Cost-Effectiveness of IV-to-Oral Switch Therapy*

Azithromycin vs Cefuroxime With or Without Erythromycin for the Treatment of Community-Acquired Pneumonia

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Study objective: To conduct a cost-effectiveness analysis of IV-to-oral regimens of azithromycin vs cefuroxime with or without erythromycin in the treatment of patients hospitalized with community-acquired pneumonia (CAP).

Patients: Of the 268 evaluable patients enrolled into a randomized, multicenter clinical trial of adults, 266 patients had sufficient data to be included in this cost-effectiveness analysis. One hundred thirty-six patients received azithromycin, and 130 patients received cefuroxime with or without erythromycin.

Methods: A pharmacoeconomic analysis from the hospital provider perspective was conducted. Health-care resource utilization was extracted from the clinical database and converted to national reference costs. Decision analysis was used to structure and characterize outcomes. Sensitivity analyses were performed, and statistics were applied to the cost-effectiveness ratios.

Results: The clinical success and adverse event rates and antibiotic-related length of stay were 78%, 11.8%, and 5.8 days for the azithromycin group and 75%, 20.7%, and 6.4 days for the group receiving cefuroxime with or without erythromycin, respectively. Geometric mean treatment costs were $4,104 (95% confidence interval [CI], $3,874 to $4,334) for the azithromycin group, and $4,578 (95% CI, $4,319 to $4,837) for the group receiving cefuroxime with or without erythromycin (p = 0.06). The cost-effectiveness ratios were $5,265 per expected cure for the azithromycin group, and $6,145 per expected cure for group receiving cefuroxime with or without erythromycin (p = 0.05).

Conclusions: Despite a higher per-dose purchase price, overall costs with azithromycin tended to be lower due to decreased duration of therapy, lower preparation and administration costs, and reduced hospital length of stay. As empiric therapy, azithromycin monotherapy was cost-effective compared to cefuroxime with or without erythromycin for patients hospitalized with CAP who have no underlying cardiopulmonary disease, and no risk factors for either drug-resistant pneumococci or enteric Gram-negative pathogens.

Key words: azithromycin; cefuroxime; community-acquired pneumonia; pharmacoeconomics

Abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; CER = cost-effectiveness ratio; CI = confidence interval; DRG = diagnosis-related group; GMC = geometric mean cost; Ln = natural logarithm; LOSAR = antibiotic-related length of stay

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Despite an array of potent antimicrobials from which to choose, community-acquired pneumonia (CAP) remains a serious illness accounting for the sixth leading cause of death in the United States and the number one cause of death from infectious...
diseases. There are approximately four million cases of CAP annually, with 20 to 50% of these patients being hospitalized accounting for 6% of all Medicare discharges. Among those hospitalized with CAP, mortality approaches 25%, especially if the patient requires admission to an ICU.

Because there is much uncertainty in treating pneumonia, many hospitals have instituted clinical pathways to improve care in a cost-effective manner. Initial therapy is necessarily empiric because clinical and radiographic findings are typically non-specific and identifying an etiologic pathogen is problematic. In one third to one half of all cases, no pathogen is identified. In selecting initial therapy, many factors must be carefully considered, such as age, coexisting illness, smoking history, severity of illness, and the patient setting prior to hospitalization. In 1993 the American Thoracic Society (ATS) published guidelines for the initial management of adults with CAP. These guidelines divide CAP into four severity categories and suggest empiric antimicrobial regimens for each category: ATS categories 1 and 2 concern outpatient management, category 3 includes hospitalized patients with CAP, while category 4 addresses hospitalized patients with severe CAP, for whom anti-Pseudomonas coverage is suggested.

Cefuroxime is a second-generation cephalosporin commonly employed in category 3 of the original ATS guidelines for empiric treatment of patients hospitalized with CAP. A macrolide, often erythromycin, is added when an atypical pathogen is suspected. Azithromycin is an azalide antimicrobial with a spectrum of activity for respiratory pathogens similar to the combination of a second-generation cephalosporin plus a macrolide but without enteric Gram-negative coverage. Therefore azithromycin can be an appropriate single agent for empiric coverage for patients who are not at risk of infections caused by either enteric Gram-negative bacilli or anaerobes.

