START (Stewardship Tactics for Antimicrobial Resistance Trends)

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This supplement to the Journal of Managed Care Pharmacy (ISSN 1083-4087) is a publication of the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314, 703.683.8416; 703.683.8417 (fax).
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Dr. File is a Master of the American College of Physicians, a Fellow and member of the Board of Directors of the Infectious Diseases Society of America (IDSA) and a Fellow of the American College of Chest Physicians. He is Vice President of the National Foundation for Infectious Diseases and is a member of many other professional societies, including the American Society for Microbiology, the American Thoracic Society (ATS), and the American Society of Hospital Epidemiologists. He is past Chairperson of the Standards and Practice Guidelines Committee of the IDSA and has also served as a member of the IDSA and ATS committees for guidelines on community-acquired pneumonia. He is a past president of the Infectious Diseases Society of Ohio and of the Northeastern Ohio Task Force on AIDS.

Dr. File has pursued research on community-acquired respiratory tract infections, bacterial resistance in respiratory infections, infections in patients with diabetes, and evaluation of new antimicrobial agents. A frequent lecturer both nationally and internationally, Dr. File has published more than 200 articles, abstracts, and textbook chapters, focusing on the diagnosis, etiology, and treatment of infectious diseases, especially respiratory tract infections. He co-authored Contemporary Diagnosis and Management of Skin and Soft Tissue Infections, 2nd edition (File TM, Jr., and Stevens DL [eds], 2007) and co-edited Expert Guide to Infectious Diseases, 2nd edition (Tan JS, File TM, Jr., Salata RA, Tan MJ [eds], 2008). In addition, he is Editor-in-Chief of Infectious Diseases in Clinical Practice.

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Dr. Nicolau’s investigations of antibiotic activity against infection and his examinations of alternative methods in antimicrobial therapy are reported in over 380 published articles and 256 abstracts. He serves on the editorial board of several peer-reviewed journals, including Diagnostic Microbiology and Infectious Diseases, Surgical Infections, Infectious Diseases in Clinical Practice, and Expert Opinion in Pharmacotherapy.

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After completing a bachelor of science degree in pharmacy at the University of Rhode Island and a residency in hospital pharmacy at Duke University Medical Center, Dr. Drew went on to earn a master of science degree in hospital pharmacy and a doctor of pharmacy degree at the University of North Carolina at Chapel Hill. He is a board-certified pharmacotherapy specialist with added qualifications in infectious diseases.

Dr. Drew is the author of numerous articles and several book chapters. He serves as a reviewer for several journals including, Clinical Infectious Diseases, Annals of Pharmacotherapy, American Journal of Health-System Pharmacy, and Antimicrobial Agents and Chemotherapy. Dr. Drew’s chief areas of research interest are infections due to gram-positive bacteria, fungal infections, Dravid-Dhib, respiratory infections, and influenza infections.

Drew’s research was acknowledged in 2008 when he received the Dean’s Award for Research Excellence, Campbell University School of Pharmacy. An active member of several professional associations, Dr. Drew is a past president of the Society of Infectious Diseases Pharmacists.
Educational Overview

We are entering a period when antimicrobial stewardship programs are of critical importance. Until recently, the focus has been chiefly on patient outcomes, safety, and cost containment. However, it is likely in the decade to come that reducing or stabilizing levels of antimicrobial resistance will be paramount.

Antimicrobial stewardship initiatives require a multidisciplinary team of health care professionals. Through its combined efforts, this team can devise effective strategies for changing and directing antimicrobial use at hospitals and other health care institutions. Concern about resistance is worldwide, but problem solving begins at the local level, since resistant microbes, such as *Streptococcus pneumoniae*, occur in individual communities and spread outward. The team members’ responsibilities extend to initiating stewardship programs and driving their acceptance. A unified, multidisciplinary team that includes physicians, pharmacists, nurses, and case managers will represent the vanguard in our battle against antimicrobial resistance.

Appropriate management of hospitalized community-acquired pneumonia (CAP) patients through effective antimicrobial stewardship programs has many benefits, not the least of which is the reduction of morbidity and mortality associated with the disease. The multidisciplinary team responsible for treating the hospitalized CAP patient, including the infectious diseases specialist, the clinical pharmacist, and other team members, should serve as passionate advocates for appropriate antimicrobial use.
Purpose Statement
The purpose of this activity is to review the potential benefits of antimicrobial stewardship programs as a way to minimize the emergence and spread of resistant pathogens while improving clinical outcomes and minimizing health care costs for patients hospitalized with community-acquired pneumonia.

Fee Information
There is no fee to participate in this educational activity.

DISCLOSURES
This supplement is supported by an educational grant from Schering-Plough Corporation.

The START (Stewardship Tactics for Antimicrobial Resistance Trends) educational program commenced in 2006 and has been repeated in each subsequent year as a series of regional meetings originally designed for hospital-based pharmacists. The program was subsequently expanded to include physicians and other health care professionals interested in learning about the latest guidelines and management strategies related to CAP and antimicrobial stewardship.

The authors acknowledge the medical writing and editorial assistance provided by Marco P. Cicero, PhD, of Vemco MedEd, LLC.

Disclosures of Conflicts of Interest
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Faculty Disclosures
Keith A. Rodvold serves as a consultant to Johnson & Johnson, Astellas, GlaxoSmithKline, Theravance, Targanta, and Intranasal Therapeutics. He is on the advisory committees of Johnson & Johnson, Targanta, Baxter, and Pfizer and is a member of speakers’ bureaus for Johnson & Johnson, Wyeth, Pfizer, and Schering-Plough.

