This Is Not Your Typical Pneumonia Presentation
Recommendations for Treatment of Atypical Pneumonias

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PGY2 Emergency Medicine Pharmacy Resident

Pharmacy Grand Rounds
April 18th, 2017
Objectives

• Recognize clinical characteristics of various atypical pneumonias
• Discuss appropriate populations who warrant empiric antimicrobial coverage
• Review the evidence supporting different treatment regimens for atypical pneumonias
Question #1

How do you define an “atypical” pneumonia?
1. Atypical symptoms
2. Atypical diagnosis
3. Atypical pathogens
4. Atypical antibiotics
Being “Atypical” is controversial

- Atypical symptoms
  - Minimal sputum production, extrapulmonary involvement
- Atypical terminology
  - Outdated definitions, ambiguity
- Atypical diagnosis
  - Difficult to culture
- Atypical pathogens
  - Intracellular vs. extracellular
Atypical Bugs & Drugs

- Chlamydia pneumoniae
- Mycoplasma pneumoniae
- Legionella pneumophila

**Fluoroquinolones**
- Topoisomerase II/IV inhibitor

**Macrolides**
- 50-S Inhibitor

**Tetracyclines**
- 30-S Inhibitor

*Others include: chloramphenicol, streptogramins, ketolides*
Epidemiology

• Atypical pathogens responsible for 5-25% of CAP
• Incidence varies with geography, age, and diagnostic tools available

CAP pathogen incidence
- Atypical: 50%
- Strep pneumo: 25%
- Unknown: 15%
- Other: 10%

Atypical pathogen incidence
- Mycoplasma: 20%
- Chlamydophila: 30%
- Legionella: 50%

CAP: community-acquired pneumonia

<table>
<thead>
<tr>
<th>Chlamydophila</th>
<th>Mycoplasma</th>
<th>Legionella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation 21 days</td>
<td>Most common CAP organism</td>
<td>Incubation 2-10 days</td>
</tr>
<tr>
<td>50-75% of population have serological evidence of previous infection</td>
<td>Incubation 1 – 3 weeks</td>
<td>Risk factors</td>
</tr>
<tr>
<td>Reinfection common</td>
<td>Female &gt; male</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Ages 5-20 at highest risk; mini-endemems may occur</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic CVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Freshwater</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recent Travel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extrapulmonary involvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mostly seasonal (Summer/Fall)</td>
</tr>
</tbody>
</table>

Legionella in Minnesota (2015)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported cases, n</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>ICU admission, n (%)</td>
<td>29</td>
<td>57</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>33</td>
<td>65</td>
</tr>
<tr>
<td>≥50 years of age, n (%)</td>
<td>42</td>
<td>82</td>
</tr>
<tr>
<td>Onset June-Sept, n (%)</td>
<td>37</td>
<td>53</td>
</tr>
<tr>
<td>Travel-associated, n (%)</td>
<td>14</td>
<td>29</td>
</tr>
</tbody>
</table>

Legionellosis. MN Dept of Health 2015; accessed April 11, 2017
Question #2

Which atypical pathogen is the most common cause of pneumonia?

1. Mycoplasma pneumoniae
2. Legionella pneumonophila
3. Chlamydophila pneumoniae
4. Streptococcus pneumoniae
Question #3

Which risk factors most likely support infection from Legionella?

1. Female
2. 30 pack-year smoking history w/ COPD
3. Worsening SOB x 30 days
4. Aspiration while windsurfing in Gulf of Mexico
Typical vs. Atypical

