Beta-Lactam Monotherapy in Community-Acquired Pneumonia: Is it Beta or Worse?

R. Joel Moore, PharmD
Master’s Pharmacotherapy Resident
Pharmacotherapy Division, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center, UT Health San Antonio
May 5, 2017

Learning Objectives
1. Describe the current epidemiology and microbiology of community-acquired pneumonia
2. Describe available empiric treatment strategies for community-acquired pneumonia, focusing on the potential advantages and disadvantages of each strategy
3. Evaluate current literature regarding empiric treatment of community-acquired pneumonia in hospitalized adults with beta-lactam/macrolide combination therapy, beta-lactam monotherapy, and fluoroquinolone monotherapy
4. Given a patient case, determine the appropriateness of beta-lactam monotherapy as empiric treatment for community-acquired pneumonia
Background & Introduction

1) Pneumonia has been described for thousands of years; however, its causes have only been elucidated recently.

2) Causes of pneumonia
   a) Bacterial
      i) Many potential pathogens (*Streptococcus pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae*, etc.)
      ii) *Mycobacterium tuberculosis*
         1) Acid-fast staining bacillus
         2) Incidence much lower in US compared to other countries
   b) Viral
      i) Influenza, respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, coronaviruses, and rhinovirus
      ii) Viral infections commonly predispose individuals to secondary bacterial infections
   c) Fungal
      i) *Histoplasma* and *Coccidioides*
         1) *Histoplasma* endemic to Ohio and Mississippi River valleys
         2) *Coccidioides* endemic to southwestern United States
   d) Undetermined cause in half of those hospitalized for CAP in the US.

3) Costs of pneumonia
   a) In the U.S., accounts for an estimated 63,000 deaths, 1.2 million hospitalizations, and 2.3 million emergency department visits annually
   b) Mean cost per stay is $9,500
      i) Costs increased by approximately $2,000 per stay in past decade

4) Pneumonia classification
   a) Community-acquired pneumonia (CAP)
      i) An acute infection of the pulmonary parenchyma contracted from the community
      ii) May be either bacterial or viral
   b) Hospital-acquired pneumonia (HAP)
      i) Develops 48-72 hours after admission to acute care facility
      ii) Associated with different causative pathogens than CAP
   c) Ventilator-associated pneumonia (VAP)
      i) Pneumonia occurring >48 hours post-endotracheal intubation
      ii) Associated with pathogens similar to those found in HAP
   d) Healthcare-associated pneumonia (HAP) was described previously but has now been removed from current guidelines.

Epidemiology

1) Early literature described *Streptococcus pneumoniae* as causative pathogen for approximately 95% of cases of pneumonia.

2) *S. pneumoniae* currently detected in approximately 10-15% of inpatient cases in the U.S.
   a) Attributable in part to the implementation of pneumococcal vaccines
      i) 7-valent pneumococcal conjugate vaccine (PCV7)
         1) Introduced into U.S. infant immunization schedule in 2000
         2) Resulted in 168,000 fewer hospitalizations for pneumonia annually
      ii) 13-valent pneumococcal conjugate vaccine (PCV13)
         1) Serotypes corresponding to >60% of disease isolates in children
         2) Replaced PCV7 in 2010
iii) 23-valent pneumococcal polysaccharide vaccine (PPSV23)
   (1) Serotypes corresponding to 85-90% of invasive pneumococcal disease (IPD)
   (2) Lacks the superior immunogenicity of the conjugate vaccine
b) Decline also due to decreased rates of cigarette smoking\textsuperscript{16}
c) Higher proportion in Europe and other countries of \textit{S. pneumoniae} compared to other pathogens\textsuperscript{17}
3) Disproportionately affects the young and elderly\textsuperscript{6}
a) 7\% of hospital stays in those aged 1-17 years
b) 4\% of hospital stays in those aged 65-84 years
c) 6\% of hospital stays in those aged >85 years

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Incidence of pneumonia-related hospitalization by age group\textsuperscript{18}}
\end{figure}

4) 30-day mortality in elderly patients who are hospitalized for CAP is 10-12\%\textsuperscript{19}
a) Approximately 18\% of these patients are readmitted within 30 days\textsuperscript{20}

\textbf{Diagnosis & Clinical Manifestations}

1) Definitive diagnosis based on presence of select clinical features\textsuperscript{4,8}
a) Symptoms: cough, fever, sputum production, shortness of breath, leukocytosis, and pleuritic chest pain
b) Imaging: newly recognized lung infiltrate on chest imaging
   i) Difficult to identify in those with chronic lung disease and obese patients
   ii) Differential diagnosis of an abnormal chest radiograph\textsuperscript{21}
      (1) Congestive heart failure with viral syndrome
      (2) Aspiration pneumonitis
      (3) Pulmonary infarction
      (4) Acute exacerbation of pulmonary fibrosis
      (5) Pulmonary vasculitis
2) Role of cultures and urine tests\textsuperscript{8,22}
   a) Blood and sputum cultures recommended for moderate- or high-severity CAP
   b) Pneumococcal and legionella urinary antigen tests should be considered in severe CAP, but are not otherwise recommended
i) Both have good specificity, but sensitivity approximately 70-80%
ii) Only *L. pneumophila* serogroup 1 (accounts for ~80% of community-acquired cases of *L. pneumophila*) identifiable via urinary antigen

