Cost-effectiveness of 4 empiric antimicrobial regimens in patients with community-acquired pneumonia

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Abstract: This study compares the cost-effectiveness of the 4 most common empiric antimicrobial regimens used for the treatment of adults with community-acquired pneumonia (CAP) at a community health system during a 6-month period. Associations between initial antimicrobials and total hospital costs were determined. Cost-effectiveness ratios were determined by dividing the total hospital costs by the percent survival. A total of 415 patients met criteria for the Pneumonia Severity Index (PSI) risk class IV or V. Costs (adjusted for inflation) were as follows (median, 25th and 75th percentile): total hospital costs ($5,078 [$3,218–$8,144]), pharmacy costs ($753 [$455–$1,357]), and antibiotic costs ($139 [$82–$229]). The most favorable cost-effectiveness ratio was observed for patients who received levofloxacin monotherapy ($4,635 per life saved), followed by ceftriaxone plus a macrolide ($5,278), ceftriaxone monotherapy ($5,368), and ceftriaxone plus levofloxacin ($6,317). Among patients admitted to the medical floor for class IV or V CAP, empiric levofloxacin monotherapy was associated with greater cost-effectiveness than ceftriaxone monotherapy, ceftriaxone plus a macrolide, or ceftriaxone plus levofloxacin. (Formulary. 2005;40:298–303.)

Expenditures for community-acquired pneumonia (CAP) exceed $8 billion annually in the United States.\(^1\) Outpatient care is relatively inexpensive ($150–$350/patient), whereas costs increase greatly when patients are admitted to the hospital ($5,785/patient).\(^1\)–\(^3\) Although less than one-quarter of CAP patients are hospitalized, these patients consume approximately 90% of all resources used for the treatment of CAP.\(^1\) Furthermore, the cost of care increases exponentially for patients admitted to the intensive care unit (ICU) ($21,144/patient).\(^2\) The fact that CAP imposes such a huge financial burden on society warrants careful attention to factors that impact cost of care.

Room and board charges are the chief contributor to the total cost of care for hospitalized CAP patients. Niederman and colleagues used national incidence data and paid claims databases to evaluate direct charges associated with CAP.\(^1\) Room and board accounted for the greatest proportion of total hospital charges (26%), followed by pharmacy (20%), laboratory (13%), respiratory services (11%), and medical/surgical supplies (9%). For Medicare patients, medications accounted for 12% of the total hospital charge. Multiple other studies have identified a positive association between increased hospital costs and either duration of intravenous antimicrobials or length of hospital stay.\(^4\)–\(^11\) Finally, appropriate antimicrobial prescribing has been shown to significantly reduce hospital costs.\(^12\)

Cost studies among hospitalized CAP patients have not traditionally differentiated between patients with and without severe disease.\(^1\) Historically, severe disease was defined as admission to the ICU.\(^13\) Fine and colleagues developed the Pneumonia Severity Index (PSI) as a mortality prediction rule that quantifies disease severity.\(^14\) The PSI has been endorsed by the Infectious Diseases Society of America as a hospital admission criterion.\(^14,\)\(^15\) Patients stratified to risk classes I and II should be treated as outpatients, while patients stratified to risk classes IV or V should be admitted to the hospital.\(^14\) Patients stratified to risk class III may be hospitalized briefly for observation.\(^14\)

This study evaluated the cost of care for CAP patients admitted to the medical floor with PSI class IV or V disease.\(^14\) Risk classes IV and V were chosen because national recommendations state that these patients should be admitted to the hospital. After identifying patients who fell into these risk classes, the proportion of costs attributable to multiple aspects of patient care was determined. Then, a cost-effectiveness analysis was conducted to evaluate the cost-effectiveness of the 4 most common empiric antimicrobial regimens used within a private healthcare system (ie, levofloxacin monotherapy, ceftriaxone monotherapy, ceftriaxone plus a macrolide, and ceftriaxone plus levofloxacin).
METHODS

Prior to study initiation, approvals were obtained from the Institutional Review Board of the Baptist Health System and The University of Texas Health Science Center at San Antonio. All adult CAP patients admitted to Baptist Health System from November 1, 1999, to April 30, 2000, with a principal discharge diagnosis code (International Classification of Diseases, 9th Revision) of 481–484 and 486 were identified by the Department of Medical Records. Patients were excluded if they had a history of HIV or AIDS, were hospitalized within the previous 7 days, or were immunocompromised secondary to chemotherapy or solid organ transplant.