Thomas M. File, Jr., has received research funding from CereXa, Ortho-McNeil, Pfizer, Protez, Rib-X, and Wyeth. He serves as a consultant to Advanced Life Sciences, Bayer, CereXa, Cubist, GlaxoSmithKline, Ortho-McNeil, Merck, Nabriva, Oscient, Protez, sanofi-aventis, Schering-Plough, and Wyeth. He is also a member of the speakers’ bureaus for Astellas, Theravance, Merck, Ortho-McNeil, Oscient, Pfizer, Schering-Plough, and Wyeth.

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Richard H. Drew serves as a consultant to Merck, Theravance, Ortho-McNeil, and Schering-Plough. He receives research support from Schering-Plough, NeuTec, and Cubist and has received honoraria as a speaker from Schering-Plough, Ortho-McNeil, Enzon, sanofi-aventis, Wyeth-Ayerst, and Astellas. Dr. Drew is on the Development Team for CustomID.

Disclosure of Off-Label Use
The faculty reported that there is no mention of off-label use of antimicrobial agents or other drugs in this educational activity.

Disclosure: Planning Committee
Employees of the Center for Independent Healthcare Education and Vemco MedEd have no relevant financial relationships to disclose.

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Center has assigned 2.0 contact hours (0.20 CEUs) of continuing pharmacy education credit to this activity (ACPE Universal Activity Number: 473-999-09-003-H01-P). For questions regarding the accreditation of this activity, please contact Center at info@jointspoonor.com.

Release Date: March 1, 2009
Expiration Date: March 1, 2010
Type of Activity: Knowledge-based

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Introduction

Keith A. Rodvold, PharmD, FCCP, FIDSA

Today's Health Care Environment
Among infectious diseases, community-acquired pneumonia (CAP) is the leading cause of death in the United States and is associated with billions of dollars in health care costs.1,2 Despite the availability of several classes of antimicrobial agents, elevated resistance rates challenge appropriate antimicrobial selection and increase the risk of treatment failure. Against this backdrop, antimicrobial stewardship programs (ASPs) are being implemented in a growing number of institutions with the goal of encouraging the appropriate use of antimicrobial agents to optimize clinical outcomes while minimizing unintended consequences, including the emergence of resistance.

Appropriate management of hospitalized patients with CAP through effective ASPs has several potential benefits—reduction in morbidity, mortality, and overall health care costs associated with CAP. However, studies are needed to fully evaluate the benefits of ASPs in CAP management. An effective and successful ASP is dependent on the multidisciplinary team responsible for treating the hospitalized patient with CAP—the infectious diseases (ID) specialist, the clinical pharmacist, and other members—serving as a passionate advocate for appropriate antimicrobial use. Educating personnel on the issues related to antimicrobial use and resistance when managing patients with CAP is essential. As a result, several ID physicians and pharmacists from across the country are becoming involved in the START educational program to address this critical need at both the regional and local levels.

What Is START?
The START (Stewardship Tactics for Antimicrobial Resistance Trends) educational program commenced in 2006 and has been repeated in each subsequent year as a series of regional meetings originally designed for hospital-based pharmacists. The program was subsequently expanded to include physicians and other health care personnel interested in learning about the latest guidelines and management strategies related to CAP and antimicrobial stewardship.

The objective of the START educational program was to educate and familiarize the health care team on the following topics:
- The epidemiology and impact of hospital-acquired infections in U.S. hospitals
- The common pathogens associated with CAP and national and regional resistance trends
- The importance of pharmacokinetics and pharmacodynamics as factors in appropriate selection of empiric antimicrobial therapy
- Cost-containment strategies for appropriate antimicrobial therapies
- The goals of antimicrobial stewardship and roles of key team members in running a stewardship initiative

This supplement reflects the topics covered in the START program. Three articles are based on the 3 main talks from the START program while a fourth article answers the most commonly asked questions during START meetings.

Overview
In the first article, Dr. Thomas M. File, Jr., discusses new guidelines for the diagnosis and treatment of CAP released in 2007 by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS).3,4 These guidelines, intended as an update of the 2003 IDSA guidelines, provide evidence-based recommendations for proper management of patients with CAP and address several issues that are evolving in the management of these patients. A portion of the guidelines is devoted to choosing the appropriate site of care guided by mortality prediction tools. This is to ensure that hospitalization is reserved only for those who require it—a response to manage the rising cost of health care. The guidelines also address increasing resistance, selection of the most appropriate therapy, monotherapy versus combination therapy, and the optimal duration of therapy.

The second article, by Dr. David P. Nicolau, addresses cost considerations when treating patients with CAP. The article emphasizes that clinical outcome is only one aspect of gauging the success of patient management strategies. Given the growing economic burden, the health care team must also take into account tactics that improve cost-effectiveness. When considering hospitalization costs, length of stay is a major portion of overall health care cost, while antimicrobial agents are a relatively small proportion of overall cost.5,6 Not surprisingly, antimicrobial resistance and subsequent treatment failure is a major reason for high costs. The article discusses several tactics that can be used to improve cost-effectiveness while maintaining the quality of care, including choosing the appropriate agent, optimizing dosing (improving the probability of a successful clinical outcome while minimizing the risk of resistance development), active IV-to-oral switch therapy, and short-course regimens.

