Mycoplasma pneumoniae
does treatment help?

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The Netherlands
Community-acquired pneumonia: known etiology

- S. pneumoniae
- H. influenzae
- M. pneumoniae
- C. pneumoniae
- L. pneumophila
- Anaerobes
- Other

~85% of these cases in children ≤14 years of age
15-40% of hospitalizations because of CAP in children

Mycoplasma pneumoniae: does treatment help?

- Mycoplasma pneumoniae short introduction

- Case Rick:
  - Clinical signs and symptoms
  - Diagnostics
  - Therapeutics

- Does treatment help?
Mycoplasma pneumoniae

- 1944 Eaton’s agent
- Thought to have evolved from gram-positive bacteria
- Genome 816 kbp (± 1/3 genome S. pneumoniae)
- Smallest self-replicating organism
- “Minimalist cell”
- Lack a cell wall and still maintain cell rigidity

Why is M. pneumoniae called atypical?

Not sensitive to betalactam antibiotics or cefalosporines

Mycoplasma lack a cell wall
Rick, 4 years old

- No medical history
- Coughing since 1-2 weeks, not feeling too well
- 3-4 days fever 38-38.5 °C, vomiting, malaise
- Physical examination:
  - mild tachypnea,
  - left basal crepitations on lung auscultation

- White blood cell count 5800/ul with 45% neutrophils.
- CRP 48 mg/L
- Chest X-ray

"Numerous studies have shown that chest radiography findings lack precision in defining the etiology of childhood pneumonia. There is no single test that reliably distinguishes bacterial from non-bacterial causes."

McIntosh K et al. N Engl J Med. 2002
Wilkins TR et al. Radiol Technol. 2005
Lynch T et al. Plos one 2010
When to think of *Mpn*? Radiology

**Radiology**

Chest X-ray:
- Bilateral, diffuse, reticular
  - Lobar: 38%
  - Interstitial: 36%
  - Lobar en interstitial: 27%
  - Pleura effusion: 14%

*Scan J Respir Dis* 1978:179-89

When to think of *Mpn*? Age

*M.pneumoniae* pneumonia also < 5 years!

1083 patients admitted because of LRTI: 191 *Mpn* infection

Incidence rates of acute Mycoplasma pneumoniae infection on the basis of serological and PCR findings.

<table>
<thead>
<tr>
<th>Positive test result, diagnosis</th>
<th>Proportion (%) of patients with infection, by age group</th>
<th>2–4 y</th>
<th>5–7 y</th>
<th>&gt;7 y</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>12/62 (19.3)</td>
<td>8/34 (23.5)</td>
<td>9/17 (52.9)</td>
<td>29/113 (25.6)</td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>12/53 (22.6)</td>
<td>4/15 (26.6)</td>
<td>7/14 (50.0)</td>
<td>23/82 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>42/209 (20.0)</td>
<td>53/123 (43.0)</td>
<td>47/86 (54.6)</td>
<td>142/418 (33.9)</td>
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</tr>
<tr>
<td>All</td>
<td>66/324 (20.4)</td>
<td>65/172 (37.6)</td>
<td>63/117 (53.8)</td>
<td>194/613 (31.6)</td>
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<tr>
<td>PCR</td>
<td></td>
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<tr>
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<td>8/62 (12.9)</td>
<td>6/34 (17.6)</td>
<td>6/17 (35.3)</td>
<td>20/113 (17.7)</td>
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<tr>
<td>Wheezing</td>
<td>7/53 (13.2)</td>
<td>3/15 (20.0)</td>
<td>4/14 (28.6)</td>
<td>14/82 (17.1)</td>
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<tr>
<td>Pneumonia</td>
<td>33/209 (15.8)</td>
<td>36/123 (29.3)</td>
<td>39/86 (45.3)</td>
<td>108/418 (25.8)</td>
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</tr>
<tr>
<td>All</td>
<td>48/324 (14.8)</td>
<td>45/172 (26.2)</td>
<td>49/117 (41.9)</td>
<td>142/613 (23.2)</td>
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</tr>
<tr>
<td>Serological and/or PCR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>14/62 (22.5)</td>
<td>10/34 (29.4)</td>
<td>12/17 (70.5)</td>
<td>36/113 (31.8)</td>
<td></td>
</tr>
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<td>51/86 (59.3)</td>
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<tr>
<td>All</td>
<td>69/324 (21.3)</td>
<td>71/172 (41.3)</td>
<td>70/117 (59.9)</td>
<td>210/613 (34.3)</td>
<td></td>
</tr>
</tbody>
</table>


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When to think of Mpn? Clinical signs and symptoms

Clinical symptoms and signs for the diagnosis of Mycoplasma pneumoniae in children and adolescents with community-acquired pneumonia (Review)

Forest plot of tests:
1. Cough
2. Wheeze
3. Coryza
4. Crepitations
5. Fever
6. Rhonchi
7. Shortness of breath
8. Headache
9. Chestpaint
10. Diarrhoea
11. Myalgia

Only statistical significant indicator of Mpn: Absence of wheeze
Chestpain doubles chance of Mpn

Persistent hacking cough: CARDS toxin

- First publication in 2006
- Pertussis like toxin
- Virulence factor? Strain dependent?