Trained clinical pharmacists used a standardized data collection form to extract data from the medical record pertaining to patient demographics, past medical history, physical exam findings, laboratory values, antimicrobial start and stop dates, admission and discharge dates, discharge disposition, and in-hospital mortality. The clinical information was used to calculate a score for severity of illness according to the PSI. The PSI score was used to assign each patient to 1 of 5 PSI risk classes. Only patients managed on the medical floor who met criteria for risk class IV or V were evaluated in this analysis. Patients were stratified into 4 groups (ie, levofloxacin monotherapy, ceftriaxone monotherapy, ceftriaxone plus a macrolide, and ceftriaxone plus levofloxacin) based upon the antimicrobials received in the first 24 hours of hospitalization. These 4 groups were chosen because they were the 4 most common empiric antibiotic regimens used at the institution. Collectively, these 4 regimens were administered to 75% of class IV and V CAP patients.

The perspective of the cost-effectiveness analysis was the institution. Information on hospital charges was obtained from the billing department. All charges mentioned in this article have been adjusted to represent 2005 US dollars by multiplying the charges by the Consumer Price Index (CPI) for medical care from the US Department of Labor, Bureau of Labor Statistics. The CPI for 2005 was based on the "seasonally adjusted annual rate" through June 2005. Total hospital charges reflected the sum of charges from several different areas (eg, room and board, respiratory therapy, pharmacy, laboratory, radiology, central supply, emergency room, and miscellaneous). Patients were charged per episode of treatment by the respiratory department and the charge included the cost of some respiratory medication (eg, albuterol) but not antibiotics.

Total hospital costs and pharmacy costs were derived by multiplying the total charges by the hospital cost-to-charge ratio. For antimicrobial costs, the actual cost per dose was obtained from the Department of Pharmacy. The cost per dose was multiplied by the number of dosage forms received during hospitalization.

Statistical analysis All statistical comparisons were performed with JMP 5.0.1. Significance was defined as an alpha level less than 0.05. Costs were transformed with the natural logarithm function and tested with the Shapiro-Wilk test to ensure normality for total hospital costs ($P=0.9897$), pharmacy costs ($P=0.9923$), and antibiotic costs ($P=0.9658$). Due to the relatively brief period of care, discounting was not performed. Baseline characteristics were compared using Chi-square for discrete variables. Log-transformation of patient age did not result in a normal distribution ($P<0.0001$); therefore, Kruskal Wallis one-way ANOVA was used for age comparisons. One-way ANOVA was used to evaluate associations between antimicrobials received (independent variable) and the natural logarithm of total hospital cost (dependent variable).
Cost-effectiveness ratios were determined for each antimicrobial regimen by dividing the median total hospital cost per patient by the in-hospital percent survival. A probabilistic sensitivity analysis (ie, Monte Carlo simulation) was conducted on the cost-effectiveness ratios (CER) using Crystal Ball 2000. The mortality rate was varied ±5% according to a normal distribution, whereas the total hospital cost was fit to a log-normal distribution and varied over the entire interval. For the mortality rate, a value of ±5% was chosen because recent studies among hospitalized CAP patients reported mortality rates that varied from 2%–15%. The resulting CERs were reported as median (25th and 75th percentiles). Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in cost by the difference in percent survival. The results were reported as dollars per additional life saved. Levofloxacin monotherapy was used as the reference regimen for the ICERs.

RESULTS

A total of 649 patients were managed on the medical floor. Overall, 415 of 649 (64%) were stratified to risk class IV (65%) or V (35%). Median (25th and 75th percentiles) patient age was 80 (73–87) years and 52% of patients were female. Most patients were Caucasian (56%), followed by Latin-American (36%), and African-American (6%). Twenty-four percent of patients were admitted from the nursing home and 21% received antimicrobial therapy prior to admission. Heart failure was the most common comorbid condition (52%), followed by chronic obstructive pulmonary disease (42%), diabetes mellitus (33%), cerebrovascular disease (21%), renal disease (20%), cancer (20%), and liver disease (6%). Information regarding time-to-first-dose of antimicrobials was available for 376 of 415 (92%) of patients. Median (25th and 75th percentiles) time-to-first-dose of antimicrobials was 2.8 (1.6–5.0) hours. Patients received intravenous antimicrobials for 4 (3–7) days and remained hospitalized for 5 (3–7) days. The overall in-hospital mortality rate was 7%. In-hospital mortality was significantly higher among patients in risk class V compared to those in risk class IV (13% vs 4%, P=.0006).

