CONTAINING COSTS AND CONTAINING BUGS: ARE THEY MUTUALLY EXCLUSIVE?

DAVID P. NICOLAU, PharmD, FCCP, FIDSA

ABSTRACT

BACKGROUND: The overall health care costs for managing patients with community-acquired pneumonia (CAP) in U.S. hospitals is burdensome. While pharmacy costs comprise only a minor proportion of these costs, hospital length of stay (LOS) is the greatest contributor. Infections due to antimicrobial-resistant pathogens are also associated with increased overall health care cost. Therefore, strategies that aim to minimize antimicrobial resistance and reduce hospital LOS may have the greatest impact in reducing overall health care costs in managing patients with CAP.

OBJECTIVE: To evaluate how antimicrobial resistance can impact health care costs associated with CAP and review strategies to minimize the risk of resistance development while promoting appropriate antimicrobial therapy (including optimized dosing) and decreasing hospital LOS.

SUMMARY: Antimicrobial resistance can increase the risk of clinical failure and result in higher overall health care costs. Further development of antimicrobial resistance during therapy should, therefore, be minimized. This can be achieved through optimized antimicrobial dosing strategies—using a higher dose of concentration-dependent agents or prolonged infusion of time-dependent agents—that increase the probability of attaining pharmacokinetic-pharmacodynamic targets for eradication of the pathogen and hence successful clinical outcomes. Decreasing LOS must be a priority when attempting to reduce hospital costs. Active intravenous-to-oral switch therapy has been shown to effectively reduce LOS. Appropriate short-course regimens may also offer the opportunity for effective treatment while reducing or eliminating unnecessary antimicrobial exposure that not only reduces the potential for drug-related adverse events, but may also minimize the selection of resistant organisms.

CONCLUSION: Clinical failure and antimicrobial resistance can significantly increase the cost of managing patients with CAP, primarily by increasing LOS. Therefore, strategies should be employed to minimize the risk of resistance development and reduce LOS. These include early appropriate therapy, optimized dosing based on pharmacodynamic principles, and efficient IV-to-PO switch therapy when appropriate.


Copyright © 2009, Academy of Managed Care Pharmacy. All rights reserved.

COMMUNITY-ACQUIRED PNEUMONIA (CAP) is associated with over 1 million hospitalizations each year in the United States, resulting in an estimated $6-$8 billion cost for inpatient care.1-3 Given the rising costs of managing hospitalized patients, selection of appropriate antimicrobial therapy for CAP must take into account clinical effectiveness as well as cost-efficiency. Antimicrobial costs are under constant scrutiny. However, it is important to recognize that drug-acquisition costs as a percentage of overall cost of managing patients with CAP are small. The identification of other factors that can be targeted to reduce costs is necessary.

Antimicrobial Costs as a Proportion of Total Health Care Cost

Cost of drugs, and in particular antimicrobials, is often identified as the main reason for rising costs of health care in hospitalized patients. However, studies have shown that the proportion of overall management costs attributed to these agents is less than 5% for hospitalized CAP patients.4-5 Studies that evaluated other serious infections in the hospital attribute less than 10% of overall health care costs to antimicrobials.6-9 A recent study analyzed costs associated with managing hospitalized patients with CAP (PSI [Pneumonia Severity Index] Class IV and V) at a community health system during a 6-month period.10 The median total hospital cost per patient was $35,078, while the antimicrobial acquisition cost accounted for $139 per patient (2.7% of the total cost). The biggest contributors to overall cost in this study were respiratory therapy (26%), room and board (22%), pharmacy costs (17%), and laboratory costs (14%). This study indicates that efforts focusing on shortening hospital length of stay (LOS) may be more effective in reducing hospital expenditures than those aimed at reducing antimicrobial drug-acquisition costs.

Moreover, drug-acquisition cost is only one aspect of overall cost of therapy. Other drug-related costs include resources associated with drug administration and preparation, diagnostic testing (such as monitoring drug concentration levels), and drug-related adverse events or allergic reactions.

Impact of Antimicrobial Resistance on Cost

Patients with infections caused by antimicrobial-resistant organisms are at a greater risk of delayed or inappropriate therapy. This increases the probability of clinical failure, and these infections are typically associated with higher morbidity and mortality. In addition to clinical failure, antimicrobial resistance has been shown to increase overall health care costs (Table 1).11

Macrolide Resistance Associated With Clinical Failure.