Kannan TR, Baseman JB. *Proc Natl Acad Sci USA* 2006;103:6724–6729
Rick, 4 years

- *M. pneumoniae* serology:
  - IgM weak positive
  - IgG negative

- Nasopharyngeal washing:
  - *M. pneumoniae* PCR positive
  - Viral panel PCR: negative

- Bloodcultures: negative

Who thinks this is a *Mycoplasma pneumoniae* pneumonia because PCR is positive?
Diagnosis of *Mycoplasma pneumoniae* infections

1. Serology
   - Retrospective diagnosis (fourfold increase of IgG)
   - Unreliable in immunocompromised patients and young children

2. Culture
   - Time consuming (2-6 weeks), labor intensive, insensitive

3. PCR
   - Fast, sensitive, specific

Does asymptomatic carriage with *Mycoplasma pneumoniae* exist?
Main objectives:
1. Determine the existence of asymptomatic carriage of *M. pneumoniae*
2. Differentiate carriage from respiratory tract infection (RTI) based on bacterial load

What was done?
405 asymptomatic children, 321 children with RTI 3 mos - 16 years between 2008-2011. Mpn PCR and serology, bacterial and viral testing on (nasal)pharyngeal washings and swabs.

Results PCR

What is the prevalence of *M. pneumoniae* in children?

<table>
<thead>
<tr>
<th></th>
<th>Healthy (n = 405)</th>
<th>RTI (n = 321)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. pneumoniae</em> PCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi square</td>
<td></td>
<td></td>
<td>2.546</td>
</tr>
</tbody>
</table>

Is there a difference in bacterial load?

![Oropharyngeal](Healthy RTI) ![Nasopharyngeal](Healthy RTI)
Results follow-up study

What is the ‘natural course’ of a positive PCR for *M. pneumoniae*?

Healthy

RTI

Results serology

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>RTI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-<em>M. pneumoniae</em> IgM</td>
<td>26 (9.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-<em>M. pneumoniae</em> IgG</td>
<td>40 (14.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No difference in antibody levels
Is *M. pneumoniae* a pathogen?

**TABLE 1**

<table>
<thead>
<tr>
<th>No.</th>
<th>Fourth or Greater Rise in Antibody**</th>
<th>Strps. MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Illness</td>
<td>volunteer (Hemocult)</td>
<td>Eaton</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Pneumonial</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Otitis media</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Acute upper resp. illness</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Acute lower resp. illness</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>None</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Otitis media</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Acute upper resp. illness</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>None</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>38</td>
</tr>
</tbody>
</table>

Rick, 4 years

- 20/4 hospital admission because of pneumonia left basal
- 21/4 increasing oxygen requirement, bronchospastic, crepitations
- 22/4 PICU admission because of respiratory insufficiency
- Physical examination: no facial mimic, problems swallowing, areflexia, hypotonia of all extremities
Rick, 4 years

Guillan-Barré syndrome after *M. pneumoniae* infection: molecular mimicry?

Anti-Gal-C antibodies in GBS subsequent to Mycoplasma infection: evidence of molecular mimicry
Kusunoki et al. Neurology. 2001


Acute motor axonal neuropathy after Mycoplasma infection: evidence of molecular mimicry
Susuki et al. Neurology. 2004

Pulmonary and extra-pulmonary complications of *Mpn* RTI

- **Pulmonary**
  - ARDS
  - Asthma exacerbation
  - Bronchiectasis
  - Bronchiolitis obliterans
  - Hyperlucent lung syndrome
  - Interstitial fibrosis
  - Lung abscess
  - Pleuritis, pulmonary embolism
  - Pneumatocele, pneumothorax

- **Hematologic**
  - Hemolytic anemia
  - Diffuse Intravascular Coagulation
  - Thromboembolism

- **Cardiac**
  - Pericarditis
  - Myocarditis

- **Nephrologic**
  - Glomerulonephritis
  - IgA nephropathy

- **Neurologic**
  - Encephalitis
  - Meningitis
  - Poliomyelitis-like syndrome
  - Guillain-Barré syndrome
  - Brain-stem syndrome
  - Cerebellar ataxia
  - Psychosis
Rick, 4 years

- Treatment
  - Ventilator
  - Antibiotics: cefuroxim and clarithromycin
  - Neurological: methylprednisolon and prednison and morfin

- After 3 weeks discharge from PICU

- 2 weeks later discharge to revalidation center

Treatment of \textit{M. pneumoniae} in children

- Macrolide (azithromycin, erythromycin, clarithromycin)

>8 years:
  - Tetracyclines (doxycycline)
  - Fluoroquinolones (levofloxacin, moxifloxacin, ciproxin)

- Duration?
Mycoplasma pneumoniae does treatment help?