Health-system expenditures. Cost data were available for 393 of 415 (95%) patients admitted to the medical floor with class IV or V CAP. The overall cost of care for the 393 evaluable patients was $2.5 million, for which Baptist Health System was reimbursed $1.9 million for a net loss of $600,000. Per patient, the total hospital cost (median, 25th and 75th percentiles) was $5,078 ($3,218–$8,144). As expected, patients in risk class V accrued higher total hospital costs (n=133, $5,836 [$3,690–$8,442]) than patients stratified to risk class IV (n=260, $4,584 [$3,016–$7,946]); however, this difference was not statistically significant (P=.1188). The median total hospital cost for patients aged ≥65 years (n=344, $4,979 [$3,100–$8,101]) was not different from patients aged <65 years (n=49, $5,080 [$4,098–$8,375], P=.3658). The total pharmacy cost was $753 ($455–$1,357) per patient, while the antimicrobial acquisition cost was $139 ($82–$229) per patient. Figure 1 reflects the proportion of total hospital costs by cost category.
Variables associated with increased cost. African-Americans accrued higher median (25th and 75th percentile) total hospital costs (n=20, $7,337 [$4,462–$15,603]) than Latin-Americans (n=110, $5,149 [$3,062–$7,785], P=.002) or Caucasians (n=174, $4,380 [$2,730–$6,849], P=.001). The cost difference among the different ethnic groups was attributable to significant differences in length of stay rather than severity of illness. The PSI score (median, 25th and 75th percentile) was not statistically different between Caucasians (116 [104–142] points), Latin-Americans (116 [100–132] points), and African-Americans (110 [96–124] points). However, African-Americans remained hospitalized the longest (6 [4–12] d), followed by Latin-Americans (5 [2–7] d), and Caucasians (4 [2–7] d) (P=.0038). The differences in length of stay were not due to age, as Caucasian patients were older (80 y) than Latin-American (77 y) or African-American (75 y) patients. However, African-Americans and Latin-Americans had higher rates of several comorbidities. Respective rates for African-Americans, Latin-Americans, and Caucasians were as follows: diabetes mellitus (46%, 44%, and 25%; P=.0004), stroke (35%, 21%, and 18%; P=.2536), renal disease (38%, 27%, and 13%; P=.0005), and liver disease (0%, 11%, and 4%; P=.0136).

Baseline differences by empiric antimicrobial regimen. In order to identify the most cost-effective empiric antimicrobial regimen, patients were stratified into 4 groups based upon antimicrobials received within 24 hours of hospitalization (ie, levofloxacin monotherapy
[n=151], ceftriaxone monotherapy [n=61], ceftriaxone plus a macrolide [n=61], and ceftriaxone plus levofloxacin [n=38]). These 4 groups comprised 311/393 (79%) of all patients for whom cost data were available. The remaining patients received regimens that contained a beta-lactam/beta-lactamase inhibitor (6%), clindamycin (2%), fluoroquinolone plus a macrolide (2%), or macrolide monotherapy (2%). All other regimens comprised ≤1%. Table 1 outlines the patient demographics by antimicrobial regimen. Baseline differences were noted among the 4 groups for patient age (P=.0017), gender (P=.0041), admission from a nursing home (P=.0055), chronic obstructive pulmonary disease (P=.0282), and stroke (P=.0051). Patients who received ceftriaxone plus a macrolide were significantly younger, with fewer females, and fewer patients admitted from a nursing home compared with patients who received levofloxacin monotherapy (P<.0001, P=.0027, and P=.0053, respectively) or ceftriaxone monotherapy (P=.0054, P=.0010, and P<.0001). The proportion of patients stratified to risk class V was lowest among those who received ceftriaxone plus a macrolide (27%), followed by ceftriaxone plus levofloxacin (34%), levofloxacin monotherapy (36%), and ceftriaxone monotherapy (41%) (P=.3936).

| Table 1 |
| Patient demographics by empiric antimicrobial regimen for patients admitted to the medical floor with class IV or V CAP (N=311) |