Dr. Richard H. Drew, in the third article, discusses the role of ASPs in management of infection and presents strategies that can be used to improve the appropriate use of antimicrobials. Excessive and inappropriate use of antimicrobials may render commonly used agents ineffective and lead to an increase in unintended consequences, including the emergence and spread of resistant bacteria. As a result, the guidelines on antimicrobial stewardship were released in 2007 by IDSA and the Society for Healthcare Epidemiology of America (SHEA).7 These guidelines provide important insights on implementing an ASP at an institution and present evidence pertaining to core strategies that can provide both clinical and economic benefits. The success of stewardship programs is based on the collaborative effort of physicians, pharmacists, infection control personnel, and other health care professionals with the support of hospital administrators.
The fourth article in this supplement discusses a number of questions from the participants that were addressed during the START meetings. This article offers an opportunity to discuss various topics that were not normally covered within the presentations but are relevant to the everyday practice of hospital clinicians.

Summary
Concern about antimicrobial resistance is universal, but developing a solution to combat this crisis begins at the local level within each community and institution. The responsibility for preventing and controlling the spread and emergence of resistant pathogens hinges on all health care personnel. Therefore, a unified multidisciplinary team that includes physicians and pharmacists, among others, must represent the vanguard in our battle against antimicrobial resistance.

Introduction

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DISCLOSURES
Keith A. Rodvold serves as a consultant to Johnson & Johnson, Astellas, GlaxoSmithKline, Theravance, Targanta, and Intranasal Therapeutics. He is on the advisory committees of Johnson & Johnson, Targanta, Baxter, and Pfizer and is a member of the speakers’ bureaus for Johnson & Johnson, Wyeth, 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
The Science of Selecting Antimicrobials for Community-Acquired Pneumonia (CAP)

Thomas M. File, Jr., MD, MSc, FIDSA

ABSTRACT

BACKGROUND: Among infectious diseases, community-acquired pneumonia (CAP) is the leading cause of death in the United States and is associated with a substantial economic burden to the health care system. Initiating appropriate empiric therapy can be challenging given elevated resistance rates among *Streptococcus pneumoniae* strains.

OBJECTIVE: To present current recommendations for management of CAP with respect to (a) choosing the appropriate site of care, and (b) antimicrobial selection based on bacterial etiology and the prevalence of resistance.

SUMMARY: Mortality prediction tools, such as the PORT (Pneumonia Outcomes Research Team) Severity Index, CURB-65 (Confusion, Urea concentration, Respiratory rate, Blood pressure, and age>65), or CRB-65 (Confusion, Respiratory rate, Blood pressure, and age>65), can be invaluable in determining which CAP patients require hospitalization. These tools can help reduce overall costs for CAP by limiting hospitalizations of low-risk patients. *S. pneumoniae* remains the most common causative pathogen for CAP across all disease severities, and elevated rates of resistance to penicillin and macrolides can hinder selection of appropriate antimicrobial therapy. Antimicrobial resistance can impact clinical outcomes, including increasing the risk of treatment failure and breakthrough bacteremia. Current management guidelines recommend monotherapy with a respiratory fluoroquinolone or combination therapy with a β-lactam and a macrolide (for patients admitted to the general medical ward) or with a β-lactam and either a respiratory fluoroquinolone or a macrolide (for patients admitted to the intensive care unit [ICU] and who do not have risk factors for methicillin-resistant *S. aureus* or *Pseudomonas*). Optimized dosing regimens aim to ensure that pharmacokinetic and pharmacodynamic targets are met to achieve successful clinical outcomes and minimize resistance development.

CONCLUSION: Effective management of patients with CAP requires selection of the proper site of care and appropriate empiric antimicrobial. Given the elevated rates of resistance among *S. pneumoniae*, local resistance patterns must be considered when choosing empiric therapy.


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Site of Care

Site of care in patients with CAP impacts the overall cost of treatment, the intensity of diagnostic testing, and options for empiric antimicrobial selection. The decision to admit a patient with CAP is based on (a) mortality prediction rules, such as the PORT (Pneumonia Outcomes Research Team) Severity Index (PSI) score or CURB-65 (Confusion, Urea concentration, Respiratory rate, Blood pressure, and age>65), (b) social circumstances of the patient, and (c) co-existing conditions.

Hospitalization. Hospitalization should be considered when (a) patients have pre-existing conditions that may compromise the safety of home care, (b) patients have hypoxemia, (c) patients are unable to take oral medications, or (d) psychosocial factors can...
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### TABLE 1: Common Etiologies of Community-Acquired Pneumonia

<table>
<thead>
<tr>
<th>Ambulatory Patients</th>
<th>Hospitalized (non-ICU) Patients(^b)</th>
<th>Severe (ICU) Patients(^b)</th>
</tr>
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<tbody>
<tr>
<td>S. pneumoniae</td>
<td>S. pneumoniae</td>
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<tr>
<td>M. pneumoniae</td>
<td>M. pneumoniae</td>
<td>S. aureus</td>
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<tr>
<td>H. influenzae</td>
<td>C. pneumoniae</td>
<td>Legionella spp.</td>
</tr>
<tr>
<td>C. pneumoniae</td>
<td>H. influenzae</td>
<td>Gram-negative bacilli</td>
</tr>
<tr>
<td>Respiratory viruses(^b)</td>
<td>Legionella spp.</td>
<td>H. influenzae</td>
</tr>
<tr>
<td>Aspiration respiratory viruses(^b)</td>
<td>Aspiration respiratory viruses(^b)</td>
<td></td>
</tr>
</tbody>
</table>


\(^b\)Excluding Pneumocystis spp.