Does treatment help?

Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children (Review)

Methlinch S, Gerverich JB, Gillies MB, Chang AB

THE COCHRANE COLLABORATION®
Does treatment help?

Mulholland et al. Cochrane Database of Systematic Reviews 2010;7

- No RCT’s on effectiveness of antibiotics on Mpn LRTI
- Small proportions with Mpn infection in studies comparing macrolides with amoxycilline/clavulanate
- Dose and type of ab differed between studies
- Application of diagnostic criteria differed between studies
- Inclusion criteria differed between studies
- Outcome measures differed between studies

Need for RCT on efficacy of antibiotics for the treatment of childhood LRTI due to Mpn

Rapidly emerging macrolide resistance Mpn
pointmutations in 23S rRNA (A2063G and A2064G)

- High percentages in Asia
  - Japan
    - 2007: ~ 43%
    - 2008: ~ 40%
    - 2012: 50-93%
  - China
    - 2008/2009: 60-90%

- Outside Asia:
  - Israel (30%)
  - Italy (26%)
  - France (~ 10%)
  - USA (8%)
  - Germany (3%)
  - The Netherlands (0%)


Kawai et al. 2013 Antimicrob. Agents Chemother. online ahead of print

Clinical efficacy of macrolides


188 children with Mpn pneumonia (culture and PCR positive):

- 33% < 5 years old
- 150 macrolide resistant (10% hospitalized)
- 38 macrolide sensitive (0% hospitalized)

**Macrolide resistant**

**TABLE 4 Clinical efficacies of macrolides against M. pneumoniae pneumonia**

<table>
<thead>
<tr>
<th>Treatment group (no. of patients)</th>
<th>No. (%) of patients whose fever disappeared within 48h after antibiotic administration</th>
<th>Ampicillin administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZM</td>
<td>14 (84)</td>
<td>1.62</td>
</tr>
<tr>
<td>CLR</td>
<td>22 (92)</td>
<td>1.04</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>0.038</td>
<td></td>
</tr>
</tbody>
</table>

*AZM, azithromycin.
*CLR, clarithromycin.

**TABLE 5 Clinical efficacies of macrolides, minocycline, and tosufloxacin against M. pneumoniae pneumonia**

<table>
<thead>
<tr>
<th>Treatment group (no. of patients)</th>
<th>No. (%) of patients whose fever disappeared within 48h after antibiotic administration</th>
<th>Ampicillin of class of fever after antibiotic administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZM</td>
<td>11 (69.3)</td>
<td>3.07</td>
</tr>
<tr>
<td>CLR</td>
<td>11 (60.5)</td>
<td>3.19</td>
</tr>
<tr>
<td>TXL</td>
<td>13 (68)</td>
<td>2.31</td>
</tr>
<tr>
<td>MIN</td>
<td>13 (68)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*AZM vs CLR: 0.628
*AZM vs TXL: 0.017
*AZM vs MIN: 0.002
*CLR vs TXL: 0.057
*CLR vs MIN: 0.001
*TXL vs MIN: 0.047

**Correlation between decrease in bacterial load and clinical improvement**

In ML-R more rapid decrease bacterial load with minocycline than with tosufloxacin
Macrolide resistance associated with disease severity?

Zhou et al AAC 2014: 206 children
- Prolonged clinical symptoms
- Increase in extrapulmonary manifestations (29% vs 10%)

Cardinale et al J Clin Microbiol 2013:
- Prolonged clinical symptoms
- No increase in extrapulmonary manifestations

Clinical impact of ML-R *Mpn* infection

Conclusions:
- Prolonged fever and coughing in ML-R *Mpn* infection
- Prompt cessation of fever after initiation of fluoroquinolon/tetracyclines
- Difference in severity of disease?
- No clear evidence (yet) of more complications in ML-R *Mpn* infection
- Correlation between decrease in bacterial load and clinical improvement
- A significant number of cases treated with ineffective antibiotics have similar outcomes to those observed in patients with ML-S *Mpn* infection
- Debate on inflammatory effect of ML

Take home messages

*Mycoplasma pneumoniae*: does treatment help?

Yes, cessation of fever and shorter duration of coughing.
Prevention of severe infection???

Debate: effect of reduction of bacterial load and/or anti-inflammatory effect of macrolides

- Also < 5 years of age frequent cause of lower respiratory tract infection
- Current diagnostic methods do not discriminate between asymptomatic carriage and infection
- Clinical suspicion when subacute, persistent coughing, no reaction to amoxicillin
- Think of macrolide resistance if no reaction to macrolides in children with high suspicion of *M. pneumoniae* infection.