Macrolide resistance has been associated with clinical failure in several studies.12-13 A prospective, population-based study conducted in Canada from 2000 to 2004 assessed if macrolide resistance resulted in increased failure rates in pneumococcal bacteremia cases.14 Macrolide failure was defined as bacteremia that occurred during treatment with outpatient macrolide antimicrobials or within 2 days after completing the course of macrolide therapy. Although macrolide failure occurred in 3.5% of the nearly 1,700 episodes included in the study, failures were
penicillin resistance can also impact overall costs. Klepser et al conducted a single-center, retrospective, observational cohort study of 231 hospitalized patients infected with S. pneumoniae isolated from blood or respiratory tract samples from 1995 to 1998.17 Data were collected for 36 days following the first positive culture and grouped according to penicillin susceptibility. No differences were observed when comparing the clinical outcomes between patient groups. However, patients infected with a nonsusceptible isolate (n = 142) had a longer median stay (14 days vs. 10 days; P = 0.05) and a higher total median cost ($1,600 difference, 95% CI = $257-$2,943) when compared with patients infected with a susceptible strain (n = 89).

Antimicrobial-Resistant Gram-Negative Bacteria Associated With Higher Health Care Costs. Antimicrobial-resistant gram-negative bacteria, such as extended-spectrum β-lactamase (ESBL)-producing Klebsiella pneumoniae or Escherichia coli have been shown to result in higher overall costs.16 This is likely the result of an increased probability of delayed appropriate therapy, resulting in higher mortality rates and prolonged hospital LOS.

Resistance May Impact Clinician Prescribing Behavior. Antimicrobial resistance can also have a global impact on treatment decisions. Clinician perception of resistance can affect prescribing behaviors when selecting empiric therapy.19 Therefore, not unexpectedly, in this situation of perceived “unacceptably high” resistance, more potent antimicrobial agents or combination regimens may be unnecessarily used for empiric treatment. This phenomenon then feeds the inappropriate or overuse of antimicrobials for a great many patients and highlights the need for the dissemination of local susceptibility data to the practicing prescribers of the region.
A study that investigated the relationship between amoxicillin-resistance levels with the per-patient cost of treatment for community-acquired lower respiratory tract infections showed a clear trend of increased costs as the probability of resistance increased. Therefore, strategies to minimize the risk of resistance development during treatment will be critical in extending the usefulness of current antimicrobial agents and reducing overall treatment costs.

Strategy to Minimize the Emergence of Resistance: Optimizing Antimicrobial Dosing

Dosing regimens are now designed to attain pharmacodynamic targets that increase the probability of achieving clinical efficacy and prevent the emergence of resistance. Antimicrobial agents can be classified into 2 groups—those that exhibit concentration-dependent bacterial killing and those that exhibit time-dependent bacterial killing. The characteristics of the drug dictate pharmacokinetic/pharmacodynamic targets that should be achieved (Table 3).

<table>
<thead>
<tr>
<th>Drug Classes</th>
<th>Cmax/MIC</th>
<th>AUC/MIC</th>
<th>T &gt; MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides Fluoroquinolones</td>
<td>Azithromycin Fluoroquinolones Ketolides</td>
<td>Carbenemns Cephalosporins Penicillins</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Bactericidal Activity</th>
<th>Concentration-dependent</th>
<th>Concentration-dependent</th>
<th>Time-dependent</th>
</tr>
</thead>
</table>

| Therapeutic Goal | Maximize exposure Increase dose | Maximize exposure Increase dose | Optimize duration of exposure Shorten interval |

AUC = area under the concentration-time curve; MIC = minimum inhibitory concentration; T = dosing interval.

Concentration-Dependent Agents. For concentration-dependent agents, such as the aminoglycosides and fluoroquinolones, successful outcomes have been associated with meeting targets related to the peak concentration to the minimum inhibitory concentration (MIC) ratio (Cmax/MIC) or the area under the concentration–time curve to MIC ratio (AUC/MIC). For these agents, maximizing exposure with higher doses or with less frequent dosing can be important strategies to optimize their pharmacodynamic parameters.

As a result of pharmacodynamic studies, the recommended dosing of aminoglycosides has changed from the traditional 2-3 times daily to once daily. This change in aminoglycoside dosing not only increases the Cmax/MIC but has also been shown to decrease the potential for toxicity.

