Containing Costs and Containing Bugs: Are They Mutually Exclusive?

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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.

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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 $5,078, 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

TABLE 1 Direct Costs Associated With Antimicrobial Resistance Among Inpatients[a]

Hospital Costs (general)	Costs Associated with Patient Isolation	Antimicrobial-Associated Costs	Other Costs
Per day per bed (1) by specialty (2) by ICU vs. general vs. others	• Supplies • Housekeeping • Waste disposal • Increased portable testing services • Increased staffing	• Antimicrobial acquisition (and other drug costs) • Antimicrobial administration	• Nursing staff time (specialized nurses) • Infections and complications • Other procedures • Laboratory (1) screening procedures (active surveillance) (2) diagnostic testing • Physician staff time • Infection control staff time

[a]*Source: Howard D, et al.*[11]

TABLE 2 Costs Associated With Treatment of Community-Acquired Pneumonia by Level of Macrolide Resistance in the Community[a]

	Treatment Cost				
	n	Macrolide Resistance Level <25%	n	Macrolide Resistance Level ≥25%	*P* Value
Treatment Success	4,377	$1,334	3,334	$2,193	<0.01
Treatment Failure	926	$2,841	809	$3,918	<0.05
Macrolides	4,189	$950	909	$2,130	<0.01
Quinolones	3,522	$2,604	826	$4,679	<0.01

[a]*Source: Reprinted from Asche C, McAdam-Marx C, Seal B, Crookston B, Mullins CD. Treatment costs associated with community-acquired pneumonia by community level of antimicrobial resistance. J Antimicrob Chemother. 2008;61(5):1162-68,*[16] *by permission of Oxford University Press.*

significantly lower when the minimum inhibitory concentration (MIC) of the isolates was ≤0.25 μg per mL (1.5%) than when the MIC of the isolates was 1 μg per mL (38%; *P*<0.001). Isolates with MIC >1 μg per mL were not associated with further increases in failure, suggesting that even low-level macrolide resistance increases the risk of failure.

Macrolide Resistance Associated With Higher Health Care Costs. A multicenter, retrospective, observational study involved 122 patients with CAP due to *S. pneumoniae* who required hospitalization after failing to respond to initial outpatient treatment with a macrolide for 2 or more days.[15] Over half of the patients had bacteremia, and 71% were infected with a macrolide-resistant strain. Overall, the mean hospital LOS was 8.7 days, including 1.3 days in a critical care unit and 1.4 days of mechanical ventilation. The mean cost of treating a patient with a macrolide-resistant infection was $5,139 higher than the cost of treating a patient infected with a macrolide-susceptible strain ($14,153 vs. $9,014; *P*=0.011). Among patients with bacteremia, the cost of treating those infected with a resistant strain was nearly double compared to the cost of treating those infected with a susceptible strain ($16,563 vs. $8,537, *P*=0.004).

Macrolide resistance in the community can also impact overall health care costs of CAP. A retrospective analysis used a large clinical database to obtain treatment outcome and cost data associated with CAP patients in 23 metropolitan areas.[16] Surveillance data were used to identify macrolide resistance rates for each area, and outcomes and costs were compared based on macrolide resistance rates of <25% or ≥25% for the area. The clinical success rates were not significantly different when comparing areas with higher versus lower endemic macrolide resistance rates; however, there were significant differences in cost. Table 2 shows the treatment cost by clinical outcome and by initial treatment (macrolide or a fluoroquinolone). In each case, cost of treatment was significantly higher in areas where endemic macrolide resistance was higher.

Penicillin Resistance Associated with Higher Health Care Costs. Penicillin resistance can also result in higher health care 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 also been shown to result in higher overall costs.[18] 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.

TABLE 3 Pharmacokinetic/Pharmacodynamic Parameters Correlating With Clinical Efficacy[a]

	C_{max}/MIC	AUC/MIC	T > MIC
Drug Classes	Aminoglycosides Fluoroquinolones	Azithromycin Fluoroquinolones Ketolides	Carbapenems Cephalosporins Penicillins
Type of Bactericidal Activity	Concentration-dependent	Concentration-dependent	Time-dependent
Therapeutic Goal	Maximize exposure Increase dose	Maximize exposure Increase dose	Optimize duration of exposure Shorten interval

[a]*Source: Drusano GL, Craig WA.[21] McKinnon PS, Davis SL.[22]*
AUC = area under the concentration-time curve; MIC = minimum inhibitory concentration; T = dosing interval.

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.[20] 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).[21,22]

Time-Dependent Agents. For time-dependent agents such as the β-lactams (penicillins, cephalosporins, and carbapenems), the proportion of time the drug concentration remains above the MIC during a dosing interval (T>MIC) should be considered. The optimal T>MIC varies depending on the class of agents—it is 40% for the carbapenems and 60%-70% for the cephalosporins.[23] Strategies to increase the T>MIC include shortening the dosing interval (without a subsequent increase in the dose) and extending the infusion time of intravenous agents (through continuous or prolonged infusion, which decreases the peak concentration [C_{max}] but prolongs the T>MIC without increasing the dose).[23] Using higher doses will not necessarily have a significant impact on T>MIC (that is, doubling the dose will not necessarily double the T>MIC).[24] If susceptibility results are available for the infecting organism, optimized dosing strategies may also involve using an agent with a lower MIC for that particular pathogen in order to increase the T>MIC.

