tr>
<tr>
<td>Nelson [7]</td>
<td>Double-blind, placebo-controlled</td>
<td>Troleandomycin + methylprednisolone</td>
<td>75/0</td>
<td>2 yrs</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

Crosbie PAJ & Woodhead MA. ERJ 2009; 33:171
Do macrolides improve control of asthma?

- Mycoplasma pneumoniae and Chlamydophila pneumoniae are found in lower airways on PCR
- Mild-to-moderate persistent asthma not well controlled on ICS (ACQ >1.5)
- Clarithromycin or placebo, plus FP for 16 weeks

92 patients:
- 12 (13%) with PCR M pneumoniae or C pneumoniae in endobronchial biopsies:
  - ACQ improvement 0.4+/− 0.4 vs 0.1 +/- 0.3 in placebo
- 80 (87%) PCR-negative
  - ACQ improvement 0.2 ± 0.2 units (P = .3) between treatments
  - No benefit on lung function or airway inflammation
  - AHR PC20M improved by 1.2 ± 0.5 doubling doses (P = 0.02)

Antibiotics in airways diseases

Proposed effects

Risk factor for childhood allergies? No

Improve control of asthma? No
  Sutherland ER, et al. JACI 2010;126:747-53

Improve outcomes in acute asthma exacerbations?
Inappropriate use of antibiotics for acute asthma in United States emergency departments

- National Hospital Ambulatory Medical Care Survey (1993 – 2004) 22%
- National Emergency Department Safety Study (2003 – 2006) academic ED 18%
  - African Americans (OR = 0.6; CI = 0.4 to 0.8)*
  - Hispanics (OR = 0.6; CI = 0.4 to 0.8)*

* Multivariate analysis

Antibiotics in asthma exacerbations

NAEPP 2007:
No antibiotics (except for co-morbid conditions)

GINA 2009:
No antibiotics .... not mentioned

ARIA 2010:
No antibiotics .....not mentioned

Antibiotics in airways diseases

Proposed effects

Risk factor for childhood allergies? **No**

Improve control of asthma? **No**
- Sutherland ER, *et al.* *JACI.* 2010;126:747-53

Improve outcomes in acute asthma exacerbations? **Probably not**

Improved outcomes of exacerbations in COPD?
Factors Associated With Increased Exacerbation Risk in COPD

- Increased age
- Severity of airway obstruction (FEV₁ impairment)
- Chronic bronchial mucous hypersecretion
- Longer duration of COPD
- Productive cough and wheeze
- Elevated cough and sputum
- Antibiotic or systemic corticosteroid use in the past year
- Prior use of medications for COPD
- Bacterial colonisation
- Comorbid conditions (e.g., cardiovascular disease)
- Poor health-related quality of life


Spiral of Progression in COPD

LRTI
Exacerbation

FEV<sub>1</sub>

Accelerated progression?

FEV<sub>1</sub>

Exacerbation

Q of Life

FEV<sub>1</sub>

Accelerated progression?

FEV<sub>1</sub>

Exacerbation

Q of Life

Accelerated progression

Q of Life
PEF Recovery from Exacerbation of COPD

Daily median PEFR as % baseline

In 7.1% of exacerbations, PEF did not recover to baseline at 91 days.

75.2% recovered

$n = 504$ in 91 patients

Seemungal et al AJRCCM 2000
Lower Respiratory Tract Infections in Lung Health Study

Mean number of LTRIs / year

n= 5887

Kanner et al, AJRCCM 2001
Change in FEV1 and Lower Respiratory Tract Infections in the Lung Health Study

Mean Annual Change in FEV1 (ml/yr)

- Sustained Quit
- Intermittent smokers
- Continuing smokers

n = 5,887

Kanner et al, AJRCCM 2001
Exacerbation frequency and severity and risk of death in COPD

**Group A**  patients with no acute exacerbations

**Group B**  patients with 1–2 acute exacerbations requiring hospital management

**Group C**  patients with >3 acute exacerbations

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Pathogens in AE COPD

Viruses
- Influenza
- Parainfluenza
- Respiratory syncytial virus (RSV)
- Human metapneumonia virus
- Picornaviruses
- Coronavirus
- Adenovirus