For the fluoroquinolones, higher doses increase the probability of meeting AUC/MIC targets. For S. pneumoniae infections, an AUC/MIC ratio of 30-35 is generally needed for successful clinical outcomes. The 750 mg dose of levofloxacin nearly doubles the AUC compared to the 500 mg dose and increases the probability of meeting AUC/MIC targets, particularly for isolates with higher MIC values. However, evidence also suggests that an AUC/MIC ratio of 100 is needed to prevent the development of resistance. For S. pneumoniae infections, while both levofloxacin and moxifloxacin reach the concentrations needed for clinical effectiveness, only moxifloxacin attains the levels required to prevent development of resistance. For gram-negative infections treated with the fluoroquinolones, an AUC/MIC ratio of 100-125 is generally recommended.

Strategy to Reduce Antimicrobial Costs: IV-to-PO Switch

Early intravenous-to-oral (IV-to-PO) switch therapy is a proven strategy to reduce overall health care costs without impacting clinical outcomes in patients with CAP. Studies beginning in the mid-1990s had shown evidence that critical pathways that actively select patients for IV-to-PO switch can decrease antimicrobial acquisition costs and reduce hospital LOS. Ramirez et al. investigated the impact of an early switch to oral antibiotics (within 3 days of hospitalization) in 133 patients with CAP. Criteria for early switch included improving cough and shortness of breath, temperature below 37.8°C for at least 8 hours, normalizing white blood cell count, and adequate oral intake and gastrointestinal absorption. Using similar criteria for switch, Kut et al. also demonstrated that a pharmacist could manage the transition from IV-to-PO therapy and that these interventions could be initiated swiftly and safely, thereby reducing the LOS and the overall cost of care.

Candidates for IV-to-PO Switch Therapy. The latest CAP guidelines issued by the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) support early IV-to-PO switch therapy and provide recommendations for selecting patients appropriate for an IV-to-PO switch. According to these guidelines, IV-to-PO switch therapy should be considered in patients who are hemodynamically stable, improving clinically, able to ingest oral medications, and have a normally functioning gastrointestinal tract. The guidelines also suggest that patients should be discharged as soon as they are clinically stable.
stable, have no other active medical problems, and have a safe environment for continued care. Inpatient observation while taking oral antimicrobials is not necessary. IV-to-PO switch should be typically done within 2–4 days of initiation of treatment, though this depends on the overall clinical condition of the patient. 37 It is important to note that certain patient or infection types are contraindicated for IV-to-PO switch therapy (Table 4). 38

Types of IV-to-PO Switch Therapy. IV-to-PO switch therapy is defined in several ways depending on the antimicrobial agents used. 37 Sequential therapy uses the same agent for both IV and oral formulations with similar potency. Switch therapy uses different agents for the IV and oral formulations while maintaining the same or similar potency. Step-down therapy can use the same agent or different agents for the IV and oral formulations, though potency decreases with the oral formulation.

Some studies have investigated the differences in cost and clinical outcomes with each of these conversion strategies. A study by Dresser et al. compared sequential therapy with a fluoroquinolone (gatifloxacin) and step-down therapy with a cephalosporin ± a macrolide (IV ceftriaxone ± IV erythromycin, then oral clarithromycin). 39 There was no significant difference in clinical cure rates (98% with sequential therapy and 92% with step-down therapy) or in mean LOS (4.1 days for those receiving gatifloxacin and 4.9 days for those receiving ceftriaxone). However, the mean cost per patient was significantly lower with sequential therapy ($5,109) than with step-down therapy ($6,164, \(P=0.011\)). The higher cost associated with step-down therapy was attributed to the nearly one-day increase in mean LOS driven by 4 clinical failures.

Sequential therapy has also been associated with improved efficiency of IV-to-PO conversion compared to switch therapy. Davis et al. compared antimicrobial use during 3 separate time periods: period of no pharmacist intervention (January–March 2001), period of pharmacist intervention to switch therapy to an oral agent (January–March 2002), and period of pharmacist intervention recommending initiation of IV therapy with a fluoroquinolone (moxifloxacin) followed by conversion to its oral formulation (sequential therapy) from January–March 2004. 38

• During the period of no pharmacist intervention, IV therapy was most frequently initiated with a β-lactam plus a macrolide, and only about half of the patients were converted to oral therapy (Table 5). Forty-six percent were treated completely with an IV regimen, while several different agents were used for switch therapy among those who received oral formulations.