3) Microscopic evaluation of pulmonary secretions\(^4,23\)
   a) Gram staining and sputum culture are positive in 80% of cases of pneumococcal pneumonia
   i) Good-quality specimen required (>10 inflammatory cells per epithelial cell)
   ii) Should be obtained before, or within 6-12 hours after, initiation of antibiotics

4) Role of biomarkers
   a) C-reactive protein\(^24\)
      i) Protein of the acute phase, synthesized by hepatocytes
      ii) Production stimulated by IL-6, IL-1β, and TNFα in response to infection or tissue inflammation
      iii) Insufficient evidence to support its routine use in diagnosing CAP or assessing its likely etiology
   b) Procalcitonin (PCT)\(^25\)
      i) Precursor to calcitonin, a hormone, and is a component of the innate pro-inflammatory response
      ii) Released within 4 hours of inoculation with bacteria or bacterial endotoxin
      iii) PCT threshold ≥0.1 ng/ml
         1) 80.9% sensitive and 51.6% specific in detecting any bacterial CAP vs. viral CAP
         2) 87.6% sensitive and 49.3% specific in detecting typical bacterial CAP vs. viral and atypical CAP
      iv) PCT values for patients with atypical bacteria more similar to those with viruses than typical bacteria
         (except for *Legionella*)

5) Several tools available to stratify patients by severity and for resource allocation
   a) CURB-65\(^26\)
      i) Five variables with a single point awarded for each

---

*Figure 2: Severity assessment in a hospital setting: the CURB-65 score.*\(^26\)
i) 0 or 1: low risk of death (<3%)
ii) 2: intermediate risk (3-15%)
iii) 3 to 5: high risk (>15%)

b) Pneumonia Severity Index (PSI) (Appendix A)\textsuperscript{27}
   i) Composed of 20 items and classifies patients into five categories
      (1) Class I-II – 0.1-0.7% 30-day mortality
      (2) Classes III-IV – 1-9% 30-day mortality
      (3) Class V – 27% 30-day mortality
   ii) Age and comorbidities highly weighted and may underestimate severity of pneumonia in young patients and those without previous diseases

c) Comparisons between PSI and CURB-65 are mixed
   i) Recent meta-analysis concluded that PSI is superior at identifying low risk patients and CURB-65 is superior to PSI for identifying patients at the highest risk\textsuperscript{28}

**Microbiology**

1) Typical pathogens
   a) *Streptococcus pneumoniae*
      i) Most commonly isolated bacterial cause of CAP\textsuperscript{18}
      ii) Gram-positive diplococci
      iii) Lancet shaped or arranged in chains
      iv) Normal upper respiratory tract flora in 5-40% of humans

b) *Haemophilus influenzae*
   i) Small, gram-negative, pleomorphic bacteria
   ii) Found on mucous membranes of the upper respiratory tract in humans
   iii) Up to 25% produce beta-lactamase

c) *Staphylococcus aureus*
   i) Gram-positive, coagulase-positive spherical cells arranged in grapelike irregular clusters
   ii) Nasal carriage occurs in 20-50% of humans

2) Atypical pathogens
   a) *Mycoplasma pneumoniae*
      i) “Atypical” due to their small size and growth on complex but cell-free media
      ii) Incubation period varies from 1-3 weeks with an insidious onset
      iii) Initially associated with a nonproductive cough, but is occasionally paroxysmal

b) *Legionella pneumophila*
   i) Fastidious, aerobic gram-negative bacteria
   ii) Gram stain unreliable as stains poorly
   iii) Ubiquitous in warm, moist environments
   iv) Antigens can be detected in the patient’s urine by immunologic methods

c) *Chlamydia pneumoniae*
   i) Gram-negative bacteria
   ii) Obligate intracellular parasites
3) Community-acquired pneumonia requiring hospitalization among U.S. adults (EPIC-CAP) study.\textsuperscript{18}
   a) Active population-based surveillance for CAP requiring hospitalization
      i) Age $\geq$ 18 years
      ii) Five hospitals in Chicago and Nashville
   b) 2,488 adults enrolled from January 2010 through June 2012

![Venn Diagram](image)

Figure 3: Pathogen Detection among U.S. Adults with Community-Acquired Pneumonia Requiring Hospitalization, 2010–2012.\textsuperscript{18}

c) Of those in whom a pathogen was detected, bacteria were implicated in only 37% of cases
   i) \textit{S. pneumoniae} was the most commonly detected bacterium
      (1) Five times greater incidence in those $\geq$ 65 years compared to younger adults
   ii) Atypical pathogens (\textit{M. pneumoniae}, \textit{L. pneumophila}, and \textit{C. pneumoniae} combined) detected in 4% of adults

Table 1. Bacterial pathogens detection among hospitalized adults with CAP by age group.\textsuperscript{18}