Bacteria
- Common
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
- Common in Severe Disease
  - *Pseudomonas aeruginosa*
  - *Gram-negative bacilli*
- Rare
  - *Chlamydia pneumoniae*
  - *Mycoplasma pneumoniae*
  - *Legionella spp*

## Viruses detected with PCR in AE COPD

<table>
<thead>
<tr>
<th>Virus</th>
<th>General Adult Population</th>
<th>COPD</th>
<th>Inpatient COPD</th>
<th>ICU COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>4.5-11.6</td>
<td>4.3-12.0</td>
<td>2.6-15.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Influenza A</td>
<td>18.4</td>
<td>3.4</td>
<td>15.6-17.6</td>
<td>13.1</td>
</tr>
<tr>
<td>Influenza B</td>
<td>1.9</td>
<td>NR</td>
<td>4.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>10.2</td>
<td>25.6</td>
<td>11.7-24.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>0.8</td>
<td>8.5</td>
<td>7.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>1.1</td>
<td>5.1</td>
<td>3.9</td>
<td>10.3</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>1.5</td>
<td>0%</td>
<td>0%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>0.8%</td>
<td>0%</td>
<td>1.3%</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported

Neutrophils in AE COPD

E = Exacerbation requiring hospitalisation
C = Stable

Viruses
Viruses + Bacteria
Bacteria
No Pathogens

** P < 0.001

Combined viral and bacterial infection: Impact on pulmonary function and symptom severity

PPM = potentially pathogenic microorganisms

* P<0.05 versus cold and bacterial pathogen

Examination of sputum in AE COPD

N=121 sputum samples

Percent of Samples

PMN >25
Gram Stain
Culture Positive
>10^7 cfu/mL

Purulent (n=87)
Mucoid (n=34)

### Meta-analysis of efficacy of antibiotics and risk of treatment failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibiotic Group n/N</th>
<th>Placebo Group n/N</th>
<th>Relative Risk ( Forced )</th>
<th>Weight (%)</th>
<th>Relative Risk ( Forced ) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alonso 1992</td>
<td>2/29</td>
<td>6/29</td>
<td>3.5</td>
<td>0.33</td>
<td>[0.07, 1.52]</td>
</tr>
<tr>
<td>Anthonisen 1987</td>
<td>19/57</td>
<td>28/59</td>
<td>16.2</td>
<td>0.70</td>
<td>[0.45, 1.11]</td>
</tr>
<tr>
<td>Elmes 1965a</td>
<td>6/29</td>
<td>19/29</td>
<td>11.2</td>
<td>0.32</td>
<td>[0.15, 0.68]</td>
</tr>
<tr>
<td>Jorgenson 1992</td>
<td>49/132</td>
<td>49/136</td>
<td>28.4</td>
<td>1.03</td>
<td>[0.75, 1.41]</td>
</tr>
<tr>
<td>Pines 1968</td>
<td>6/15</td>
<td>15/15</td>
<td>8.8</td>
<td>0.40</td>
<td>[0.22, 0.74]</td>
</tr>
<tr>
<td>Pines 1972</td>
<td>31/89</td>
<td>53/86</td>
<td>31.8</td>
<td>0.57</td>
<td>[0.41, 0.79]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>351</td>
<td>354</td>
<td>100.0</td>
<td>0.67</td>
<td>[0.56, 0.80]</td>
</tr>
</tbody>
</table>

Total events: 113 (Antibiotic Group), 170 (Placebo Group)
Test for heterogeneity: d² = 15.46 df = 5 p = 0.009 F = 67.7%
Test for overall effect: z = 4.27 p = 0.00002

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Ram FS, et al. *Cochrane Database Syst Rev.* 2006;CD004403
Meta-analysis of efficacy of antibiotic therapy and risk for treatment failure

Favors Antibiotics

Elmes et al, 1965
Pines et al, 1968
Anthonisen et al, 1987
Jorgensen et al, 1992
Nouira et al, 2001

Pooled summary
(RR, 0.54; 95% CI, 0.32-0.92)

Favors Placebo

Relative Risk (95% Confidence Interval)