Typical
- Streptococcus

Atypical
- Mycoplasma
- Chlamydophila
- Legionella
Diagnostic Options

- Serum antibody
- PCR
- Culture
  - Legionella
  - Mycoplasma
  - Chlamyphila

- Blood

- Sputum

- Urine
  - Urinary antigen
  - Legionella

Chlamydompha: Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Test ID</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>FCPC</td>
<td>High specificity; test 7 days/wk</td>
<td>3-8 days minimum results</td>
</tr>
<tr>
<td>Serum Ab (ELISA)</td>
<td>SCLAM</td>
<td>Same day results (Mon-Fri)</td>
<td>No Acute Dx (IgM vs. IgG)</td>
</tr>
<tr>
<td>PCR</td>
<td>FCPP</td>
<td>High specificity</td>
<td>1-7 days, batched (Colorado)</td>
</tr>
</tbody>
</table>
### Mycoplasma: Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Test ID</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>FMPNC</td>
<td>Test 7 days/wk; high specificity</td>
<td>21-28 days minimum</td>
</tr>
<tr>
<td>Serum Ab</td>
<td>MYCPN</td>
<td>Same day results (Mon-Fri)</td>
<td>No Acute Dx (IgM vs. IgG)</td>
</tr>
<tr>
<td>(ELISA)</td>
<td>FMYPN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>MPRP</td>
<td>High sensitivity, specificity (~100%); Test 7 days/wk</td>
<td>72 hour minimum</td>
</tr>
</tbody>
</table>
# Legionella: Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Test ID</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>LEGI</td>
<td>High specificity (&gt;95%)</td>
<td>Min 7-10 days</td>
</tr>
<tr>
<td>Serum Ab (ELISA)</td>
<td>SLEG</td>
<td>Same day results (if Tues/Thurs @ 2pm)</td>
<td>No Acute Dx; low sensitivity (25-70%)</td>
</tr>
<tr>
<td>Urinary Antigen</td>
<td>LAGU</td>
<td>Moderate sensitivity (70-90%), high specificity (~100%); results w/in 24hrs (15 min)</td>
<td>Only serogroup 1; Mon-Fri testing</td>
</tr>
<tr>
<td>PCR</td>
<td>LEGRP</td>
<td>High sensitivity, specificity (~100%); Test 7 days/wk</td>
<td>72 hr minimum</td>
</tr>
</tbody>
</table>

Increased association with: **hyponatremia, dry cough, ↑LDH, ↑CRP, ↑PLT**

LDH: Lactate dehydrogenase  
CRP: C-reactive protein  
PLT: Platelet count  

Mayo Medical Laboratory; accessed April 4, 2017  
# Clinical indications for diagnostic testing

<table>
<thead>
<tr>
<th>Indication</th>
<th>Chlamyphilia PCR</th>
<th>Mycoplasma PCR</th>
<th>Legionella UAT</th>
<th>Legionella PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Outpatient ABX failure</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cavitary infiltrates</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Chronic EtOH use</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>COPD</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Travel (2 weeks)</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Legionella UAT</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

2007 IDSA Recommendations

2007 IDSA CAP Guidelines

Outpatient

Healthy
Macrolide
Doxycycline

Comorbid Disease
Respiratory FQ
PO β-lactam + Macrolide

Inpatient: non-ICU

Respiratory FQ
IV β-lactam + Macrolide
Doxycycline

Inpatient: ICU

IV β-lactam + Respiratory FQ
IV β-lactam + Macrolide

### FQ or Doxycycline – Non-ICU CAP (Unknown Atypical %)

<table>
<thead>
<tr>
<th>Type</th>
<th>Prospective, double-blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>n=75</td>
</tr>
<tr>
<td>Population</td>
<td>Non-ICU CAP</td>
</tr>
<tr>
<td>Intervention</td>
<td>Levofloxacin 500mg daily vs. Doxycycline 200mg BID</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Clinical success, 60 days</td>
</tr>
<tr>
<td>Secondary outcome(s)</td>
<td>LOS, AE, cost</td>
</tr>
</tbody>
</table>

No difference in clinical success at 60 days

<table>
<thead>
<tr>
<th>Levo (n=30)</th>
<th>Doxy (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>93.3%</td>
<td>97.1%</td>
</tr>
</tbody>
</table>

$p = 0.844$

Shorter length of stay

<table>
<thead>
<tr>
<th>Levo (n=30)</th>
<th>Doxy (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.7 ± 2.05</td>
<td>4.0 ± 1.82</td>
</tr>
</tbody>
</table>

$p < 0.001$

Reduced cost

<table>
<thead>
<tr>
<th>Levo (n=30)</th>
<th>Doxy (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>122.07 ± 15.84</td>
<td>64.98 ± 24.4</td>
</tr>
</tbody>
</table>

