Learning Objectives

- **Upon successful completion of this activity, pharmacists should be able to:**
  - 1. Review the role of noninferiority studies and how they compare to randomized controlled trials.
  - 2. Differentiate between the various treatment lengths of antibiotics for community acquired pneumonia and their potential impact on drug resistance.
  - 3. Discuss potential pros and cons of shorter treatment lengths for CAP.
  - 4. Interpret the results of this study and apply its findings to a patient case.
  - 5. Determine how to utilize the results of this study for antimicrobial stewardship.
Disclosure

• Jennifer Ball reports no actual or potential conflicts of interest associated with this presentation

Patient Case

• RJ is a 47yo male who presents to the ER with altered mental status, SOB and coughing up rust-colored phlegm x 1 week. Vitals are 101.2°F, 130/84mmHg, 84bpm, 32rpm, O₂ sat 93%
• PMH: COPD, HTN, Hyperlipidemia
• Labs: WNL
• PE: Well nourished male, A&O x 2 (missing place). Crackles and decreased breath sounds heard on lower right lobe
• CXR: right lower lobe infiltrate
• Allergies: penicillin (rash)
• Meds: tiotropium Handihaler 1 capsule inhaled once daily, Albuterol 2 puffs Q6 hr pm SOB, hydrochlorothiazide 25mg once daily, atorvastatin 20mg once daily
• The physician diagnoses him as having community-acquired pneumonia (CAP).
Patient Case
- What organism is the most likely cause of CAP in this patient?
  - A) Streptococcus pneumoniae
  - B) Streptococcus aureus
  - C) Pseudomonas pneumoniae
  - D) Pseudomonas aeruginosa

Community Acquired Pneumonia Etiology
- Community-acquired pneumonia can be caused by:
  - Bacteria
  - Viruses
  - Fungi

- Most common bacterial pathogens:
  - Streptococcus pneumoniae
  - Mycoplasma pneumoniae
  - Haemophilus influenzae
  - Chlamydia pneumoniae
  - Legionella

Mandell LA. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72
Patient Case

• What therapy would you start?
  • A) Levofloxacin 500mg IV daily
  • B) Levofloxacin 750mg oral daily
  • C) Azithromycin 500mg oral daily
  • D) Ampicillin/sulbactam 1.5g IV Q6hr PLUS azithromycin 500mg IV daily

Journal Article


• Study funding
  • Grant 2010111095 from the Health Department of Basque Country government
  • Grant EC10-157 from the Pharmacy Department of the Spanish government
  • Fellows Scholarship 011/2013 from the Spanish Pulmonology and Thoracic Surgery Society
  • Funding grants had no role in trial design, data collection, analysis, or manuscript preparation

Background

- Lower respiratory tract infections are the most common infectious cause of death
  - Incidence of 3.1 million cases worldwide in 2012

- Annual incidence of CAP hospitalizations ranges from 2.5-24.8/1000 people in the United States with increasing rates with age

Centers for Disease Control and Prevention. 2013.
Mandell LA. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72

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Background

- Concerns for increasing rates of resistance
  - 30% of cases of pneumonia caused by S. pneumoniae are resistant to at least 1 drug

- Studies show that resistance can be decreased by
  - Using narrow spectrum antibiotics
  - Only using antibiotics if needed
  - Considering patient and disease specific factors
  - Switching from IV to PO therapy
  - **Shortening duration of therapy**

Centers for Disease Control and Prevention. 2013.
## Background

<table>
<thead>
<tr>
<th>Place of Treatment</th>
<th>Infectious Diseases Society of America (IDSA)/ American Thoracic Society (ATS) 2007 Guidelines</th>
<th>Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) 2010 Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient, non-ICU</td>
<td>• β-lactam PLUS a macrolide OR a respiratory fluoroquinolone x minimum of 5 days should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability</td>
<td>• Third generation cephalosporins or amoxicillin-clavulanic acid plus a macrolide IV x 7-10 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Levofloxacin IV/PO x 7-10 days</td>
</tr>
</tbody>
</table>