Quon BS et al, Chest 2008; 133
<table>
<thead>
<tr>
<th>Oral treatment</th>
<th>Alternative oral treatment</th>
<th>Parenteral treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong>&lt;br&gt;Patients with only one symptom should not receive antibiotics&lt;br&gt;If indicated: β-lactam (penicillin, ampicillin/amoxicillin), tetracycline, trimethoprim/sulfamethoxazole</td>
<td>β-lactam/β-lactamase inhibitor (Co-amoxiclav)&lt;br&gt;Macrolides (azithromycin, clarithromycin, roxithromycin)&lt;br&gt;Cephalosporins (2nd or 3rd generation)&lt;br&gt;Ketolides (telithromycin)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Group B</strong>&lt;br&gt;β-lactam/β-lactamase inhibitor (Co-amoxiclav)</td>
<td>Fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin)</td>
<td>β-lactam/β-lactamase inhibitor (Co-amoxiclav, ampicillin/sulbactam)&lt;br&gt;Cephalosporins (2nd or 3rd generation)&lt;br&gt;Fluoroquinolones (levofloxacin, moxifloxacin)</td>
</tr>
<tr>
<td><strong>Group C</strong>&lt;br&gt;At risk for pseudomonas infections:&lt;br&gt;Fluoroquinolones (ciprofloxacin, levofloxacin - high dose)</td>
<td>-</td>
<td>Fluoroquinolones (ciprofloxacin, levofloxacin - high dose) or β-lactam with <em>P. aeruginosa</em> activity</td>
</tr>
</tbody>
</table>

**Group A:** Mild exacerbation, no risk factors for poor outcome  
**Group B:** Moderate exacerbation with risk factor(s) for poor outcome  
**Group C:** Severe exacerbation with risk factors for *P. aeruginosa* infection

Antibiotics in airways diseases

Proposed effects

Risk factor for childhood allergies? **No**

Improve control of asthma? **No**
*Sutherland ER, et al. JACI 2010;126:747-53*

Improve outcomes in acute asthma exacerbations? **Probably not**

Improved outcomes of exacerbations in COPD? **Yes!**

Prevents exacerbations in COPD?
Does antibiotic prophylaxis reduce AE COPD?


Percent of Patients with Exacerbation

* P<0.007 versus control

Erythromycin: 11%

Control: 56%
Does clarithromycin prophylaxis reduce AE COPD?

- Prospective, randomised, double-blind, placebo-controlled trial
- Clarithromycin 500mg once daily for 3 months
- 67 adults
- Results:
  - Health status unchanged
  - Exacerbation rate unchanged
  - Sputum bacterial counts unchanged
  - One withdrawal for gastro-intestinal side effect

Does moxifloxacin prophylaxis reduce AE COPD?

Moxifloxacin for reducing bronchial colonisation in 119 moderate-severe COPD patients colonised with pathogens

Prospective, randomised, double-blind, placebo-controlled trial

- Moxifloxacin 400mg daily for 5 days
- Eradication 75% vs 30% with placebo at 2 weeks (p<0.001)
- At 8 weeks 25% vs 5% (n.s.)
- High new potential pathogens equal in both groups
- Re-colonisation at 8 weeks with new pathogens was associated with higher rate of AE COPD in both groups

Miravitlles MA, et al. ERJ 2009; 34: 1066-71
Does pulsed moxifloxacin prophylaxis reduce AE COPD?

- Prospective, randomised, double-blind, placebo-controlled trial
- Clarithromycin 500mg once daily for 5 days every 8 weeks for 6 courses (48 weeks plus 24 follow-up); n = 1157 patients with COPD

- 48 weeks: fewer AE COPD
  \[ \text{OR } 0.75, 95\% \text{ CI } 0.565-0.994, \ p = 0.046 \]
- No effect on SGRQ total, lung function, hospitalisations or mortality
- No microbial resistance developed
- Side effects >4%

Antimicrobials in asthma and COPD

Concluding remarks

- In asthma
  - No causative association with asthma in children
  - No role in acute exacerbations of asthma
  - No evidence that immune modulation with macrolides improves asthma control or risk of infection

- In COPD
  - Antibiotics should be used in all purulent and complicated AE COPD – may influence progression
  - Antibiotic prophylaxis is under investigation