Frequently, formulary and treatment decisions are made after comparing the cost per dose or cost per day of an antibiotic. Azithromycin costs more per dose and more per day than either cefuroxime or erythromycin. However, medication costs are only a small portion of health-care costs, accounting for approximately 8% of the total health-care expenditures in the United States. A pharmacoeconomic analysis, in contrast to a simple price comparison, can provide a more accurate and complete description of the true cost of health care. Since pharmacoeconomics is an outcomes-based science, determining an economic outcome requires a clinical outcome. This economic study was conducted to compare the cost-effectiveness of azithromycin vs cefuroxime with or without erythromycin for the treatment of adult patients hospitalized with CAP.

Materials and Methods

Clinical Trial

A multicenter, parallel group, randomized, open-label, comparative clinical study is the basis for this economic evaluation. Adult inpatients with a new infiltrate on chest radiograph and a clinical diagnosis of CAP that required treatment with IV antibiotics were eligible for enrollment. Key exclusion criteria were major allergic reactions to macrolides or β-lactams; significant renal, hepatic, cardiovascular, or hematologic disease; HIV infection; AIDS; metastatic tumor; septic shock; cystic fibrosis; mechanical ventilation; infection due to non-Haemophilus influenzae Gram-negative organisms; history of terfenadine, loratadine, or astemizole; and female patients who were pregnant or nursing. Patients had to be able to sign their own informed consent; no surrogates were allowed.

Thirty-nine investigators from 36 centers enrolled 403 patients between November 1993 and May 1995. The sample size was based on the anticipated evaluability rate and clinical response. Patients were randomized 1:1 to receive azithromycin or cefuroxime (control). Patients in the azithromycin group received 500 mg IV qd for 2 to 5 days, followed by 500 mg po qd for a total of 10 to 14 days of therapy. Patients in the control group received cefuroxime, 500 mg IV q8h, for 2 to 7 days, followed by cefuroxime axetil, 500 mg po bid, for a total of 7 to 10 days of therapy. For patients in the control group suspected of having atypical pathogens (Mycoplasma, Legionella, or Chlamydia), erythromycin, 500 to 1,000 mg IV q6h/500 mg po qid, for up to 21 days, could be added at the discretion of the investigator. The decision to switch from IV to oral therapy was made by the individual clinical investigators on the basis of the patient’s clinical response.

Safety, clinical, microbiological, and radiographic assessments were performed and recorded during therapy, 10 to 14 days after therapy, and at long-term follow-up 4 to 6 weeks after therapy. Detailed information on the conduct of the trial, demographic descriptions of the study population, and clinical, bacteriological, and radiologic results have been published. Retrospective calculation of the pneumonia severity index scores were conducted.

Methods of the Economic Analysis

Since the major expense in the treatment hospitalized patients with CAP is the hospital per diem cost, a cost-effectiveness analysis from the hospital provider’s perspective was taken. Costs were analyzed from three diverse levels. Level 1 (drug budget perspective) only considers study drug-acquisition costs. Level 2 adds antibiotic-related costs, such as preparation and administration, therapeutic drug monitoring, and additional costs of resources used to manage adverse events and therapeutic failures. Level 3 adds the cost of hospitalization and all other nonprotocol-driven resources. A key economic outcome measure is level 3 cost at 10 to 14 days after therapy. Clinical outcome was categorized as success (cure or improvement) or failure, as determined by the original clinical investigators. Adverse events included in this analysis are those determined by the clinical investigators to be likely due to the study drug.

The clinical evaluation at 10 to 14 days after therapy is the most pertinent outcome relative to the hospital perspective. The
economic evaluation period, antibiotic-related length of stay (LOSAR), is used to define the duration of hospital stay attributed to the treatment of CAP and its sequelae. With few exceptions, LOSAR was equivalent to overall length of stay. Any resources (procedures or medications) not directly related to the inpatient treatment of CAP were not included. In some patients, documentation of follow-up antibiotics/treatments was incomplete. A blinded economic investigator assigned expected values to the data in question.