\(^c\)Influenza A and B, adenovirus, respiratory syncytial virus, parainfluenza.

ICU = intensive care unit.

potentially impact effective treatment (such as an unstable home environment or psychiatric disorders that may hinder adherence to therapy).\(^b\) Mortality prediction tools can also help guide clinicians in making the decision to hospitalize the patient.

The PORT Prediction Rule, developed over 10 years ago, offers important insights into the risk of mortality (Figure 1).\(^c\) This technique uses a combination of demographic variables, co-morbidities, physical observations, and laboratory and radiographic variables to assign patients to 1 of 5 classes. Those belonging to PSI Class 1 or 2 have a low risk of mortality (<1%) and can be treated as outpatients. Those in PSI Class 3 have a slightly higher risk of mortality (<5%) and may require a brief observational stay in a hospital. Those in PSI Class 4 or 5 have the highest mortality risk (8%-30%) and will require hospitalization—those in PSI Class 5 should be admitted to an ICU. Though the PORT Prediction Rule is effective in determining mortality risk, it is not the most practical approach in the clinical setting as it is based on laboratory findings that can be costly and time consuming.

The CURB-65 Rule uses 5 aspects in making a clinical determination—confusion, urea concentration, respiratory rate, blood pressure, and age (Figure 2).\(^d\) Those meeting 2 or more of the criteria should be considered for hospitalization. However, this method requires a blood sample and laboratory analysis for urea concentration. In response to this, the CRB-65 was designed. It omitted the blood urea measurement and was practical for office-based settings.\(^e\) In CRB-65, a score of 0 equates to home treatment, a score of 1 to hospital-supervised treatment, and a score of 2 or more to hospitalization.

A study comparing the mortality rates using PSI, CURB-65, and CRB-65 showed a strong correlation among the 3 methods.\(^f\)

### Admission to the ICU

Recommendation regarding admission to the ICU is provided by the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines about management of CAP. According to the IDSA/ATS guidelines, direct admission to the ICU is essential for patients with septic shock requiring vasopressor or for patients with acute respiratory failure requiring intubation and mechanical ventila-

### Bacterial Etiology of CAP

Bacterial etiology varies slightly according to the severity of CAP (Table 1).\(^b\) Streptococcus pneumoniae remains the most common cause of CAP across all severities. Mycoplasma pneumoniae, Haemophilus influenzae, and Chlamydia pneumoniae are associated with mild-to-moderate CAP and Staphylococcus aureus, Legionella species, and gram-negative pathogens, including Klebsiella pneumoniae and Pseudomonas aeruginosa, are more likely to be associated with severe CAP. Recently, community-associated methicillin-resistant Staphylococcus aureus (MRSA) has also been observed as a cause of severe CAP. The probable causative pathogens influence the diagnostic measures and empiric treatment strategies, including the use of combination therapy and gram-negative coverage.

### Bacterial Resistance

Among community-acquired respiratory tract pathogens, S. pneumoniae remains the primary focus given its predominance as the causative pathogen, including severe infections\(^g\) and antimicrobial resistance to several commonly used agents.\(^h\) Multiple antimicrobial surveillance programs have been instituted in the United States to track the susceptibility trends of S. pneumoniae.

#### Penicillin Resistance

Increasing penicillin resistance of S. pneumoniae has been reported since the early 1990s with a peak at about 40% (high-level plus intermediate-level resistance) in 2000 (Figure 3).\(^i\) Since 2000, resistance to penicillin has remained stable, though at an elevated level. A surveillance study in 2005-2006 involving 1,543 isolates showed high-level penicillin resistance at 16% and intermediate resistance at 21%.\(^j\)

The clinical relevance of penicillin-resistant S. pneumoniae (PRSP) is controversial. Available data suggest that clinically relevant levels of penicillin resistance most likely occur at a minimal inhibitory concentration (MIC) of ≥4 μg per mL. This is reflected in the new 2008 Clinical and Laboratory Standards Institute breakpoints (formerly NCCLS) for parenteral penicillin G—susceptible (≤2 μg per mL), intermediate (4 μg per mL), and resistant (≥8 μg per mL)—for nonmeningeval infections such as CAP.\(^k\) These changes will reduce the reported rate of resistance and hopefully assist clinicians in predicting which patients are at a greater risk for clinical failure due to a resistant strain.

#### Macrolide Resistance

Macrolide resistance of S. pneumoniae has increased steadily since the 1990s, approaching 30% by the early 2000s (Figure 3).\(^l\) The level of macrolide resistance has remained steady over the past few years, though a recent surveillance study from 2005-2006 estimated 34% macrolide resistance in the United States.\(^m\)

#### Fluoroquinolone Resistance

Fluoroquinolone resistance of S. pneumoniae is rare—surveillance studies demonstrate resistance rates of 1% or less.\(^n\) A recent study showed nonsusceptibility to levofloxacin to be less than 1% in 2005-2006 (0.6% resistance.
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**FIGURE 1** Pneumonia PORT Prediction Rule for Mortality Risk Assessment

1. **Step 1**
   - Is the patient >50 years of age?
     - Yes
     - No

2. **Step 2**
   - Does the patient have any of the following coexisting conditions?
     - Neoplastic disease
     - Congestive heart failure
     - Cerebrovascular disease
     - Renal disease
     - Liver disease
     - Age ≥65 years
     - Nursing home resident: +10
   - Does the patient have any of the following abnormalities?
     - Altered mental status
     - Pulse ≥125/min
     - Respiratory rate ≥30/min
     - Systolic blood pressure <90 mmHg
     - Temperature <35 °C or ≥40 °C