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 (C_{max}/MIC) or the area under the concentration–time curve to MIC ratio (AUC/MIC).[25] 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 C_{max}/MIC but has also been shown to decrease the potential for toxicity.[26]

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.[27,28] 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.[29] For gram-negative infections treated with the fluoroquinolones, an AUC/MIC ratio of 100-125 is generally recommended.[22,23]

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.[30-34] Ramirez et al. investigated the impact of an early switch to oral antibiotics (within 3 days of hospitalization) in 133 patients with CAP.[31] 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, Kuti 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.[35]

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.[36] 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

TABLE 4 Contraindications for Intravenous-to-Oral Switch[a]

Type of Infection	Patient Condition
Most central nervous system infections	Status: NPO (nothing by mouth)
Persistent febrile neutropenia	Any pathology rendering patient absorption of oral medications unreliable
Endocarditis	Active upper GI bleeding
Persistent bacteremia	Refusal of oral medications
Necrotizing pneumonia	
Necrotizing fasciitis	
Severe or life-threatening infections	

[a]*Source: Davis SL, Delgado G, Jr., McKinnon PS.*[38]

TABLE 5 Comparison of Pharmacist Intervention Strategies Over 3 Time Periods[a]

Therapy	Community-Acquired Pneumonia Treatment Protocol (n = 251)		
	No Pharmacist Intervention % (Jan-Mar 2001) (n = 79)	Pharmacist Intervention - Switch[b] % (Jan-Mar 2002) (n = 81)	Pharmacist Intervention - Sequential[c] % (Jan-Mar 2004) (n = 91)
IV Therapy			
β-lactam + Macrolide	94.9	96.3	0
Levofloxacin	1.3	3.7	0
Moxifloxacin	0	0	100
None (oral therapy only)	3.8	0	0
Oral Therapy			
β-lactam Monotherapy	12.7	6.2	0
Macrolide Monotherapy	11.4	19.8	1.1
Levofloxacin	25.3	40.7	0
Moxifloxacin	0	0	94.5
Other	3.8	3.7	2.2
None (IV therapy only)	46.8	29.6	2.2

[a]*Source: Reprinted with permission from Davis SL, Delgado G, Jr., McKinnon PS. Pharmacoeconomic considerations associated with the use of intravenous-to-oral moxifloxacin for community-acquired pneumonia. Clin Infect Dis. 2005; 41(Suppl 2):S136-S43.*[38] *Published by University of Chicago Press; ©2005 The University of Chicago Press. All rights reserved.*

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

[c]*Sequential = pharmacist-initiated automatic switch from IV to oral moxifloxacin.*

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).[5] 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 6 Costs Associated With Short-Course Therapy[a]

Study Phase	Mean Cost (EUROs €)		
	Short-Course Therapy for 3 Days (n = 56)	Standard Therapy for 8 Days (n = 63)	Difference
Hospital Admission	3,721	3,930	-209
Follow-up	238	172	66
Total	3,959	4,102	-143

[a]*Source: Opmeer BC, et al.*[46]

($215) periods ($P<0.001$). Similarly, total antimicrobial costs were lower as well ($119 vs. $230 and $233, respectively; $P<0.001$).

Strategy to Minimize Emergence of Resistance and Reduce Overall Costs: Short-Course Therapy

Over the past few years, there has been a growing preference of shorter courses (5 days or less) of antimicrobial regimens to the traditionally longer courses (7-14 days) for the treatment of CAP.[1,39] The rationale is that the availability of more potent agents allows for more rapid eradication of pathogens, and the shorter courses reduce selection pressure for resistance development by decreasing time of antimicrobial exposure and reduced total antimicrobial usage.[40] Other advantages of short-course regimens include improved safety (that is, reduced potential of drug-related adverse events), increased patient convenience and, thus, adherence to therapy, and potentially reduced costs. It should be noted that short-course regimens must be based on sound pharmacodynamic data and must achieve adequate tissue penetration in order to be successful.

Several studies have investigated the clinical effectiveness of short-course regimens.[41-43] Though these studies show that the efficacy of short-course regimens is comparable to the efficacy of longer courses, they tend to only include patients with mild-to-moderate disease and/or who were primarily treated on an outpatient basis. A study by Dunbar et al., however, compared the 750 mg dose of levofloxacin for 5 days with 500 mg for 10 days for patients with mild-to-severe CAP.[44] The short-course regimen was comparable to the longer-course regimen, even for patients with severe disease (PSI Class IV). Interestingly, patients receiving the 750 mg dose experienced more rapid resolution of fever and other CAP-related symptoms.[45]

The question that remains is whether short-course therapy can reduce overall health care costs. In a study from the Netherlands, a cost-minimization analysis was performed based on direct medical and indirect nonmedical costs for the 28 days following hospital admission for patients with mild-to-moderate CAP, who received either 3 days or 8 days of antimicrobial therapy.[46] The shorter course was not associated with any significant difference in clinical results compared with standard therapy. Lower costs were observed with short-course therapy during hospital admission, but some of the savings were offset by follow-up visits to primary health care providers (Table 6). Total savings with short-course therapy were approximately 4%. The authors concluded 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.[36] 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.

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