Pneumonia and Antibiotic Use: Why Less is More

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Northern Michigan Family Medicine Update
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Overview

• Why Antibiotic Use Matters
• First Comes Diagnosis!
• Antibiotic Duration Targets—Turns out Less is More
• The Case Against Fluoroquinolones
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Harm from Antibiotic Use

- Antibiotic resistant organisms cause:
  - 2 million infections; 23,000 deaths annually in US
- Adverse events (rashes, diarrhea, allergic reactions)
  - 143,000 emergency department visits annually
- \textit{Clostridium difficile} infection:
  - 453,000 cases annually
  - One third are community-associated infections
  - A 10\% reduction in overall outpatient antibiotic prescribing could reduce community-associated C. difficile infections by 17%
Other Consequences of Antibiotic Exposure

- We are increasingly recognizing just how important our microbiome is to protecting our health
- Antibiotics imperil that protection
Outpatient Antibiotic Use

• 60% of antibiotic expenditures are related to outpatient care
  – 269 million antibiotic prescriptions (10% of all visits)

• ~50% of outpatient antibiotic prescribing is inappropriate
  (including selection, dosing, or duration)

• At least 30% is unnecessary
  – Mostly prescribed for “Acute Respiratory Infections”

CDC 2013.
Shapiro DJ. JAC. 2014
Fleming-Dutra KE. JAMA 2016/
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## ARIs: Antibiotic-Appropriateness

<table>
<thead>
<tr>
<th>Yes</th>
<th>Occasionally</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Otitis</td>
<td>• Sinusitis</td>
<td>• Non-specific URIs</td>
</tr>
<tr>
<td>• Pneumonia</td>
<td>• Pharyngitis</td>
<td>• Acute bronchitis</td>
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<tr>
<td></td>
<td></td>
<td>• Influenza</td>
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</table>
How do you Diagnose Pneumonia?
### How do you Diagnose Pneumonia?

<table>
<thead>
<tr>
<th>Radiographic Component</th>
<th>Clinical Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Air Space Density/Opacity/Disease</td>
<td>• Cough</td>
</tr>
<tr>
<td>• Bronchopneumonia</td>
<td>• Sputum production</td>
</tr>
<tr>
<td>• Cavitation</td>
<td>• Dyspnea or tachypnea</td>
</tr>
<tr>
<td>• Consolidation</td>
<td>• Hypoxemia</td>
</tr>
<tr>
<td>• Ground Glass</td>
<td>• Fever or hypothermia</td>
</tr>
<tr>
<td>• Infiltrate (Single Lobe)</td>
<td>• Exam consistent with pneumonia</td>
</tr>
<tr>
<td>• Infiltrate (Multiple Lobes)</td>
<td>○ Rales, crackles</td>
</tr>
<tr>
<td>• Loculations</td>
<td>○ Dullness on percussion, bronchial breath sounds, or egophony</td>
</tr>
<tr>
<td>• New or Worsening Infiltrates</td>
<td>• WBC &gt; 10,000 or &gt; 15% bands or WBC &lt; 4,000</td>
</tr>
<tr>
<td>• Nodular Airspace Disease</td>
<td></td>
</tr>
<tr>
<td>• Mass</td>
<td></td>
</tr>
<tr>
<td>• Pleural Effusion</td>
<td></td>
</tr>
<tr>
<td>• Pneumonia</td>
<td></td>
</tr>
</tbody>
</table>
Antibiotic prescriptions in excess of the number expected to treat bacterial infections amounted to 55% (22.6 million) of all antibiotics prescribed for acute respiratory infections, at a cost of approximately $726 million.
Outpatient clinics randomized to
  – Suggested alternatives (order set)
  – Accountable justification (entered in medical record)
  – Peer comparison

Compared to your peers, you are not a top performer
B  Peer comparison

![Graph showing adjusted inappropriate prescribing rate over days relative to intervention start.](image)

- **Intervention period**
- **Control**
- **Peer comparison**

Days Relative to Intervention Start
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Why duration?

• For pneumonia, shorter durations are equally effective
• Change in dogma
• Longer durations
  – Kill off healthy, normal flora
  – Select for resistant pathogens
  – Increase risk of *Clostridium difficile*
  – Increase risk of adverse events (e.g., side effects)

Appropriate Antibiotic Duration for Pneumonia

- Depends on patient factors, disease, clinical stability, and rate of improvement
  - Most patients with community-acquired pneumonia (CAP) should receive 5 days of treatment
  - Most patients with HCAP (risk factors for MDROs) should receive 7 days of treatment
    - Includes *staphylococcal* and *pseudomonal* pneumonia
      - (Excludes complicated infections, bacteremia, failure to improve, etc.)

Consistent with ATS/IDSA guidelines
5 day Treatment for CAP

- 312 patients randomized to “usual care” vs. 5 day protocol

Uranga. JAMA IM. 2016.
Criteria for 5-day Duration

- Afebrile X 48 hrs
- No more than 1 sign of Clinical Instability
  - HR $\geq$ 100 bpm
  - RR $\geq$ 24 breaths/min
  - SBP $\leq$ 90 mmHg
  - Arterial O2 sat $\leq$ 90% or pO2 $\leq$ 60 mmHg on RA
  - Altered mental status (from baseline)
5 day Treatment for CAP

- **Duration of Antibiotic Use**
  - 10 days (10-11) vs. 5 (5-6.5) days, p<0.001

- **Equal resolution of pneumonia by day 10** (48.6% control vs. 56.3%) and day 30 (88.6% vs. 92.7%)
  - Equivalent symptoms

- **Similar LOS, mortality**
  - Readmission: more in control (6.6% vs 1.4%, P=0.02)
How are we doing with antibiotic duration in Michigan?
Based on guidelines, did patients hospitalized with CAP or HCAP receive an appropriate antibiotic duration?