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Levo (n=151)</th>
<th>CTX (n=61)</th>
<th>CTX + Mac (n=61)</th>
<th>CTX + Levo (n=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), median (quartiles)</td>
<td>92 (76-88)</td>
<td>92 (72-89)</td>
<td>76 (67-82)</td>
<td>80 (75-85)</td>
<td>0.0017</td>
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<td>Female (%)</td>
<td>54</td>
<td>61</td>
<td>31</td>
<td>58</td>
<td>0.0041</td>
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<td>Nursing home (%)</td>
<td>24</td>
<td>39</td>
<td>8</td>
<td>26</td>
<td>0.0005</td>
</tr>
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<td>Pre-admission antibiotics (%)</td>
<td>21</td>
<td>18</td>
<td>15</td>
<td>24</td>
<td>0.6365</td>
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<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>61</td>
<td>48</td>
<td>60</td>
<td>51</td>
<td>0.3775</td>
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<td>Latin American</td>
<td>31</td>
<td>45</td>
<td>35</td>
<td>43</td>
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<tr>
<td>African American</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>0.9109</td>
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<td>Comorbidities (%)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Heart failure</td>
<td>54</td>
<td>59</td>
<td>49</td>
<td>55</td>
<td>0.7515</td>
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<td>COPD</td>
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<td>Diabetes mellitus</td>
<td>32</td>
<td>34</td>
<td>28</td>
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<tr>
<td>Stroke</td>
<td>21</td>
<td>34</td>
<td>10</td>
<td>13</td>
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<tr>
<td>Renal disease</td>
<td>23</td>
<td>20</td>
<td>20</td>
<td>24</td>
<td>0.9027</td>
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<td>Cancer</td>
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<td>8</td>
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<td>Liver disease</td>
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<td>PSI Risk Class (%)</td>
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<td>IV</td>
<td>64</td>
<td>59</td>
<td>73</td>
<td>66</td>
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<tr>
<td>V</td>
<td>36</td>
<td>41</td>
<td>27</td>
<td>34</td>
<td>0.3996</td>
</tr>
</tbody>
</table>

Levo—levofloxacin; CTX—ceftriaxone; Mac—macrolide; COPD—chronic obstructive pulmonary disease.

Cost-effectiveness of empiric antimicrobial regimens. Cost data and cost-effectiveness ratios are listed by antimicrobial regimen in Table 2. Levofloxacin monotherapy was associated with lower total hospital costs (median, 25th and 75th percentiles; $4,356 [$2,772–7,294]) than ceftriaxone monotherapy ($4,670 [$3,406–7,544]), ceftriaxone plus a macrolide ($5,173 [$3,852–7,115]), and ceftriaxone plus levofloxacin ($6,002 [$3,646–9,186]) (P=.0921). Empiric treatment with ceftriaxone plus a macrolide was associated with the highest in-hospital survival (98%), followed by ceftriaxone plus levofloxacin (95%), levofloxacin monotherapy (94%), and ceftriaxone monotherapy (87%) (P=.0734). The most favorable cost-effectiveness ratio was observed among patients who received levofloxacin monotherapy ($4,635 per life
saved), followed by ceftriaxone plus a macrolide ($5,278), ceftriaxone monotherapy ($5,368),
and ceftriaxone plus levofloxacin ($6,317). The association was robust after conducting a
saved), followed by ceftriaxone plus a macrolide ($5,503 [$3,608–$8,336] per life saved),
ceftriaxone monotherapy ($5,768 [$3,682–$8,967] per life saved), and ceftriaxone plus
levofloxacin ($6,067 [$3,929–$9,465] per life saved). The incremental cost-effectiveness ratio
(ICER) for ceftriaxone plus a macrolide compared with levofloxacin alone was $20,409 per
additional life saved, whereas the ICER for ceftriaxone plus levofloxacin compared to
levofloxacin alone was $164,514 per additional life saved.

### Table 2

**Cost-effectiveness associated with empiric antimicrobial alternatives for patients admitted to the medical floor with class IV or V CAP**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Cost/patient*</th>
<th>Survival</th>
<th>CER†</th>
<th>CER sensitivity analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levo</td>
<td>151</td>
<td>$4,356 ($2,772–$7,294)</td>
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<td>$4,781 ($3,033–$7,575)</td>
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<tr>
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<td>61</td>
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</tr>
<tr>
<td>CTX + Levo</td>
<td>38</td>
<td>$6,002 ($3,646–$9,186)</td>
<td>95%</td>
<td>$6,317</td>
<td>$6,067 ($3,929–$9,465)</td>
</tr>
</tbody>
</table>

CAP=community-acquired pneumonia; CER=cost-effectiveness ratio; sens=sensitivity; Levo-levofloxacin;
CTX=ceftriaxone; Mac=macrolide

*Values reflect costs inflated to 2005 US dollars and are reported as median (25th and 75th quartiles).
†The CER was calculated by dividing the median cost/patient by the in-hospital survival rate.
‡For the sensitivity analysis, the mortality rate was varied ±5% according to a normal distribution, and the total hospital
cost was fit to a log-normal distribution and varied over the entire interval.