   **Assign points for:**
   - Demographic variables
   - Comorbid conditions
   - Physical observations
   - Laboratory and radiographic findings

   **Treatment Options**
   - Class I: Likely suitable for home treatment
   - Class II: Management in hospital as severe pneumonia
   - Class III: Consider hospital-supervised treatment
     - Options may include:
       - Short-stay inpatient
       - Hospital-supervised outpatient
   - Class IV: Consider ICU admission especially if CURB-65 score = 4 or 5
   - Class V: Manage in hospital as severe pneumonia

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**FIGURE 2** Applying the CURB-65 Rule

- Any of:
  - Confusion
  - Urea >7 mmol/l
  - Respiratory rate ≥30/min
  - Blood pressure (SBP <90 mmHg or DBP ≤60 mmHg)
  - Age ≥65 years

  **CURB-65 Score**
  - 0 or 1: Group 1: Mortality Low (1.5%)
  - 2: Group 2: Mortality Intermediate (9.2%)
  - 3 or more: Group 3: Mortality High (22%)

  **Treatment Options**
  - Likely suitable for home treatment
  - Consider hospital-supervised treatment
    - Options may include:
      - Short-stay inpatient
      - Hospital-supervised outpatient
  - Manage in hospital as severe pneumonia

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*Defined as a Mental Test Score of 8 or less, or new disorientation in person, place, or time.

Note: 1 point is assigned to each of the components if present.

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and 0.2% intermediate resistance). Despite the continued low level of resistance to fluoroquinolones, it is important to use them judiciously to preserve their utility.

Antimicrobial Resistance by Geographic Region. Antimicrobial resistance can vary considerably by geographic region. The Prospective Resistant Organism Tracking for the Ketolide Telithromycin (PROTEKT) study showed that the highest levels of penicillin and macrolide resistance were in the southeastern and south-central regions of the United States (high-level penicillin resistance of 33%-36% and macrolide resistance of 39%-40%), and the lowest were in the northwestern region (high-level penicillin resistance of 17% and macrolide resistance of 23%). Therefore, the knowledge of local resistance profiles is critical to guide appropriate selection of an antimicrobial agent.

Clinical Impact of Resistance. The clinical relevance of β-lactam resistant pneumococcal pneumonia appears most relevant to specific MICs for specific antimicrobials. Many studies are hampered by small sample sizes, biases inherent in observational design, and the relative infrequency of clinical isolates showing high-level resistance. One study evaluated time to symptom resolution in 17 pneumococcal pneumonia patients (5 of whom were infected with a penicillin-resistant strain) who were treated with procaine penicillin. Those with a resistant infection experienced a longer time before resolution of fever (3.6 vs. 1.9 days), cough and sputum production (6.0 vs. 2.7 days), and pleuritic pain (3.6 vs. 2.1 days), compared to patients with susceptible infections. In a study from the Centers for Disease Control and Prevention of bacteremic pneumococcal pneumonia, investigators found that after hospital day 4, the risk of death was 7 times greater in patients infected with high-level PRSP (MIC ≥ 4.0 µg per mL; 19/1,151 patients) than in patients infected with intermediate isolates (MIC = 0.012–1.0 µg per mL; 81/1,151 patients). However, treatment and severity of disease were not recorded. Subsequently, a follow-up, case-control study of patients with bacteremic pneumococcal pneumonia was conducted, which addressed the limitations of the trial by Feikin et al. (2000) and controlled for risk factors, severity, and treatment. The findings from this multivariate analysis showed no contribution of antimicrobial resistance to mortality or requirement for ICU admission, but determined that more important predictors of outcome included severity of illness and whether there was a “do not resuscitate” order on the patient’s chart. Findings from a more recent large observational study suggest that current levels of β-lactam resistance generally do not cause treatment failures when appropriate agents (i.e., amoxicillin, ceftriaxone, cefotaxime) and doses are used. However, discordant therapy with cefuroxime in patients with pneumococcal bacteremia has been associated with an excessively high failure rate com-

**FIGURE 3** Penicillin-Resistant and Macrolide-Resistant *S. pneumoniae* In Vitro

- Penicillin-resistant Intermediate (MIC 0.12–1 µg per mL)
- Penicillin-resistant (MIC ≥ 2 µg per mL)
- Macrolide-resistant (erythromycin-resistant; MIC ≥ 1 µg per mL)

Sources: Karchmer AW;13 Doern GV, Brown SD;14 The Alexander Network;15 Karlowsky JA, et al.17

Penicillin-resistant intermediate = MIC 0.12–1 µg per mL; penicillin-resistant = MIC ≥ 2 µg per mL; macrolide-resistant = erythromycin-resistant = MIC ≥ 1 µg per mL.
pared with other discordant therapies.

The clinical impact of macrolide resistance is well established. Antimicrobial resistance is associated with an increased risk of breakthrough bacteremia in patients with CAP. In a prospective, population-based study by Daneman et al. (2006), pneumococcal bacteremia cases were identified among patients who received macrolide treatment.24 These treatment failures were then documented based on the isolate MIC. Clinical failure was observed in 1.5% (21 of 1,397) of episodes where isolates were susceptible to erythromycin (MIC ≤ 0.5 μg per mL) but it was 16% (37 of 230) for infections caused by resistant strains (MIC ≥ 1 μg per mL). Other studies are associated with similar results suggesting that macrolide resistance can be an important cause of clinical failure.25-27

Several case reports of treatment failures due to fluoroquinolone-resistant pneumococcal infections in adults with CAP have also been reported.28,29 Many of the patients described in these reports had been previously treated with fluoroquinolones.