N = 4539 patients at 48 hospitals

Data collected from the Michigan Hospital Medicine Safety Consortium
# Antibiotic Duration for Pneumonia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Community-Acquired (n=3156)</th>
<th>Healthcare-Associated (n=1383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected Duration Based on Guidelines</td>
<td>90% 5 days</td>
<td>97% 7 days</td>
</tr>
</tbody>
</table>

Median duration was 8 days
Proportion of Patients Who Received an Excess Antibiotic Duration

77.8% (3531/4539)
Patients who received excess duration were more likely to have an antibiotic-related adverse event (OR 1.59, p=0.004)
Proportion of Patients who Received an Excess Antibiotic Duration by Hospital

Each Bar = 1 Hospital
Is 5 days too long??
3 vs. 8 day therapy (amox) for CAP

- 119 hospitalized patients in Netherlands
- Randomized to 3 days of amox vs. 8 days
- LOS 7.9 days in 3 day group vs. 8.9 days in 8 day group
- 11% mild adverse events in 3 day vs. 21% in 8 day group

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Three day treatment group</th>
<th>Eight day treatment group</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 10:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure (per protocol analysis)</td>
<td>50/54 (93)</td>
<td>56/60 (93)</td>
<td>0.1 (−9 to 10)</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>50/56 (89)</td>
<td>56/63 (89)</td>
<td>0.4 (−11 to 12)</td>
</tr>
<tr>
<td>Bacteriological success</td>
<td>22/25 (88)</td>
<td>19/20 (95)</td>
<td>−7 (−23 to 9)</td>
</tr>
<tr>
<td>Radiological success</td>
<td>48/56 (86)</td>
<td>52/63 (83)</td>
<td>3 (−10 to 16)</td>
</tr>
<tr>
<td><strong>Day 28:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure (per protocol analysis)</td>
<td>47/52 (90)</td>
<td>49/56 (88)</td>
<td>2 (−9 to 15)</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>47/56 (84)</td>
<td>49/63 (78)</td>
<td>6 (−8 to 20)</td>
</tr>
<tr>
<td>Bacteriological success</td>
<td>20/25 (80)</td>
<td>15/20 (75)</td>
<td>5 (−20 to 30)</td>
</tr>
<tr>
<td>Radiological success</td>
<td>48/56 (86)</td>
<td>50/63 (79)</td>
<td>6 (−7 to 20)</td>
</tr>
</tbody>
</table>

All analyses were by intention to treat, unless indicated otherwise.

What does this mean for outpatient prescribing?

• For outpatients:
  – Less evidence on duration, but
  – Patients with pneumonia (generally) need MAX 5 days of antibiotic therapy

• When a patient is discharged for pneumonia
  – Typically don’t need more antibiotic therapy
    • (They probably already got too much)
    • Symptoms can persist for weeks
    • Antibiotics don’t speed recovery
    • Recurrence of fever should prompt evaluation
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Fluoroquinolone Antibiotics

- Ciprofloxacin, moxifloxacin, levofloxacin
- Associated with:
  - Antimicrobial resistance
  - Adverse-events (27% of inpatients)
  - *Clostridium difficile* infections

Dingle. Lancet. 2017
Werner. BMC Infect Dis. 2011
Stewardship vs. Infection Control to Reduce *C. difficile*

If decreases in *C. difficile* infection were driven by improvements in hospital infection control and NOT antimicrobial stewardship, then CDI cases should decline regardless of antimicrobial susceptibility of the strains.
Figure 2. Incidence of *Clostridium difficile* infections together with fluoroquinolone and cephalosporin prescribing for Oxfordshire (A) and incidence of *C. difficile* infections by fluoroquinolone susceptibility for Oxfordshire (B)

Intro of national control policies: June 2007
RCT of 3 treatments for adults with CAP hospitalized in non-ICUs
- Beta-lactam: amox, amox-clav, 3rd ceph
- Beta-lactam + macrolide
- Quinolone

Treatment Regimens for CAP

- No statistical differences between groups in:
  - Mortality
  - Length of stay

- Conclusion: Empiric treatment with beta-lactam monotherapy was noninferior to beta-lactam–macrolide combination or fluoroquinolone monotherapy with regard to 90-day mortality

Outpatient Treatment for CAP

- Avoid fluoroquinolones if possible
- *S. pneumoniae*, *Mycoplasma pneumoniae*, and respiratory viruses most common; don’t want to miss atypical coverage
- Macrolide! (azithro)
- If comorbidities, add beta lactam (helps cover potentially resistant *S. pneumonia*)
  - e.g., amoxicillin/clavulanate or cefpodoxime plus azithro/clarithro/doxy

Consistent with ATS/IDSA guidelines
Summary

- Inappropriate antibiotic use is common and causes patient harm
- Don’t prescribing antibiotics to patients with URIs, bronchitis, or influenza
- Pneumonia diagnosis includes CXR and symptoms
- Treatment for pneumonia typically shouldn’t > 5 days
- When possible, avoid fluoroquinolone antibiotics
Thanks

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AST Members