$p < 0.001$

2007 IDSA CAP Guidelines

Outpatient

- Healthy
- Comorbid Disease
- Macrolide
- Doxycycline

Inpatient: non-ICU

- Respiratory FQ
- IV β-lactam + Macrolide
- IV β-lactam + Doxycycline

Inpatient: ICU

- IV β-lactam + Respiratory FQ
- IV β-lactam + Macrolide
- IV β-lactam + Doxycycline

Macrolide or Doxycycline – All CAP (45% Atypical)

<table>
<thead>
<tr>
<th>Type</th>
<th>Retrospective review of ACAPS* (prospective, observational)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>n=858</td>
</tr>
<tr>
<td>Population</td>
<td>All CAP severity (Australia), inpatient</td>
</tr>
<tr>
<td>Intervention</td>
<td>BLA-M vs. BLA-D</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Etiology, Severity, Empiric Antibiotics, Clinical Outcomes</td>
</tr>
</tbody>
</table>

- **No difference in 30 day mortality**
  - BLA-D (n=178): 5 (2.8) deaths
  - BLA-M (n=680): 43 (6.3) deaths
  - p = 0.1

- **No difference in days to clinical stability**
  - BLA-D (n=178): 2 (0-7) days
  - BLA-M (n=680): 2 (0-22) days
  - p = 0.006

- **Shorter length of stay**
  - BLA-D (n=178): 5 (0-26) days
  - BLA-M (n=680): 6 (0-78) days
  - p < 0.001

---

2007 IDSA CAP Guidelines

Outpatient

- Healthy
  - Macrolide
  - Doxycycline

- Comorbid Disease
  - Respiratory FQ
  - PO β-lactam + Macrolide

Inpatient: non-ICU

- Respiratory FQ
- IV β-lactam + Macrolide
- IV β-lactam + Doxycycline

Inpatient: ICU

- IV β-lactam + Respiratory FQ
- IV β-lactam + Macrolide
- IV β-lactam + Doxycycline

### FQ or Macrolides – CAP (Unknown Atypical %)

<table>
<thead>
<tr>
<th>Type</th>
<th>Meta analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>n=4989 (16 RCTs)</td>
</tr>
<tr>
<td>Population</td>
<td>All CAP severity, inpatient or outpatient</td>
</tr>
<tr>
<td>Intervention</td>
<td>FQ vs. Macrolides (+/- β-lactam)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>30-day mortality, treatment failure</td>
</tr>
</tbody>
</table>

#### All-cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaillat 1994 EryOfloBL</td>
<td>0.96 (0.33-2.78)</td>
</tr>
<tr>
<td>Lode 1995 ErySpar</td>
<td>0.93 (0.44-1.99)</td>
</tr>
<tr>
<td>Ortquist 1996 RoxSpar</td>
<td>0.97 (0.06-15.33)</td>
</tr>
<tr>
<td>Moola 1999 ClaGrepa</td>
<td>5.04 (0.24-104.45)</td>
</tr>
<tr>
<td>Remirez 1999 ClaSpar</td>
<td>3.14 (0.13-76.61)</td>
</tr>
<tr>
<td>Hoeffken 2001 ClaMoxi</td>
<td>0.69 (0.22-2.14)</td>
</tr>
<tr>
<td>D’Ignazio 2005 AziLevo</td>
<td>1.99 (0.18-21.79)</td>
</tr>
</tbody>
</table>