• During the period of pharmacist intervention recommending switch therapy to an oral agent, the strategy was to aggressively convert patients to oral levofloxacin. Since many patients were started on a β-lactam or a macrolide, physicians were reluctant to switch to a different class of agents, and some patients continued to receive a β-lactam or a macrolide for the duration of treatment, while only about 40% received oral levofloxacin. About 30% of the patients were not switched to an oral formulation.

• During the period of pharmacist intervention recommending initiation of IV therapy with a fluoroquinolone followed by conversion to its oral formulation (sequential therapy), patients were started on an IV formulation of moxifloxacin and then switched to its oral formulation. During this period, 95% of the patients were converted to oral moxifloxacin, suggesting that sequential therapy may improve acceptance of IV-to-PO conversion by clinicians.

In this study, IV antimicrobial costs were significantly lower during the period of sequential therapy ($108) compared with costs during no pharmacy intervention ($222) or switch therapy

### Table 4

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Patient Condition</th>
<th>Contraindications for Intravenous-to-Oral Switch a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most central nervous system infections</td>
<td>Status: NPO (nothing by mouth)</td>
<td></td>
</tr>
<tr>
<td>Persistent febrile neutropenia</td>
<td>Any pathology rendering patient absorption of oral medications unreliable</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Active upper GI bleeding</td>
<td></td>
</tr>
<tr>
<td>Persistent bacteremia</td>
<td>Refusal of oral medications</td>
<td></td>
</tr>
<tr>
<td>Necrotizing pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe or life-threatening infections</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Davis SL, Delgado G, Jr., McKinnon PS. 38

### Table 5

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Community-Acquired Pneumonia Treatment Protocol (n = 251)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Therapy</td>
<td></td>
</tr>
<tr>
<td>β-lactam + Macrolide</td>
<td>94.9, 96.3, 0</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1.3, 3.7, 0</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0, 0, 100</td>
</tr>
<tr>
<td>None (oral therapy only)</td>
<td>3.8, 0, 0</td>
</tr>
<tr>
<td>Oral Therapy</td>
<td></td>
</tr>
<tr>
<td>β-lactam Monotherapy</td>
<td>12.7, 6.2, 0</td>
</tr>
<tr>
<td>Macrolide Monotherapy</td>
<td>11.4, 19.8, 1.1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>25.3, 40.7, 0</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0, 0, 94.5</td>
</tr>
<tr>
<td>Other</td>
<td>3.8, 3.7, 2.2</td>
</tr>
<tr>
<td>None (IV therapy only)</td>
<td>46.8, 29.6, 2.2</td>
</tr>
</tbody>
</table>


**Switch** = intravenous (IV) β-lactam + macrolide with pharmacist intervention to switch to oral quinolone.

**Sequential** = pharmacist-initiated automatic switch from IV to oral moxifloxacin.
that since 3-day therapy did not result in inferior clinical results for these patients, short-course therapy is a more efficient strategy for treatment of CAP.

The current IDSA/ATS guidelines now recommend that patients with CAP should receive treatment for a minimum of 5 days, though patients should be afebrile for 48-72 hours and should have no more than one CAP-associated sign of clinical instability before discontinuation of therapy.30 A longer duration of treatment may be needed for some patients, such as those whose initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis.

**Summary**

The costs of treating patients with CAP can increase significantly with antimicrobial resistance and treatment failure. Therefore, strategies should be employed to minimize these risks. Such strategies include early appropriate therapy, optimized dosing strategies based on pharmacodynamic principles, and efficient IV-to-PO switch when appropriate. Moreover, the use of short-course regimens that take advantage of available potent therapies provides a new opportunity to optimize clinical outcomes, improve medication adherence, and reduce the burden of prolonged antimicrobial exposures.

**DISCLOSURES**

David P. Nicolau has received grant/research support from and serves on the speakers’ bureaus for AstraZeneca, Johnson & Johnson, Cubist, Wyeth, Merck, Pfizer, and Schering-Plough.

Marco P. Cicero, PhD, of Vemco MedEd, LLC, contributed medical writing and editorial assistance. This article is being published as part of a supplement to the START continuing education program for pharmacists and physicians. It is supported by an educational grant from Schering-Plough Corporation.

**REFERENCES**