**Resource Utilization**

Information collected by the clinical investigators on the electronically maintained case report form included comprehensive data for each patient. Length of stay, procedures performed, medications administered, adverse events, clinical response, and other factors were extracted and used to construct the pharmacoeconomic database. A partial listing of the procedures that were documented includes computer axial tomography scans; bronchoscopies; respiratory, physical, and occupational therapy; radiographic studies; laboratory tests; thoracentesis; concomitant medications, including those used to treat adverse events and treatment failures; ventilation-perfusion scans; ECGs; ultrasound; nebulizer treatments; IV site changes; heat and cold packs for phlebitis; incentive spirometry; echocardiograms; oxygen therapy; and telemetry.

**Resource Costs**

The cost for procedures was obtained by applying the cost-to-charge ratio (70.46%) to the charges of a reference hospital, and then adjusting to a national cost basis. A published cost of IV site changes was used. Since the clinical investigators were not required to report whether the patients were admitted to a regular floor bed or to an ICU, the cost per bed day was derived from the weighted average time spent in each of seven intensity levels of care for diagnosis-related group (DRG) 89 and DRG 90 (simple pneumonia with and without effusion, n = 2,187 patients) to the direct cost of supplying that care at the reference hospital (Table 1). The weighted-average intensity level accounts for the cost of time spent in intensive care settings. The resulting per diem cost was indexed to the national average, then applied to each day of hospitalization. The cost for azithromycin was calculated at $18.00/500 mg IV and $10.00/500 mg oral. The cost for cefuroxime was $3.50/750 mg IV and $4.75/500 mg oral. The cost for erythromycin was $1.75/500 mg IV and $0.15/500 mg oral. Preparation and administration costs were $7.75 per IV dose and $1.50 per oral dose.

**Economic Calculations**

Because costs in clinical infectious diseases studies are typically right skewed, the geometric mean was used as the measure of central tendency. The geometric mean cost (GMc) was determined for each outcome: success or failure for each of the three treatment alternatives (azithromycin, cefuroxime, cefuroxime plus erythromycin). The GMc was computed as follows: \( \text{Exp.}(P(S) \times \ln(GMc-s) + P(F) \times \ln(GMc-f)) \), in which \( P(S) \) signifies the exponential, \( P(S) \) and \( P(F) \) are observed outcomes of success and failure, and \( \ln(GMc-s) \) and \( \ln(GMc-f) \) are the natural logarithms (Lns) of the GMc for success and failure. The GMc for the overall control group was computed by combining the costs and probabilities for cefuroxime alone with those for cefuroxime plus erythromycin, using an equation similar to that above.

A cost-effectiveness ratio (CER) was calculated for each treatment arm by dividing the GMc of treatment by the probability of success for that regimen. The CER represents the cost per likelihood of producing a successful outcome, and provides a meaningful measure of both costs and outcomes. The treatment arm with the lowest CER is considered to be the most cost-effective regimen, and is the primary outcome measure in this pharmacoeconomic study. As a secondary economic outcome measure, the control group was separated into monotherapy (cefuroxime alone) and combination therapy (cefoxime plus erythromycin) subgroups, and each was compared to the azithromycin group.

**Statistical Analysis**

Patient demographics at baseline were compared by contingency tables or the Fisher exact test. Between-treatment comparisons of level 3 costs were made by constructing 95% confidence intervals (CIs) about the GMcs and by Kruskal-Wallis one-way analysis of variance. Differences in clinical response rates were analyzed by contingency tables. All tests were two sided, with a probability of a type-1 error of 0.05 used to