**Risk Factors for an Antimicrobial-Resistant Infection.** Given the clinical significance of antimicrobial resistance, it is important to identify factors that may increase the risk of an infection by a resistant organism. These include age (either >65 years or <5 years), noninvasive disease, alcoholism, exposure to a child who attends day care, or multiple co-morbidities.30-32 Prior exposure to an antimicrobial is also a major cause of antimicrobial resistance.30,31 One study showed that exposure to a β-lactam in the previous 3 months significantly increased the risk of penicillin resistance in a subsequent infection.30 Prior macrolide use has also been shown to increase the risk of a macrolide-resistant infection, though the risk is significantly greater with prior azithromycin use than with prior clarithromycin or erythromycin use.31 Prior fluoroquinolone use also increases the risk of a fluoroquinolone-resistant infection.31

The strong association of prior antimicrobial use with subsequent antimicrobial resistance should be an important consideration when selecting empiric therapy for patients with CAP. Antimicrobial usage during the previous 3 months should be noted for each patient, and if possible, a different antimicrobial class should be used.

**Selecting the Appropriate Antimicrobial Regimen**

**Goal of Therapy.** Inappropriate treatment can lead to failed bacterial eradication, the selection of resistant bacteria, complications due to the spread of these organisms, and a resulting infection that is more challenging to treat. The goal of appropriate antimicrobial treatment, therefore, is to maximally reduce or eradicate the bacterial load in order to achieve clinical success and minimize the potential for development of resistance.

To minimize the risk of resistance development, current IDSA/ATS guidelines suggest reducing the duration of therapy to a minimum of 5 days, though a longer duration may be required if the initial therapy was not active against the infection or if an extrapolmonary infection exists.9

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*aSource: Mandell LA, et al.9
bIf community-associated methicillin-resistant Staphylococcus aureus (MRSA) is a concern, add vancomycin or linezolid.

CAP = community-acquired pneumonia; IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society.
The Science of Selecting Antimicrobials for Community-Acquired Pneumonia (CAP)

### IDSA/ATS Guidelines for Empiric Treatment of CAP

The IDSA/ATS guidelines for the empiric treatment of patients with CAP take into account the site of care and the potential pathogens (Figure 4). For hospitalized patients in the general medical ward, monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin, or gemifloxin) or combination therapy with a β-lactam and macrolide is generally recommended.

For severe cases requiring ICU admission, antimicrobial selection will depend on the presence of risk factors for *Pseudomonas* infection. *P. aeruginosa*, a typical hospital-acquired pathogen, is sometimes associated with CAP. The risk factors for infection by *P. aeruginosa* include a Gram stain consistent with a gram-negative infection, the presence of structural lung disease (bronchiectasis), repeated exacerbations of severe chronic obstructive pulmonary disease, corticosteroid therapy, recent broad-spectrum antimicrobial use, and malnutrition.

For patients with no risk of a *Pseudomonas* infection, combination therapy with a β-lactam and either a macrolide or a respiratory fluoroquinolone is recommended. For patients allergic to β-lactams, a respiratory fluoroquinolone and aztreonam are recommended. If methicillin-resistant *S. aureus* (MRSA) is suspected (such as the case if prior influenza-like illness, necrotizing severe pneumonia, or if a sputum Gram stain shows Gram-positive cocci in clusters), vancomycin or linezolid should be added to the regimen.

Patients at risk of a *Pseudomonas* infection should be given combination therapy that includes an antipseudomonal β-lactam (e.g., piperacillin/tazobactam, ceftazidime, imipenem, meropenem) plus an antipseudomonal fluoroquinolone, or the above β-lactam plus an aminoglycoside and azithromycin or the above β-lactam plus an aminoglycoside and an antipseudomonal fluoroquinolone (for patients allergic to penicillin substitute aztreonam for the β-lactam).

### Optimizing Pharmacokinetic and Pharmacodynamic Parameters

In addition to choosing an appropriate antimicrobial agent, it is important to use a regimen that optimizes a drug’s pharmacokinetic-pharmacodynamic parameters to ensure bacterial eradication. For concentration-dependent agents, such as the fluoroquinolones, clinical outcomes and prevention of resistance development correlate with the peak concentration to MIC ratio and the area under the concentration–time curve (AUC) to MIC ratio. Therefore, increased dosing of these agents by increasing the Cmax and AUC would maximize their ability to eradicate bacteria.

Optimizing pharmacokinetic-pharmacodynamic parameters is the rationale for the development of the 750 mg, 5-day levofloxacin regimen in contrast to the traditional 500 mg, 10-day course. Increasing the levofloxacin dose from 500 mg to 750 mg nearly doubles the AUC and increases the AUC/MIC ratio, thus increasing the probability of achieving pharmacokinetic-pharmacodynamic targets. A randomized, double-blind, clinical trial showed no significant differences between the 2 regimens even when stratified by disease severity. Moreover, the short-course regimen is associated with less total drug usage, which can potentially reduce the risk of emergence of resistance.

Of the respiratory fluoroquinolones, gemifloxacin and moxifloxacin have higher AUC/MIC ratios for *S. pneumoniae* than either levofloxacin regimens (Table 2). Does this difference translate into improved clinical outcomes?