<table>
<thead>
<tr>
<th>Pathogen detected</th>
<th>18-49 years (n=681)</th>
<th>50-64 years (n=773)</th>
<th>65-79 years (n=506)</th>
<th>$\geq$ 80 years (n=299)</th>
<th>All ages (n=2259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{S. pneumoniae}</td>
<td>5%</td>
<td>5%</td>
<td>7%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>\textit{M. pneumoniae}</td>
<td>4%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>\textit{S. aureus}</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>\textit{L. pneumophila}</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>
d) 65% of the study population was PSI class I-III, 26% class IV, and 9% class V
   i) Median PSI score was 76

Table 2. Bacterial pathogen detection among hospitalized adults with CAP by PSI and ICU admission

<table>
<thead>
<tr>
<th>Pathogen detected</th>
<th>PSI I-III (n=1475)</th>
<th>PSI IV-V (n=784)</th>
<th>P-value*</th>
<th>Non-ICU (n=1777)</th>
<th>ICU (n=482)</th>
<th>P-value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>4%</td>
<td>7%</td>
<td>0.02</td>
<td>4%</td>
<td>8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>3%</td>
<td>1%</td>
<td>0.001</td>
<td>2%</td>
<td>1%</td>
<td>0.06</td>
</tr>
<tr>
<td>S. aureus</td>
<td>1%</td>
<td>3%</td>
<td>0.001</td>
<td>1%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>L. pneumophila</td>
<td>2%</td>
<td>1%</td>
<td>0.06</td>
<td>2%</td>
<td>1%</td>
<td>0.43</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1%</td>
<td>2%</td>
<td>0.002</td>
<td>1%</td>
<td>3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P value comparing proportion of each detection between PSI I-III and PSI IV-V
§P value comparing proportion of each detection between non-ICU and ICU admission

Treatment Options

Table 3. Representative MICs (range) (mcg/mL) of selected antimicrobials against CAP organisms

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.25 (0.06-0.5)</td>
<td>0.12 (0.06-0.25)</td>
<td>1 (0.13-1)</td>
<td>0.03-0.06</td>
<td>0.12-0.3</td>
<td>0.06</td>
<td>0.06-1</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>1 (1-2)</td>
<td>0.25 (0.25-0.5)</td>
<td>0.5 (0.03-8)</td>
<td>0.015-0.5</td>
<td>0.5-2.5</td>
<td>0.016-0.03</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1.0a</td>
<td>&gt;128</td>
<td></td>
<td>8</td>
<td>≤0.015</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1.0a</td>
<td>-</td>
<td></td>
<td>2</td>
<td>0.015</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.25a</td>
<td>&gt;128</td>
<td></td>
<td>16</td>
<td>≤0.015</td>
<td>0.046</td>
<td>0.03</td>
</tr>
<tr>
<td>2nd Generation Cephalosporins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.25</td>
<td>2</td>
<td>16</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3rd Generation Cephalosporins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.06</td>
<td>2</td>
<td>0.25</td>
<td>0.015</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>0.06</td>
<td>4</td>
<td>0.25</td>
<td>0.015</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Aminopenicillins

| Ampicillin, Amoxicillin         | 0.03a      | 0.12 | 50 | 0.25 | - | - | - |
| Aminopenicillin/Beta-Lactamase Inhibitor |
| Amoxicillin-Clavulanate         | 0.03a      | 1    | 2  | 0.5  | - | - | - |
| Ampicillin-Sulbactam            | 0.03a      | 1    | 4  | 0.25 | - | - | - |


*aPenicillin-susceptible S. pneumoniae (MIC ≤ 0.06 mcg/mL)
Guideline Recommendations

1) Guidelines generally recommend coverage for both typical and atypical pathogens commonly found in CAP; however, atypical coverage is controversial

Table 4. Empiric antibiotics suggested for community-acquired pneumonia

<table>
<thead>
<tr>
<th></th>
<th>American (IDSA/ATS)</th>
<th>British (NICE/BTS)</th>
<th>European (ESCMID/ERS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferred</td>
<td>Alternative</td>
<td>Preferred</td>
</tr>
<tr>
<td>Inpatient not in ICU; moderate severity</td>
<td>Beta-lactam&lt;sup&gt;a&lt;/sup&gt; + macrolide</td>
<td>Respiratory fluoroquinolone</td>
<td>Amoxicillin + macrolide</td>
</tr>
</tbody>
</table>

ATS = American Thoracic Society; BTS = British Thoracic Society; IDSA = Infectious Diseases Society of America; ESCMID = European Society for Clinical Microbiology and Infectious Diseases; ERS = European Respiratory Society; NICE = National Institute for Health and Care Excellence

<sup>a</sup> Preferred beta-lactam drugs include cefotaxime (third generation), ceftriaxone (third generation), and ampicillin

<sup>b</sup> Respiratory fluoroquinolone limited to situations in which other options cannot be prescribed or are ineffective (e.g., hepatotoxicity, skin reactions, cardiac arrhythmias, and tendon rupture).