## Objectives of Study

- **Primary outcomes:**
  - Clinical success rate at day 10
  - Clinical success at late follow-up (day 30) since admission
  - Clinical success defined as resolution or improvement in signs and symptoms related to pneumonia without further antibiotics, and CAP-related symptoms at day 10 measured with the 18-item CAP symptom questionnaire

- **Changes from initial plans**
  - Did not include all cause mortality or major complications due to low number

Uranga et al. JAMA. July 2016
CAP Symptom Questionnaire

Do you feel the primary objectives were appropriate?

a. Yes
b. No

Scoring
- Total: 90 points
- Higher score is worse response
- Clinical cure average: 12.4 points
- Clinical failure average: 21 points
Objectives of Study

- Secondary outcomes:
  - Duration of antibiotics - *initially planned as a primary outcome*
  - Time to clinical improvement - patient response at 30 days
  - Time to return to normal activity - patient response at 30 days
  - Radiographic resolution at 30 days
  - In-hospital mortality
  - Mortality at 30 days
  - CAP reoccurrence if cured at day 10
  - Hospital readmission within 30 days
  - Complications of hospitalization
  - Number of days with adverse effects up to day 30
  - Length of hospital stay

Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 years or older</td>
<td>History of HIV or chronic immunosuppression</td>
</tr>
<tr>
<td>Hospitalized with a diagnosis of CAP (pulmonary infiltrate with at least 1 symptom of pneumonia)</td>
<td>Lived in a nursing home</td>
</tr>
<tr>
<td></td>
<td>Discharged from an acute care hospital, subacute care unit, or palliative care unit in the last 14 days</td>
</tr>
<tr>
<td></td>
<td>Taken antibiotics in the last 30 days</td>
</tr>
<tr>
<td></td>
<td>Require longer duration of therapy</td>
</tr>
<tr>
<td></td>
<td>Require chest tube placement</td>
</tr>
<tr>
<td></td>
<td>Condition is complicated by an extrapulmonary infection</td>
</tr>
<tr>
<td></td>
<td>Died or transferred to ICU prior to randomization</td>
</tr>
</tbody>
</table>
Do you feel the inclusion/exclusion criteria were appropriate?

a. Yes
b. No

Study Design

- Multicenter, noninferiority randomized clinical trial from January 1, 2012, through August 31, 2013
- All hospitalized patients diagnosed with CAP in 4 teaching hospitals in the Basque Country in Spain
- Randomized at day 5 using a random number generator
- Stratified by pneumonia severity index (PSI), antibiotic group, or hospital


### Study Design

- **Intervention group:**
  - Treated with antibiotics for a minimum of 5 days,
  - Antibiotic treatment was stopped at this point if temp ≤100°F x 48 hrs and no more than 1 CAP-associated sign of clinical instability (SBP ≤90mmHg, HR ≥100/min, RR ≥24 /min, O2 sat 90%, or PaO2 ≤60 mm Hg RA)

- **Control group:**
  - Treated with antibiotics with duration decided per clinician

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### Statistics

- 142 people in each branch needed if 80% power, 0.025 1-sided α error, and CAP symptom score of 18±11

- Intent to Treat and Per-protocol statistics completed

- Categorical variables
  - X2 and Fisher exact test

- Continuous variables
  - 2-tailed t-test or nonparametric Wilcoxon rank sum test

- Return to normal activity
  - Used Kaplan-Meier curves compared by log-rank test

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Statistics

- Primary outcome
  - Clinical success
    - Generalized linear mixed models
  - CAP symptom questionnaire
    - Linear mixed models