**Table 1—Calculations for Cost per Bed Day**

<table>
<thead>
<tr>
<th>Variables</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room-related direct (fixed and variable supplies)</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>123</td>
<td>123</td>
<td>123</td>
</tr>
<tr>
<td>Indirect (depreciation)</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>126</td>
<td>126</td>
<td>126</td>
</tr>
<tr>
<td>Direct salaries</td>
<td>141</td>
<td>169</td>
<td>196</td>
<td>225</td>
<td>593</td>
<td>801</td>
<td>891</td>
</tr>
<tr>
<td>Indirect salaries</td>
<td>132</td>
<td>159</td>
<td>196</td>
<td>212</td>
<td>420</td>
<td>568</td>
<td>631</td>
</tr>
<tr>
<td>Total cost per bed day per intensity of care provided (sum)</td>
<td>332</td>
<td>357</td>
<td>441</td>
<td>496</td>
<td>1262</td>
<td>1618</td>
<td>1771</td>
</tr>
<tr>
<td>Percentage of time</td>
<td>3.09</td>
<td>36.81</td>
<td>36.94</td>
<td>13.93</td>
<td>7.03</td>
<td>1.76</td>
<td>0.44</td>
</tr>
<tr>
<td>Percentage of time times cost per bed day</td>
<td>10</td>
<td>142</td>
<td>163</td>
<td>70</td>
<td>89</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>Calculated national average cost per bed day</td>
<td>510</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Costs are presented in US dollars ($).
†Percentage of time spent in each intensity of care for CAP (DRG 89 and DRG 90) 1996 data.
determine statistical significance. The statistical analysis was performed using software (SYSTAT version 7.0; SYSTAT Software; Evanston, IL).

Cost and outcome data were further analyzed using modeling software (ADAPT II: Biomedical Simulation Resource, University of Southern California; Los Angeles, CA). This was done so that statistical procedures could be performed on the CER, which is a dual measure of costs and outcomes, each of which contain independent experimental uncertainty. Model input was the treatment group, response to treatment (success or failure) and the Ln of the Level 3 cost were the model outputs. The fitted parameters were probabilities of success and the mean Ln (cost), for success and failure, for each of the three treatment paths (azithromycin, cefuroxime alone, cefuroxime plus erythromycin).

The derived functional parameters were the three probabilities of failure, the GMCs of success and failure for each of the three groups (azithromycin, cefuroxime alone, cefuroxime plus erythromycin) and for the combined control group (cefuroxime with or without erythromycin), and the CERs for all three groups (azithromycin, cefuroxime alone, cefuroxime plus erythromycin) and for the combined control group (cefuroxime with or without erythromycin).

Sensitivity analyses were performed to assess whether different bed costs ($200 to $1,200/d), antibiotic prices ($500–$1,100), and clinical success rates (varied to the threshold point to force equal cost-effectiveness) would change the economic outcome. Hospital per diem costs vary by region, hospital type, and size. Therefore, testing the cost per bed day over a wide range will account for this. By varying key factors over reasonable ranges, sensitivity analysis allows for a more feasible extrapolation of the results to a variety of divergent clinical settings while also testing the robustness of the economic conclusions.

An agreement was made between the owner of the clinical database (Pfizer; New York, NY) and the researchers, granting us full access and complete freedom in the study design, analysis, and publication. Any assumptions or blinded assessments were conservative in nature, specified, and justified with appropriate sensitivity analysis.

**RESULTS**

Of the 268 clinically evaluable patients, 266 patients were economically evaluable. Posttherapy data from two patients (one in each group) were insufficient for a comprehensive economic analysis. Thus, 136 patients in the azithromycin group and 130 patients in the control group, of which 66 patients received cefuroxime alone and 64 patients received cefuroxime plus erythromycin, comprise the economic study. Baseline demographics and comorbidities of the patients are presented in Table 2. There were no statistically significant differences noted in the baseline characteristics between the groups.

Clinical success rates at 10 to 14 days after therapy were similar to the follow-up at 4 to 6 weeks (Table 3). No statistically significant differences in clinical outcome were observed between the two treatment groups at 10 to 14 days after therapy (p = 0.54) or 4 to 6 weeks after therapy (p = 0.46).

Geometric mean LOSAR and level 3 economic analysis data are depicted in Figure 1. The decision tree combines the probabilities of success or failure with the cost of each treatment and outcome path. The results shown at the terminal end of each branch are the GMC and LOSAR for each path. For all treatment options, successful treatment resulted in a shorter length of stay and a lower mean cost than did clinical failure. Comparing level 3 costs by Kruskal-Wallis one-way analysis of variance revealed a p = 0.06 while the 95% CIs about the geometric mean overlap only slightly: $3,874 to $4,334 for the azithromycin group and $4,319 to $4,837 for the group receiving cefuroxime with or without erythromycin. The CERs were $5,265 per expected successful outcome with azithromycin and $6,145 per expected successful outcome with cefuroxime with or without erythromycin.