**DISCUSSION**

In this study, antimicrobial acquisition costs accounted for only 3% of the total hospital costs and
18% of the total pharmacy costs. Nevertheless, antimicrobial choice has been shown to impact
total hospital cost for CAP patients in 2 prior studies. Paladino and colleagues determined that
azithromycin mono-therapy was more cost-effective than cefuroxime with or without
erthyromycin ($5,265 vs $6,145). In addition, Dresser and colleagues found that gatifloxacin
monotherapy was more cost-effective than ceftriaxone plus a macrolide ($5,236 vs $7,047). These
studies differed from the present study in that patients were randomized to treatment and
the authors determined the costs attributable solely to pneumonia.
The present study supports the findings by Dresser and colleagues in that fluoroquinolone monotherapy was associated with greater cost-effectiveness than ceftriaxone plus a macrolide. Furthermore, ceftriaxone plus a macrolide was associated with greater cost-effectiveness than ceftriaxone monotherapy. For the present study, in-hospital patient survival was used to calculate cost-effectiveness ratios because the outcome measure was less ambiguous than clinical success. One limitation of this study was that the investigators were unable to determine which deaths were attributable solely to pneumonia.

Furthermore, this study is subject to the limitations of all observational studies, including selection bias (eg, significant differences in age, gender, admission from a nursing home, and comorbidities) and confounding bias (ie, older patients are more likely to be admitted to a nursing home). However, it is notable that the stratification to PSI risk class is based upon a validated composite scoring system that incorporates the influence of each of these variables on patient mortality. Importantly, the proportion of patients stratified into PSI risk classes IV and V was statistically similar among the 4 groups in this study. Finally, the pharmacists did not collect information regarding patients who returned to the hospital shortly after discharge ("bounce-backs"). If the proportion of bounce-backs was greater in one group than the others, then that group may have actually had a higher cost due to the costs of re-admission and retreatment.

While costs were not vastly different ($5,173 vs $4,670), ceftriaxone plus a macrolide was associated with lower mortality than ceftriaxone monotherapy (2% vs 13%). Notably, patients who received ceftriaxone monotherapy were older and were much more likely to be admitted from the nursing home. The mortality rate for patients who received ceftriaxone plus a macrolide was lower than a comparison study, but the present study excluded ICU patients, which should have resulted in a lower mortality rate. Furthermore, the lower than expected in-hospital mortality for patients who received ceftriaxone plus a macrolide is potentially attributable to differences in baseline characteristics (eg, fewer patients admitted from a nursing home and fewer patients stratified to risk class V). It is important to recognize that 2 of the regimens evaluated in this study are not endorsed by current guidelines for the empiric selection of antibiotics for CAP (ie, ceftriaxone monotherapy and ceftriaxone plus levofloxacin). These guideline-discordant regimens were associated with poorer cost-effectiveness ratios than guideline-concordant regimens. In addition, the current study provides further reason to avoid the combination of ceftriaxone plus levofloxacin, because this regimen was associated with a very large incremental cost compared with levofloxacin monotherapy.

While antimicrobial choice impacts hospital costs, it is important to realize that antimicrobials account for only a small proportion of the total cost of hospitalization. The major factors that impact cost are respiratory services and room and board charges; therefore, attempts to reduce health-system expenditures should focus on shortening the length of hospital stay. Fortunately, criteria have been developed to assist with intravenous to oral switch and hospital discharge decisions. Finally, clinicians must consider factors other than cost-effectiveness when choosing an antimicrobial regimen (eg, likely pathogens, prior drug exposure, comorbid diseases, and antimicrobial resistance).
CONCLUSIONS

Among patients admitted to the medical floor for class IV or V CAP, empiric levofloxacin monotherapy was associated with greater cost-effectiveness than ceftriaxone monotherapy, ceftriaxone plus a macrolide, or ceftriaxone plus levofloxacin. Combination therapy with ceftriaxone plus levofloxacin was not associated with improved cost-effectiveness compared to guideline-endorsed regimens; therefore, this antimicrobial regimen should be avoided. Finally, the best way to achieve cost-containment is to reduce the duration of hospitalization.

REFERENCES