a) Recommendations for fluoroquinolone monotherapy or beta-lactam/macrolide dual therapy largely based on retrospective studies (Appendix, Tables 5 and 6)

b) *Mycoplasma* and *Chlamydophila* infections are often self-limited and associated with low mortality risk<sup>35</sup>

c) A 2012 Cochrane review and meta-analysis assessed treatment failure with regimens containing atypical antibiotic coverage compared to typical coverage only<sup>36</sup>

i) 28 trials and 5,939 patients

ii) Primary outcome: clinical failure in all studies

iii) Non-significant trend toward an advantage in the atypical arm (RR 0.93; 95% CI 0.84 to 1.04)

iv) Authors concluded no benefit with empirical atypical coverage in hospitalized patients with CAP

d) Fluoroquinolone treatment considerations

i) May be more strongly associated with *Clostridium difficile*-associated diarrhea (CDAD) than other antibiotics<sup>37,38</sup>

ii) Monotherapy may result in better adherence to guideline-concordant therapy

iii) More readily switch to PO<sup>39</sup>

e) Macrolide treatment considerations

i) Development of resistance of *S. pneumoniae* against multiple antibiotic classes<sup>40-43</sup>

ii) Possible increased risk of cardiac events<sup>44,45</sup>

iii) Might favorably affect the host inflammatory response through nonantibiotic effects<sup>46</sup>

Clinical Question

Is empiric therapy with a beta-lactam noninferior in treating CAP in non-ICU, hospitalized patients compared to beta-lactam-macrolide combination therapy or fluoroquinolone therapy?
### Literature Review


<table>
<thead>
<tr>
<th><strong>Purpose</strong></th>
<th>Determine variation in use of single vs. combination antibiotic therapy in CAP and whether observed differences are related to clinical outcomes by pneumonia severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Retrospective cohort study conducted in the United Kingdom</td>
</tr>
</tbody>
</table>
| **Population** | **Inclusion:**
- Age > 16 years
- New infiltrates on CXR consistent with CAP
- Symptoms suggestive of lower respiratory tract infection
- Treatment given as for CAP
**Exclusion:**
- Discharged from hospital within 10 days prior to current admission
- Receipt of fluoroquinolone antibiotics |
| **Intervention** | **Single-agent therapy with beta-lactam antibiotic:** any penicillin or cephalosporin
**Combination therapy with beta-lactam and macrolide:** erythromycin, clarithromycin, azithromycin |
| **Endpoints** | **Primary:**
- 30-day inpatient death rate
**Secondary:**
- Length of stay
- ICU admission
- Need for mechanical ventilation (MV)
- Need for inotropic support (INS)
- Time of death
- 30-day readmission |
| **Methods** | **All trusts across England and Wales invited to participate in BTS adult CAP national audit**
**Sites asked to include consecutive immunocompetent adults hospitalized with CAP during the periods December 1, 2009 – January 31, 2010 and December 1, 2010 – January 31, 2011** |
| **Statistical Analyses** | **Pearson’s $\chi^2$ used to compare categorical variables, perform univariate analyses and generation of ORs and 95% CIs**
**Mann-Whitney U test used to compare non-parametric continuous variables**
**Association between combination antibiotic therapy and 30-day IP death rate examined using a logistic regression model**
  - Adjusted for age, sex, binary variables within CURB65 score (excluding age), comorbidities, IV antibiotic use, nursing home residency and ICU admission
**Subgroup analysis based on CURB65 score performed following adjustment for sex, comorbidities, IV antibiotic use and nursing home residency**
**Statistical significance defined as P value < 0.05**
**Results expressed as OR with 95% CI** |
Results

- 6312 patients in national audit dataset
  - 1072 (17%) received antibiotic other than a beta-lactam or a beta-lactam/macrolide combination → 5240 for analysis
  - Single-agent therapy: 2001 patients (38.2%)
    - Amoxicillin-clavulanate (42.7%), amoxicillin (23.3%), benzylpenicillin (17.6%), piperacillin-tazobactam (12.8%), cephalosporins (3.6%)
  - Combination therapy: 3239 patients (61.8%)
    - Clarithromycin (96.1%), erythromycin (3.7%), azithromycin (0.2%)
  - Approximately 50% CURB score ≥ 2

- Significant differences at baseline
  - Combination therapy patients were younger (73 years vs. 76 years, p=0.001), had less coexisting stroke, renal disease, active malignancy
  - ICU support (OR 0.66, p<0.001) and IV ABX use (8.7% vs. 6.8%, p=0.009) were more common in the combination therapy group

Multivariate analyses of the association between antibiotic therapy and clinical outcomes

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Total (n=5240)</th>
<th>Beta-lactam/macrolide combination therapy (n=3239)</th>
<th>Beta-lactam therapy (n=2001)</th>
<th>Adj. OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day IP death rate</td>
<td>1281 (24.4)</td>
<td>745 (23.0)</td>
<td>536 (26.8)</td>
<td>0.72 (0.60 to 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU admission</td>
<td>419 (8)</td>
<td>282 (8.7)</td>
<td>136 (6.8)</td>
<td>0.94 (0.72 to 1.22)</td>
<td>0.635</td>
</tr>
<tr>
<td>Need for MV</td>
<td>151 (2.9)</td>
<td>93 (2.9)</td>
<td>58 (2.9)</td>
<td>0.99 (0.71 to 1.38)</td>
<td>0.508</td>
</tr>
</tbody>
</table>