Total (95% CI) 1.03 (0.63-1.68)
2007 IDSA CAP Guidelines

Outpatient

Healthy

Comorbid Disease

Macrolide

Respiratory FQ

Doxycycline

PO β-lactam + Macrolide

Inpatient: non-ICU

Respiratory FQ

IV β-lactam + Macrolide

IV β-lactam + Doxycycline

Inpatient: ICU

IV β-lactam + Respiratory FQ

IV β-lactam + Macrolide

Legionella only

### FQ or Macrolides – All CAP (100% Legionella)

<table>
<thead>
<tr>
<th>Type</th>
<th>Prospective, Observational, Non-randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>n=292</td>
</tr>
<tr>
<td>Population</td>
<td>Confirmed Legionella diagnosis; Spain</td>
</tr>
<tr>
<td>Intervention</td>
<td>Levofloxacin vs. Macrolide (Azithromycin/Clarithromycin)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Clinical Cure</td>
</tr>
<tr>
<td>Secondary outcome(s)</td>
<td>Duration of fever, adverse drug effects, LOS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Fine score ≤ 3 (non-ICU)</th>
<th>Fine score ≥ 4 (ICU)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Macrolide (n=54)</td>
<td>Levo (n=114)</td>
<td>Macrolide (n=11)</td>
</tr>
<tr>
<td>Clinical cure, n (%)</td>
<td>54 (100)</td>
<td>114 (100)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Fever duration (d), mean (CI)</td>
<td>4.7 (4.1-5.3)</td>
<td>4.5 (4.1-4.9)</td>
<td>4.2 (2.6-4.6)</td>
</tr>
<tr>
<td>LOS (d), mean (CI)</td>
<td>4.3 (3-5.6)</td>
<td>4 (3.7-4.3)</td>
<td>11.3 (5.9-16.7)</td>
</tr>
<tr>
<td>Type</td>
<td>Systematic Review/Meta-Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrollment</td>
<td>n=879 (12 studies, no RCT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>ICU and non-ICU confirmed Legionella disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>FQ or Macrolide (monotherapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcome(s)</td>
<td>Clinical cure, time to apyrexia, LOS, complications</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comparison of FQ vs. Macrolide for ICU CAP (100% Legionella)**

- **Mortality (8)**
- **Clinical Cure (4)**
- **Time to apyrexia, h (1)**
- **LOS, d (3)**
- **Complications (2)**

The diagram illustrates the comparative outcomes, favoring FQ for LOS (days) and Macrolide for mortality and clinical cure.
“Not all that glitters is gold”

- **2007**: IDSA CAP Guidelines
- **2008**: Black Box Warning: Tendonitis/Tendon Rupture
- **2011**: Black Box Warning: Myasthenia Gravis
- **2013**: Irreversible neuropathy
- **2014**: Investigation of neurodegenerative, psychiatric association

Limitations abundant

• No consensus regarding benefit of empiric treatment for atypical pathogens in all patients
• Nonspecific diagnosis of atypical pneumonia
• Low mortality rate of non-legionella atypical pneumonias
• Few studies assess early outcomes; most studied long-term mortality
• Unknown confounders – anti-inflammatory profile of macrolides?

Question #4

Levofloxacin is the preferred treatment for Mycoplasma pneumoniae

1. True
2. False
Inpatient Non-ICU Recommendations

Do symptoms fit atypical pneumonia?

1st Line:
Azithromycin
Doxycycline

Clinically improving after 48-72 hours?

Y
Continue Treatment Course

+ Change to Levofloxacin
Order Legionella UAT/PCR
Order Mycoplasma PCR

N
Consider Alternative Diagnosis

No Antibiotics
Inpatient ICU Recommendations

Risk factors for Legionella?

1st Line: β-lactam (IV) + Respiratory FQ

Legionella UAT

+ Y N

Legionella PCR

+ Y N

Clinically improving after 48-72 hours?

1st Line: β-lactam + Doxycycline

2nd Line: β-lactam + Macrolide

Clinically improving after 48-72 hours?

Consider Alternative Diagnosis

Legionella risk factors

- Male
- Smoking
- Chronic CVD
- COPD
- Immunosuppression
- Freshwater
- Recent Travel

Clinically improving after 48-72 hours?

Y N

Legionella PCR

Clinically improving after 48-72 hours?

Y N

Consider Alternative Diagnosis

Clinically improving after 48-72 hours?

Y N

Consider Alternative Diagnosis

Clinically improving after 48-72 hours?

Y N

Consider Alternative Diagnosis

Clinically improving after 48-72 hours?

Y N

Consider Alternative Diagnosis

Clinically improving after 48-72 hours?

Y N

Consider Alternative Diagnosis

Clinically improving after 48-72 hours?

Y N

Consider Alternative Diagnosis
Questions & Discussion
roy.david@mayo.edu

Community-Acquired Pneumonia (CAP) Guidelines

Infectious Diseases Society of America
Projected Publication, Spring 2018