**Table 2—Patient Demographics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Azithromycin (n = 136)</th>
<th>Control (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>58 (43)</td>
<td>61 (47)</td>
</tr>
<tr>
<td>Weight (mean, SD), kg</td>
<td>76.9 (±18.2)</td>
<td>76.4 (±20.0)</td>
</tr>
<tr>
<td>Age (mean, SD), yr</td>
<td>60.5 (±17.6)</td>
<td>60.1 (±17.7)</td>
</tr>
<tr>
<td>White race</td>
<td>75.3</td>
<td>76.9</td>
</tr>
<tr>
<td>Black race</td>
<td>21.3</td>
<td>20.8</td>
</tr>
<tr>
<td>Asian</td>
<td>0.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Other race</td>
<td>2.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Signs and symptoms at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough with sputum production</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>Rales</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>Fever</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Abnormal respiratory rate</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>47</td>
<td>45</td>
</tr>
<tr>
<td>Other</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Concurrent disease syndromes at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>COPD</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>History of pneumonia</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Emphysema</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Asthma</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

*Data are presented as % unless otherwise indicated. The baseline demographics between groups were not significantly different (p > 0.05).*

**Table 3—Treatment Outcomes**

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Azithromycin No. (%)</th>
<th>Control No. (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to 14 d posttherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure/Improved</td>
<td>106 (78)</td>
<td>97 (75)</td>
<td>0.54</td>
</tr>
<tr>
<td>Failure</td>
<td>30 (22)</td>
<td>33 (25)</td>
<td></td>
</tr>
<tr>
<td>4 to 6 wk posttherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>98 (75)</td>
<td>87 (71)</td>
<td>0.46</td>
</tr>
<tr>
<td>Failure</td>
<td>32 (25)</td>
<td>35 (29)</td>
<td></td>
</tr>
</tbody>
</table>
mycin (p = 0.05). Results of all three levels of costs are shown in Table 4. Since the success rate was greater for the least costly treatment, an incremental cost analysis was not necessary.29

Subgroup Analysis

There were no statistically significant differences noted in the baseline demographics between patients who received azithromycin, cefuroxime, or cefuroxime plus erythromycin. The costs associated with the azithromycin group and two control subgroups (cefuroxime alone, cefuroxime plus erythromycin) are shown in Figure 2. There were overlapping CIs of the GMCs at the 95% confidence level between the azithromycin group ($4,104; 95% CI, $3,874 to $4,334) and the cefuroxime subgroup ($4,451; 95% CI, $4,101 to $4,800; p > 0.05); the corresponding CERs were not different (p = 0.36). Between the azithromycin group and the cefuroxime plus-erythromycin subgroup ($4,713; 95% CI, $4,329 to $5,097) the CIs overlapped by only $5 (p = 0.051); the CERs were statistically different (p = 0.04).

Adverse Events

Adverse events with economic consequences were identified in 16 of 136 patients (11.8%) in the azithromycin group and 28 of 130 patients (21.5%) in the control arm consisting of 5 of 66 patients (7.6%).

Table 4—Level 1, 2, and 3 Costs in US Dollars for Patients Treated With Azithromycin or Control Regimens

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Success, %</th>
<th>CER, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (n = 136)</td>
<td>113</td>
<td>231</td>
<td>4,104</td>
<td>78.0</td>
<td>5,265</td>
</tr>
<tr>
<td>Cefuroxime with or without</td>
<td>110</td>
<td>339</td>
<td>4,578*</td>
<td>74.5</td>
<td>6,145†</td>
</tr>
<tr>
<td>erythromycin (n = 130)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*p = 0.06.
†p = 0.05.
in the cefuroxime-only subgroup and 23 of 64 patients (35.9%) in the cefuroxime-plus-erythromycin subgroup. The costs of treating the adverse events are included in the appropriate groups. While there were more adverse events in the patients who received erythromycin, they were relatively mild and transient (such as nausea, diarrhea, and insertion site pain), and did not require expensive therapies. Clinical details of the adverse events have been published.\textsuperscript{32}