30 day IP death rate stratified by PNA severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Total</th>
<th>Beta-lactam/macrolide combination therapy</th>
<th>Beta-lactam therapy</th>
<th>Adj. OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low severity (CURB65=0-1)</td>
<td>201/2247 (8.9)</td>
<td>106/1339 (7.9)</td>
<td>95/908 (10.5)</td>
<td>0.80 (0.56 to 1.16)</td>
<td>0.238</td>
</tr>
<tr>
<td>Moderate severity (CURB65=2)</td>
<td>370/1480 (25)</td>
<td>199/919 (21.7)</td>
<td>171/561 (30.5)</td>
<td>0.54 (0.41 to 0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High severity (CURB65≥3)</td>
<td>710/1513 (46.9)</td>
<td>440/981 (44.9)</td>
<td>270/532 (50.8)</td>
<td>0.76 (0.60 to 0.96)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Authors’ Conclusion

Combination therapy was associated with a significantly lower death rate after adjustment for demographic factors, PNA severity and treatment factors in patients with moderate- and high-severity CAP.

Critique

Strengths:
- Large number of patients
- Multivariate analysis used to adjust for confounders

Limitations:
- High death rate (24%) related to severity
- Absence of additional details related to ABX therapy
- Absence of information about other aspects of care
- Treatment with fluoroquinolones excluded

Reviewer’s Assessment

Despite the use of robust post hoc analyses, the retrospective design, the inherent biases of this study, and differences in antimicrobials used limit its generalizability to treating hospitalized patients empirically for CAP.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To test the noninferiority of a beta-lactam alone compared with a beta-lactam and macrolide combination in moderately severe CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Open-label, multicenter, noninferiority, randomized trial conducted in Switzerland</td>
</tr>
</tbody>
</table>
| Population | **Inclusion:**  
* Age ≥ 18 years  
* Presence of at least 2 clinical findings suggestive of pneumonia  
* Presence of a new infiltrate on chest radiograph  
**Exclusion:**  
* Severe immunosuppression  
* Recent hospitalization (<14 days)  
* Residency in a nursing home  
* Severe pneumonia (PSI category V)  
* Administration of any antibiotic for more than 24 hours before inclusion |
| Intervention | **Randomized to initial treatment with a beta-lactam alone or a beta-lactam and a macrolide**  
* Beta-lactam: cefuroxime 1.5 g IV three times daily followed by 500 mg twice daily PO or amoxicillin-clavulanic acid 1.2 g IV four times daily followed by 625 mg three times daily PO  
* Macrolide: clarithromycin 500 mg IV/PO twice daily  
**Urine samples tested for *L. pneumophila* antigen**  
**Change in treatment only allowed if clinical deterioration**  
* Admission to ICU  
* Lack of resolution of fever after 72 hours  
* Isolation of a resistant pathogen |
| Endpoints | **Primary:**  
* Proportion of patients who did not reach clinical stability at day 7  
  * HR < 100/minute  
  * SBP > 90 mmHg  
  * Tympanic temperature < 38.0°C  
  * RR < 24/minute  
  * O₂ saturation > 90% on room air  
**Secondary:**  
* 30- and 90-day mortality, transfer to ICU, length of stay, readmission, recurrence of pneumonia, subsequent introduction of any new antibiotic, complicated pleural effusion requiring chest tube insertion or thoracic surgery |
| Methods | **Two pairs of blood cultures obtained before initiation of ABX**  
**Urine sample collected for detection of *L. pneumophila* antigen**  
**S. pneumoniae* urine antigen detection left to discretion of provider**  
**Pharyngeal swab obtained on first day of the study**  
  * Processed for detection of *C. pneumoniae* and *M. pneumoniae* by PCR |
| Statistical Analyses | **8% noninferiority margin**  
**280 patients per arm to have 90% power with a one-sided alpha of 0.10**  
**Continuous variables reported as mean (SD) or median (IQR)**  
**Proportion of unstable patients at 7 days measured by Kaplan-Meier method**  
  * Unstable patients who were discharged were censored  
  * Patients who died were considered unstable**  
**Subgroup analyses**  
* Pathogen identified (atypical or typical)  
* Patient age (< 65 or ≥ 65 years)  
* PSI (category IV vs. I-III)  
**Post hoc analysis conducted by the CURB-65 score (≥ 2 vs. < 2)**
Results

- 602 patients included, 22 patients excluded after randomization
  - 291 in the monotherapy arm
  - 289 in the combination arm
- Median age of 76 years (21-101) and 251 (60.5%) had 1 or more comorbidities
  - Mean PSI score was 84

<table>
<thead>
<tr>
<th>Pathogen Detected</th>
<th>Monotherapy Arm</th>
<th>Combination Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>14.8%</td>
<td>15.6%</td>
</tr>
<tr>
<td>L. pneumophila</td>
<td>4.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>2.1%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