Study Flow

- 312 randomized
- Intent to treat
  - 150 vs 162
- Per protocol
  - 137 vs 146

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n=150)</th>
<th>Intervention (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>66.2 (17.9)</td>
<td>64.7 (18.7)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>95 (63.3)</td>
<td>101 (62.3)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>Current: 32 (21.3)</td>
<td>Current: 36 (22.6)</td>
</tr>
<tr>
<td></td>
<td>Never: 68 (45.3)</td>
<td>Never: 71 (44.7)</td>
</tr>
<tr>
<td></td>
<td>Former: 50 (33.3)</td>
<td>Former: 52 (32.7)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>Heart disease: 38 (25.3)</td>
<td>Heart disease: 39 (24.1)</td>
</tr>
<tr>
<td></td>
<td>CHF: 14 (9.3)</td>
<td>CHF: 12 (7.4)</td>
</tr>
<tr>
<td></td>
<td>CVD: 16 (10.7)</td>
<td>CVD: 9 (5.6)</td>
</tr>
<tr>
<td></td>
<td>Renal disease: 12 (8.0)</td>
<td>Renal disease: 12 (7.4)</td>
</tr>
<tr>
<td></td>
<td>COPD: 21 (14.0)</td>
<td>COPD: 27 (16.7)</td>
</tr>
<tr>
<td></td>
<td>Diabetes: 25 (16.7)</td>
<td>Diabetes: 21 (13.0)</td>
</tr>
<tr>
<td>Charleston Comorbidity Index, n (%)</td>
<td>0: 61 (40.7)</td>
<td>0: 70 (43.2)</td>
</tr>
<tr>
<td></td>
<td>1: 37 (24.7)</td>
<td>1: 47 (29.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;1: 52 (34.7)</td>
<td>&gt;1: 45 (27.8)</td>
</tr>
<tr>
<td>PSI class, n (%)</td>
<td>I-II: 89 (59.3)</td>
<td>I-II: 102 (63.0)</td>
</tr>
<tr>
<td></td>
<td>IV: 61 (40.7)</td>
<td>IV: 60 (37.0)</td>
</tr>
</tbody>
</table>

Results

- Primary Outcomes

<table>
<thead>
<tr>
<th>Outcome, ITT</th>
<th>Control, n=150</th>
<th>Intervention, n=162</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success, %</td>
<td>Day 10: 48.6</td>
<td>Day 10: 56.3</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Day 30: 88.6</td>
<td>Day 30: 91.9</td>
<td>0.33</td>
</tr>
<tr>
<td>CAP symptom questionnaire score*, mean(SD)</td>
<td>Day 5: 24.7(11.4)</td>
<td>Day 5: 27.2 (12.5)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Day 10: 18.6 (9.0)</td>
<td>Day 10: 17.9 (7.6)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*CAP symptom questionnaire score: noninferiority margin is 3 points

Based on the results of the study, what is an appropriate conclusion?

A) The intervention group is superior to the clinician-directed control group

B) The intervention group is inferior to the clinician-directed control group

C) The intervention group is noninferior to the clinician-directed control group

Results

- Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcomes,ITT</th>
<th>Control</th>
<th>Intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success, % PSI classes I-III</td>
<td>Day 10: 47.7 Day 30: 94.3</td>
<td>Day 10: 57.4 Day 30: 91.2</td>
<td>0.18 0.41</td>
</tr>
<tr>
<td>Clinical success, % PSI classes IV-V</td>
<td>Day 10: 50.0 Day 30: 80.3</td>
<td>Day 10: 54.2 Day 30: 93.1</td>
<td>0.64 0.04*</td>
</tr>
</tbody>
</table>

*No results were statistically significant in the per protocol outcomes

## Results

### Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control, n=137</th>
<th>Intervention, n=146</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking antibiotics</td>
<td>10</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taking IV antibiotics</td>
<td>2</td>
<td>3</td>
<td>0.22</td>
</tr>
<tr>
<td>Until clinical improvement</td>
<td>12</td>
<td>12</td>
<td>0.41</td>
</tr>
<tr>
<td>Return to normal activity</td>
<td>18</td>
<td>15</td>
<td>0.36</td>
</tr>
</tbody>
</table>


### Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome, PP</th>
<th>Control, n=137</th>
<th>Intervention, n=146</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic resolution-day 30, %</td>
<td>73.2</td>
<td>81.2</td>
<td>0.12</td>
</tr>
<tr>
<td>In-hospital mortality, %</td>
<td>1.5</td>
<td>2.1</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>30-d mortality, %</td>
<td>2.2</td>
<td>2.1</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Reoccurrence by day 30, %</td>
<td>4.4</td>
<td>2.8</td>
<td>0.53</td>
</tr>
<tr>
<td>Readmission by day 30, %</td>
<td>6.6</td>
<td>1.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Antibiotic adverse effects by day 30</td>
<td>13.1</td>
<td>11.7</td>
<td>0.72</td>
</tr>
<tr>
<td>Length of hospital stay, mean (SD)</td>
<td>5.5 (2.3)</td>
<td>5.7 (2.8)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Discussion

• 101/146 patients in the intervention group were able to limit the duration of antibiotics to 5 days

• No change to hospital length of stay was shown due to commonly discharging from time to change IV to PO

• Higher readmissions were seen with the control group, however the intervention group was more likely to call in

What are the strengths of this study?

**Strengths**

- Allowed for comparison to standard of care with clinician-decided control group
- Included patients with severe CAP admitted to non-ICU floors
- Study follows FDA recommendations for CAP study outcomes
  - Primary endpoint of symptom resolution at day 10 (5-10 days after end of therapy)
  - Include mortality as a secondary endpoint
  - Outcomes included endpoints that are meaningful to patients (clinical improvement, return to normal activity, antibiotic adverse effects)
What are the limitations of this study?

Limitations

- Study endpoints were changed after submission of the protocol
- Study only occurred in a small area of Spain
  - No hospital resistance data was reported
- 80% were treated with fluoroquinolones
- Pathogens were not specified
- Did not include nursing home patients or those discharged from an acute care, subacute care, or palliative care unit
- Did not include higher risk populations (immunosuppressed, ICU, etc)
Author Conclusions

• The IDSA/ATS recommendations for shorter duration of antibiotic treatment based on clinical stability criteria can be safely implemented in hospitalized patients with CAP

• Patients reached stability by day 3, thus 5 days may be appropriate in most cases. Duration of antibiotic treatment based on clinical response appears to be a better strategy than using arbitrary treatment lengths

• No differences were seen in hospital length of stay as this was dependent on when patients were changed from IV to PO


Presenter’s Conclusions

• Patients with CAP admitted to an non-ICU and treated with fluoroquinolones can safely stop therapy after 5 days of treatment and no more than 1 CAP-associated sign of clinical instability

• Cannot extrapolate data to β lactam + macrolide due to low numbers in the study

• Important to also look at local antibiogram to determine resistance
Patient Case

• RJ is admitted to the internal medicine floor and started on levofloxacin 750mg once daily. After 3 days of treatment, RJ is afebrile with improved dyspnea, cough, and a normal RR. Dr. Smith is interested in discharging to complete antibiotics at home. How many days of therapy would you recommend?
  • A) 2 days
  • B) 5 days
  • C) 7 days
  • D) He has completed treatment due to clinically improved symptoms

A patient calls in to clarify how to take their prescription for levofloxacin 750mg daily for CAP. The doctor prescribed 7 days, but told him to stop taking it if he was better after 5 days. However in the past, he had always been told to always take the full supply of antibiotics. How would you respond?
Clinical Takeaways

• FOCUS on symptomatic improvement

• Inpatient Medicine
  • Consider 5 days of therapy with improvement in CAP within 3 days
  • Recommend a respiratory fluoroquinolone or β-lactam PLUS a macrolide based on local antibiogram

• Ambulatory Medicine
  • Consider 5-7 days of therapy for community-acquired pneumonia
    • Identify patients with higher health literacy that may be appropriate to stop antibiotics at 5 days
    • Recommend respiratory fluoroquinolone or β-lactam PLUS a macrolide if high rates of resistance to strep pneumoniae or macrolide OR doxycycline if low rates of resistance

LOGIN with your questions or additional discussion....
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Logon to www.GoToCEI.org
Click on My Profile.

Locate the activity title you wish to complete within your Profile and click on Exam.

Complete the Exam and Evaluation as prompted; click SUBMIT to send your information to CPE Monitor.

• There is no code associated with this activity. All participants were to have pre-registered on the CEI website.

• Once your credit has been claimed, the activity will move to your Completed Activities.