A prospective, randomized, double-blind trial compared moxifloxacin (400 mg daily) and levofloxacin (500 mg daily) for 7-14 days for the treatment of hospitalized, elderly patients (≥65 years) with CAP. At the test-of-cure visit, there was no significant difference in the clinical cure rate between the moxifloxacin group (92.9%) and the levofloxacin group (87.9%, P=0.2), even when patients were stratified by disease severity or age. However, at the on-treatment visit (3 to 5 days after the start of therapy), a significantly greater percentage of patients receiving moxifloxacin had achieved clinical recovery than those receiving levofloxacin (97.9% vs. 90.0%, P=0.01). This study suggests that using a more potent agent may allow for more rapid resolution of CAP symptoms. It is important to note that this trial used a levofloxacin dose of 500 mg and not the 750 mg dose currently recommended by IDSA/ATS Guidelines.

### Summary

When managing patients with CAP, it is important to choose the most appropriate site of care as it impacts the extent of diagnostic testing, the empiric selection of antimicrobials, as well as the overall health care costs. Hospital and ICU admission should be reserved for the more severely ill patients who are at a greater risk of death. For all disease severities, *S. pneumoniae* is the most common cause. Resistance of this pathogen is prevalent and growing and local resistance profiles should be consulted before selecting empiric therapy. Rapid initiation of appropriate antimicrobial therapy is critical in achieving successful clinical outcomes. Newer dosing regimens are attempting to optimize the pharmacokinetic-pharmacodynamic parameters of agents to ensure successful and more rapid eradication of the bacterial pathogen.

### DISCLOSURES

Thomas M. File, Jr., has received research funding from Cerexa, Ortho-McNeil, Pfizer, Procter, Rib-X, and Wyeth. He serves as a consultant to Advanced Life Sciences, Bayer, Cerexa, Cubist, GlaxoSmithKline, Ortho-McNeil, Merck, Nabriva, Oscien, Procter, sanofi-aventis, Schering-Plough, and Wyeth. He is also a member of the speakers’ bureaus for Astellas, Theravance, Merck, Ortho-McNeil, Oscien, Pfizer, Schering-Plough, and Wyeth.

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### Table 2: Pharmacodynamic Profile: Fluoroquinolones Versus *S. pneumoniae*

<table>
<thead>
<tr>
<th>Agent</th>
<th>MIC90 (mg/L)</th>
<th>24-h Serum AUC (mg/h/L)</th>
<th>Fraction Unbound</th>
<th>24-h Free AUC (mg/h/L)</th>
<th>Free AUC/MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>400 mg q24h</td>
<td>0.25</td>
<td>48</td>
<td>0.6</td>
<td>28.8</td>
</tr>
<tr>
<td>Gemifloxin</td>
<td>320 mg q24h</td>
<td>0.03</td>
<td>9.93</td>
<td>0.35</td>
<td>3.48</td>
</tr>
<tr>
<td>Levofloxin</td>
<td>750 mg q24h</td>
<td>1</td>
<td>90.7</td>
<td>0.7</td>
<td>63.5</td>
</tr>
<tr>
<td>Levofloxin</td>
<td>500 mg q24h</td>
<td>1</td>
<td>48</td>
<td>0.7</td>
<td>33.6</td>
</tr>
</tbody>
</table>

*In vitro activity does not necessarily imply clinical effectiveness. AUC = area under the concentration-time curve; MIC = minimum inhibitory concentration.
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.

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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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C ommunity-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.\(^1\) 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.\(^5\) Studies that evaluated other serious infections in the hospital attribute less than 10% of overall health care costs to antimicrobials.\(^6\)

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.\(^2\)\(^3\) 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
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. 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 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. 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. 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. 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. 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 1: Direct Costs Associated With Antimicrobial Resistance Among Inpatients

<table>
<thead>
<tr>
<th>Hospital Costs (general)</th>
<th>Costs Associated with Patient Isolation</th>
<th>Antimicrobial-Associated Costs</th>
<th>Other Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per day per bed (1) by specialty (2) by ICU vs. general vs. others</td>
<td>• Supplies</td>
<td>• Nursing staff time (specialized nurses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Housekeeping</td>
<td>• Infections and complications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Waste disposal</td>
<td>• Other procedures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased portable testing services</td>
<td>• Laboratory procedures (1) screening procedures (active surveillance) (2) diagnostic testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased staffing</td>
<td>• Physician staff time</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Costs Associated With Treatment of Community-Acquired Pneumonia by Level of Macrolide Resistance in the Community

<table>
<thead>
<tr>
<th>Treatment Cost</th>
<th>n</th>
<th>Macrolide Resistance Level &lt;25%</th>
<th>n</th>
<th>Macrolide Resistance Level ≥25%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Success</td>
<td>4,377</td>
<td>$1,334</td>
<td>3,334</td>
<td>$2,193</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>926</td>
<td>$2,841</td>
<td>809</td>
<td>$3,918</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Macrolides</td>
<td>4,189</td>
<td>$950</td>
<td>909</td>
<td>$2,130</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Quinolones</td>
<td>3,522</td>
<td>$6,040</td>
<td>826</td>
<td>$4,679</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Source: Howard D, et al.*

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`s14`
Therapeutic Goal: Maximize Activity

Type of Drug Classes: Aminoglycosides

be achieved (Table 3).21,22

dictate pharmacokinetic/pharmacodynamic targets that should
time-dependent bacterial killing. The characteristics of the drug
concentration-dependent bacterial killing and those that exhibit
cacy and prevent the emergence of resistance. Antimicrobial
targets that incr ease the probability of achieving clinical effi -

Optimizing Antimicrobial Dosing

reducing overall treatment costs.