- Amoxicillin-clavulanate used in 224 patients (77.0%) in the monotherapy arm and 215 patients (74.4%) in the combination arm
  - Remaining 141 patients treated with cefuroxime
- Median time to administration of clarithromycin was 47 hrs in patients with L. pneumophila in the monotherapy arm

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Monotherapy (n=291)</th>
<th>Combination Therapy (n=289)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>Patients not reaching clinical stability at day 7</td>
<td>120 (41.2)</td>
<td>97 (33.6)</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>ICU admission</td>
<td>12 (4.1)</td>
<td>14 (4.8)</td>
</tr>
<tr>
<td></td>
<td>LOS, median (IQR), d</td>
<td>8 (6-13)</td>
<td>8 (6-12)</td>
</tr>
<tr>
<td></td>
<td>Any change in initial ABX treatment</td>
<td>39 (13.4)</td>
<td>46 (15.8)</td>
</tr>
<tr>
<td></td>
<td>30-day death</td>
<td>14 (4.8)</td>
<td>10 (3.4)</td>
</tr>
<tr>
<td></td>
<td>90-day death</td>
<td>24 (8.2)</td>
<td>20 (6.9)</td>
</tr>
<tr>
<td></td>
<td>30-day readmission</td>
<td>23 (7.9)</td>
<td>9 (3.1)</td>
</tr>
<tr>
<td></td>
<td>90-day readmission</td>
<td>47 (16.2)</td>
<td>37 (12.7)</td>
</tr>
<tr>
<td></td>
<td>New PNA within 30 days</td>
<td>10 (3.4)</td>
<td>6 (2.1)</td>
</tr>
</tbody>
</table>

- In subgroup analyses, the effect of the treatment arm differed for patients with identification of an atypical pathogen (HR of reaching stability, 0.33; 95% CI, 0.13-0.85) and those without (HR, 0.99; 95% CI, 0.80-1.22)
- No significant interaction when stratified based on PSI or CURB65 categories, or age

Authors’ Conclusion
Noninferiority of initial empirical treatment with beta-lactam monotherapy in hospitalized patients with moderately severe CAP could not be determined

Critique
Strength: Randomized, prospective, noninferiority design
Limitations: Lack of blinding
- Inclusion of patients in PSI categories I and II
- Clinical stability as primary endpoint
- More Legionella in the monotherapy arm

Reviewer’s Assessment
While this study did not demonstrate noninferiority of beta-lactam monotherapy in hospitalized individuals with CAP, the higher prevalence of Legionella in the monotherapy arm and inclusion of PSI categories I and II make these results less applicable to patients with more severe CAP (e.g., PSI categories III and IV)

**Purpose**  
To test the noninferiority of beta-lactam monotherapy to the beta-lactam-macrolide and fluoroquinolone strategies with respect to 90-day mortality

**Design**  
Cluster-randomized, crossover trial

**Population**  
Inclusion:  
- Age ≥ 18 years  
- Clinically suspected CAP  
- Required antibiotic treatment and hospitalization  
Exclusion:  
- Patients with cystic fibrosis

**Intervention**  
- Beta-lactam (BL) monotherapy, beta-lactam with a macrolide (BLM), or fluoroquinolone (FQ) monotherapy  
- Antibiotics allowed were based on the 2005 Dutch guideline (Appendix C)

**Endpoints**  
Primary:  
- All-cause mortality within 90 days after admission  
Secondary:  
- Time to starting oral treatment, length of hospital stay, occurrence of minor or major complications during the hospital stay

**Methods**  
- Randomized into blocks of six  
  - Each with a sequence of three antibiotic strategies  
- Adherence to the strategy defined as initial treatment with the assigned antibiotic, irrespective of subsequent switches

**Statistical Analysis**  
- Intention-to-treat (ITT) population used in analyses  
- Noninferiority assessed in a one-sided test at a significance level of 0.05 (2-sided 90% confidence intervals)  
- Sensitivity analyses performed  
  - Only patients with radiologically confirmed CAP  
  - 30-day mortality  
- Missing data imputed by multiple imputation (except respiratory rate, heart rate, and confusion at admission)