\textbf{Sensitivity Analysis}

Varying study drug-acquisition costs \pm 50\% did not change the overall economic decision; costs when using azithromycin were consistently lower. The point estimate cost per bed day was $510. When the daily cost per hospital bed was varied between $200/d and $1,200/d, the results become increasingly favored toward azithromycin at the higher end of the range, while the cost difference narrows at the lower end. Again, costs when using azithromycin were consistently lower.

Results obtained by varying the clinical rate of success for each drug independently over a range of values from 50 to 95\% are depicted in a three-dimensional plot in Figure 3. Overall, cefuroxime with or without erythromycin would have to be > 15\% more effective than azithromycin to be cost-effective.

\textbf{Discussion}

The treatment regimens in this study did not differ in efficacy\textsuperscript{32}; the results are corroborated by a recently published study.\textsuperscript{41} The clinical trial was completed in 1995 in accordance with the original ATS guidelines for CAP.\textsuperscript{6} Updated and revised guidelines from recognized authoritative bodies suggest a fluo-
Roquinolone as monotherapy or a combination of a $\beta$-lactam plus a macrolide for patients in a hospital ward bed. It is important to repeat that an appropriate match of patient and empiric regimen is of utmost importance. Knowledge of local epidemiology is increasingly important with the increase of Streptococcus pneumoniae resistance to $\beta$-lactams, macrolides, fluoroquinolones, tetracyclines, and sulfonylamides. The updated ATS guidelines delineate a role for azithromycin, though it is limited to a well-defined group of inpatients who have no underlying cardiopulmonary disease, and no risk factors for either drug-resistant pneumococci or enteric Gram-negative pathogens.

Patients in each of the three study arms experienced similar adverse events although at slightly different rates. Not surprisingly, the combination of cefuroxime plus erythromycin produced the highest adverse event rate. The majority of adverse events were IV site problems after IV administration and GI problems after oral administration.

We found that patients treated with azithromycin used fewer health-care resources, and that azithromycin was cost-effective compared to the group receiving cefuroxime with or without macrolide. The GMC per patient was $474 less in the azithromycin group than the control group ($p = 0.06$ with only a $15$ overlap in $95\%$ CI), an economically important difference. If this cost savings were applied to every appropriate patient hospitalized with CAP in the United States, an estimated annual savings of $400$ to $700$ million would be realized.

GMC was used rather than arithmetic mean or median values for two reasons. In concordance with other cost-effectiveness analyses of antimicrobial therapies, the results are not normally distributed. Failures cost much more than successes (Fig 1) so the data exhibit a prominent right skew: arithmetic means are much higher than the median values while geometric means are more consistent and representative of the data. Additionally, geometric means allow for the use of more descriptive and informative statistical tests than do median values.

The sensitivity analyses demonstrated the robustness of the decision model used in this economic analysis. Varying the prices of the study drugs by $\pm 50\%$ or the cost of the hospital bed between $200/d and $1,200/d did not change the economic decision. When varying the percentage of successfully treated patients, it was determined that the cefuroxime with or without erythromycin control group would require a clinical success rate $> 15\%$ above that of azithromycin to be cost-effective.

Although it has a higher purchase price per dose, azithromycin demonstrated a cost-effectiveness advantage over cefuroxime with or without erythromycin. The overall decrease in costs was due to three factors. The group receiving cefuroxime with or without erythromycin requires three to seven parenteral doses or two to six oral daily doses, whereas azithromycin is administered only once daily with consequently lower daily preparation and administration costs. Secondly, azithromycin is administered for fewer days; thus, less resources are used. Third, there was a decrease in the length of hospital stay. There is an overall cost savings when using azithromycin as empiric therapy for hospitalized patients with CAP who are expected to be infected with penicillin-susceptible $S$ pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Legionella spp., or Chlamydia pneumoniae, without having underlying cardiopulmonary disease or risk factors for enteric Gram-negative pathogens.

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