**Results**  
- 3325 patients eligible for inclusion → 2283 (69%) gave consent  
- Median age 70 years (IQR, 59-79), baseline characteristics of included patients were similar among strategy periods  
  - PSI score 85 across groups and median CURB-65 score was 1 (IQR, 1-2)  
  - Microbial causes of CAP were similar in the three groups  
    - 15.9% *S. pneumoniae*  
    - 6.8% *H. influenzae*  
    - 2.1% atypical pathogens  
  - 27% of patients in BL monotherapy group received an antibiotic regimen covering atypical pathogens as initial therapy  
  - 38.7% of patients receiving BL monotherapy received atypical coverage during hospitalization (Table S3, Supplementary Appendix)  
    - Average of 4.5 days of treatment  
  - Resistance to the initiated antibiotic treatment was highest in the beta-lactam strategy  
- Primary Outcome  
  - Absolute difference in adjusted risk of death between BL strategy and the BLM strategy was 1.9% (90% CI, -0.6 to 4.4) in favor of the BL strategy  
  - -0.6% (90% CI, -2.8 to 1.9) difference between BL strategy and FQ strategy in favor of the FQ strategy  
  - Do not include 3% margin, thus demonstrating noninferiority  
- Secondary Outcomes  
  - Median length of hospital stay was 6 days  
  - Median duration of IV treatment was 3 days for the FQ strategy and 4 days during the other two periods  
  - Proportions of patients started on oral antibiotics  
    - 27% during the FQ strategy periods
<table>
<thead>
<tr>
<th>Authors’ Conclusion</th>
<th>Beta-lactam monotherapy was noninferior to beta-lactam-macrolide combination therapy and with fluoroquinolone monotherapy</th>
</tr>
</thead>
</table>
| Critique            | Strengths:  
|                     | • Primary endpoint was 90-day all-cause mortality  
|                     | • Pragmatic design modeling clinical behavior  
|                     | Limitations:  
|                     | • Selection bias (inherent to cluster-randomized studies)  
|                     | • More than a third of patients in the BL monotherapy group received atypical coverage  
|                     | • Noninferiority margin changed from 2% to 3% 7 months after the study began |
| Reviewer’s Assessment | The large percentage of patients in the beta-lactam monotherapy group who received atypical coverage make the results of this study difficult to apply. The beta-lactam monotherapy treatment strategy was noninferior through multiple analyses (including antibiotic-adherent, strategy-adherent, and ITT); however, this study provides inadequate evidence to recommend beta-lactam monotherapy in hospitalized patients with CAP. |

Conclusion & Recommendations

1) Guideline recommendations for empiric antibiotics for CAP largely based on retrospective studies  
   a) More severe CAP (PSI IV-V and CURB ≥ 2)  
   b) Confounding variables likely contributed to perceived mortality benefit of beta-lactam/macrolide combination therapy or fluoroquinolone monotherapy

2) Newer prospective, randomized trial data suggest that coverage of atypical pathogens may be unnecessary in certain groups  
   a) Data insufficient to recommend beta-lactam monotherapy in hospitalized patients with CAP

3) In patients hospitalized with CAP, beta-lactam-macrolide combination or fluoroquinolone therapy should be used  
   a) A cephalosporin plus a macrolide is a reasonable combination for empiric treatment, depending on susceptibilities  
   b) A respiratory fluoroquinolone could be considered in penicillin-allergic patients or those at increased risk of a cardiac event

4) Future trials should only include patients with CURB score ≥2 and/or PSI categories III, IV, and V  
   a) Stratify and treat patients according to PCT  
   b) Primary outcome: 30-day mortality  
   c) No allowance for atypical coverage in beta-lactam monotherapy group unless evidence of atypical infection  
      i) *Legionella* urinary antigen positive  
      ii) *C. pneumonia* or *M. pneumonia* nasal swab PCR positive
References


Moore | Page 16 of 20


A. Pneumonia Severity Index (PSI)

Step 1: Stratify to Risk Class I vs. Risk Classes II-V

<table>
<thead>
<tr>
<th>Presence of:</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 50 years of age</td>
<td>If Male</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>If Female</td>
</tr>
<tr>
<td>Pulse ≥125/minute</td>
<td>+Age (yr)</td>
</tr>
<tr>
<td>Respiratory rate &gt;30/minute</td>
<td>+Age (yr) - 10</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mm Hg</td>
<td>+10</td>
</tr>
<tr>
<td>Temperature &lt;35°C or ≥40°C</td>
<td>+20</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>+30</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Renal disease</td>
<td>+10</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>+10</td>
</tr>
<tr>
<td>Physical Exam Findings</td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+20</td>
</tr>
<tr>
<td>Pulse ≥125/minute</td>
<td>+10</td>
</tr>
<tr>
<td>Respiratory rate &gt;30/minute</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mmHg</td>
<td>+20</td>
</tr>
</tbody>
</table>

If any "Yes", then proceed to Step 2
If all "No" then assign to **Risk Class I**

Step 2: Stratify to Risk Class II vs. III vs. IV vs. V

<table>
<thead>
<tr>
<th>Presence of:</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Nursing home resident</td>
<td>+10</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mmHg</td>
<td>+10</td>
</tr>
<tr>
<td>Temperature &lt;35°C or ≥40°C</td>
<td>+10</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>+30</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>+10</td>
</tr>
<tr>
<td>Renal disease</td>
<td>+10</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>+10</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>+10</td>
</tr>
<tr>
<td>Sum &lt;70 = Risk Class II</td>
<td></td>
</tr>
<tr>
<td>Sum 71-90 = Risk Class III</td>
<td></td>
</tr>
<tr>
<td>Sum 91-130 = Risk Class IV</td>
<td></td>
</tr>
<tr>
<td>Sum &gt;130 = Risk Class V</td>
<td></td>
</tr>
</tbody>
</table>

B. Procalcitonin as a marker of etiology in adults hospitalized with CAP

![Procalcitonin graph]
C. Flowchart of guideline recommendations on antibiotic treatment of CAP (2005 Dutch Guidelines)
Table 5. Description of Studies Comparing Beta-Lactam Plus Macrolide Combination Therapy vs. Beta-Lactam Monotherapy for Patients Hospitalized with CAP

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Period of Data Collection</th>
<th>No. of Patients</th>
<th>Age, y</th>
<th>Illness Severity Class/Score</th>
<th>Outcomes</th>
<th>Beta-Lactam plus Macrolide No./Total (%) who Died</th>
<th>Beta-Lactam Monotherapy No./Total (%) who Died</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason et al, 1999</td>
<td>Retrospective</td>
<td>1994-1995</td>
<td>12,945</td>
<td>79 (mean)</td>
<td>PSI IV-V</td>
<td>30-day mortality</td>
<td>511/3430 (14.9)</td>
<td>511/3430 (14.9)</td>
<td>0.71 (0.52-0.96)</td>
</tr>
<tr>
<td>Houck et al, 2001</td>
<td>Retrospective</td>
<td>1993, 1995, 1997</td>
<td>10,069</td>
<td>79 (mean)</td>
<td>PSI IV-V</td>
<td>30-day mortality</td>
<td>242/1740 (13.9)</td>
<td>234/1982 (11.8)</td>
<td>0.42 (0.25-0.69)</td>
</tr>
<tr>
<td>Garcia Vázquez et al, 2005</td>
<td>Prospective</td>
<td>1996-2001</td>
<td>1188</td>
<td>68 (mean)</td>
<td>PSI IV-V</td>
<td>In-hospital mortality</td>
<td>63/918 (6.9)</td>
<td>36/270 (13.3)</td>
<td>0.50 (0.31-0.81)</td>
</tr>
<tr>
<td>Paul et al, 2007</td>
<td>Prospective</td>
<td>2002-2004</td>
<td>451</td>
<td>67 (mean)</td>
<td>PSI IV-V</td>
<td>30-day mortality</td>
<td>21/282 (7.4)</td>
<td>37/169 (21.9)</td>
<td>0.69 (0.32-1.48)</td>
</tr>
<tr>
<td>Bratzler et al, 2008</td>
<td>Retrospective</td>
<td>1998-2001</td>
<td>24,780</td>
<td>NR</td>
<td>PSI IV-V</td>
<td>30-day mortality</td>
<td>338/5963 (5.7)</td>
<td>376/4463 (8.4)</td>
<td>0.70 (0.60-0.90)</td>
</tr>
<tr>
<td>Blasi et al, 2008</td>
<td>Retrospective/ prospective</td>
<td>2002-2004</td>
<td>2,847</td>
<td>79 (mean)</td>
<td>PSI IV-V</td>
<td>Mortality at end of ABX</td>
<td>19/330 (5.7)</td>
<td>73/452 (16.2)</td>
<td>0.32 (0.19-0.56)</td>
</tr>
<tr>
<td>Tessmer et al, 2009</td>
<td>Prospective</td>
<td>2002-2006</td>
<td>1,854</td>
<td>66 (mean)</td>
<td>CRB-65 score ≥ 2</td>
<td>30-day mortality</td>
<td>42/946 (4.4)</td>
<td>78/908 (8.6)</td>
<td>1.04 (0.66-1.63)</td>
</tr>
</tbody>
</table>

Table 6. Description of Studies Comparing Respiratory Fluoroquinolone Monotherapy vs. Beta-Lactam Monotherapy for Patients Hospitalized with CAP

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Period of Data Collection</th>
<th>No. of Patients</th>
<th>Age, y</th>
<th>Illness Severity Class/Score</th>
<th>Outcomes</th>
<th>Fluoroquinolone Monotherapy No./Total (%) who Died</th>
<th>Beta-Lactam Monotherapy No./Total (%) who Died</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bratzler et al, 2008</td>
<td>Retrospective</td>
<td>1998-2001</td>
<td>24,780</td>
<td>NR</td>
<td>PSI IV-V</td>
<td>30-day mortality</td>
<td>318/5045 (6.3)</td>
<td>376/4463 (8.4)</td>
<td>0.70 (0.60-0.90)</td>
</tr>
<tr>
<td>Blasi et al, 2008</td>
<td>Retrospective/ prospective</td>
<td>2002-2004</td>
<td>2,847</td>
<td>79 (mean)</td>
<td>PSI IV-V</td>
<td>Mortality at the end of ABX therapy</td>
<td>33/363 (9.1)</td>
<td>73/452 (16.2)</td>
<td>0.59 (0.37-0.94)</td>
</tr>
<tr>
<td>Ewig et al, 2011</td>
<td>Prospective</td>
<td>2002-2007</td>
<td>2,068</td>
<td>64 (mean)</td>
<td>CRB-65 ≥ 2</td>
<td>6-month mortality</td>
<td>NR/365</td>
<td>NR/1703</td>
<td>0.57 (0.35-0.92)</td>
</tr>
</tbody>
</table>

NR, not reported
a Hazard ratio not adjusted OR