Strategies to increase the 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-dependen-
t 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).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 Cmax/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
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. 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. 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). 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 2004.39

- 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 patients were switched 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.
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. 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.

**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. 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. 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. 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. 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.

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. 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

**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 Venco 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**


Antimicrobial Stewardship Programs: How to Start and Steer a Successful Program

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ABSTRACT
BACKGROUND: Antimicrobial stewardship programs (ASPs) promote the appropriate use of antimicrobials by selecting the appropriate dose, duration, and route of administration. The appropriate use of antimicrobials has the potential to improve efficacy, reduce treatment-related costs, minimize drug-related adverse events, and limit the potential for emergence of antimicrobial resistance.

OBJECTIVE: To summarize ASP tactics that can improve the appropriate use of antimicrobials in the hospital setting. Several measures can be used to implement such programs and gain multidisciplinary support while addressing common barriers.

SUMMARY: Implementation of an ASP requires a multidisciplinary approach addressing common barriers. With an infectious diseases physician and a clinical pharmacist with infectious diseases training as its core team members. As identified by recently published guidelines, 2 proactive strategies for promoting antimicrobial stewardship include: (1) formulary restriction and pre-authorization, and (2) prospective audit with intervention and feedback. Other supplemental strategies involve education, guidelines and clinical pathways, antimicrobial order forms, de-escalation of therapy, intravenous-to-oral (IV-to-PO) switch therapy, and dose optimization. Several barriers exist to successful implementation of ASPs. These include obtaining adequate administrative support and compensation for team members. Gaining physician acceptance can also be challenging if there is a perceived loss of autonomy in clinical decision making.

CONCLUSION: ASPs have the potential to reduce antimicrobial resistance, health care costs, and drug-related adverse events while improving clinical outcomes. The efforts and expense required to implement and maintain ASPs are more than justified given their potential benefits to both the hospital and the patient.

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T he timely selection and administration of appropriate antimicrobial therapy can significantly impact treatment outcomes, especially in patients with severe or life-threatening infections.1,2 In an effort to optimize antimicrobial therapy while reducing treatment-related costs, minimizing adverse events, and decreasing the risk of development of antimicrobial resistance, many institutions are implementing antimicrobial stewardship programs (ASPs).

Justification for ASPs

Though it is difficult to establish causal relationships (because multiple factors contribute to the development and persistence of antimicrobial resistance), ASPs have the potential to limit the emergence and spread of resistant pathogens. A number of observations have suggested an association between antimicrobial use and the emergence of resistance. First, in vivo selection of resistance during antimicrobial therapy can cause de novo resistance, which can quickly spread to other patients in the setting of poor infection control measures (i.e., improper hand hygiene techniques or environmental contamination). Second, patients harboring a resistant organism (when transferred to a particular unit) may introduce the resistant strain. Third, resistance genes can also be transferred between organisms to create new resistant organisms. Fourth, ASPs attempt to reduce antimicrobial pressures that have been shown to promote resistance development.3,4 For example, several studies have reported parallel changes in antimicrobial use and the prevalence of resistance.5-9 Prior antimicrobial use is common in patients with healthcare-associated infections caused by resistant strains.10 Areas within hospitals with higher rates of antimicrobial resistance also tend to have higher rates of antimicrobial use.9 Increasing the duration of antimicrobials also increases the risk for colonization with resistant organisms.

Antimicrobial stewardship aims to promote the appropriate use of antimicrobials—the right selection, duration, dose, and route of administration. Promoting the appropriate use of antimicrobials is intended to improve clinical outcomes by reducing the emergence of resistance, limiting drug-related adverse events, and minimizing the risk of unintentional consequences associated with antimicrobial use (such as an increased risk of Clostridium difficile infection).3,11,12

ASPs also have the potential to reduce antimicrobial costs by limiting the overuse and inappropriate use of these agents and by promoting active intravenous-to-oral (IV-to-PO) switch therapy. By reducing the unnecessary use of antimicrobials, a well-designed ASP has the additional advantages of reducing (a) the risk of drug-related adverse events and their associated costs, and (b) the emergence of resistance and, hence, minimizing infections caused by resistant pathogens. Infections caused by resistant organisms are associated with poorer clinical outcomes, prolonged hospital length of stay (LOS), and higher overall costs compared to infections caused by susceptible organisms.13-15 Therefore, by promoting the appropriate use of antimicrobials, ASPs can have a broad impact on improving clinical outcomes while reducing overall health care costs.
Stewardship Tactics
The Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines identify 2 core proactive evidence-based strategies for promoting antimicrobial stewardship: (1) formulary restriction and pre-authorization, and (2) prospective audit with intervention and feedback.

Formulary Restriction and Pre-Authorization. The strategy of formulary restriction and pre-authorization involves limiting the use of specified antimicrobials to certain approved indications. An antimicrobial committee creates guidelines pertaining to the approved use of agents. If necessary, designated personnel are made available for the approval process. The strategy leads to direct control over antimicrobial use at an institution and educational opportunities for prescribers when a request is made. The major disadvantage of this strategy is that prescribers can have a perceived loss of autonomy when making clinical decisions. Personnel also need to be available for consultation at all times. As with many ASP tactics, there is an initial cost to implement and monitor the effectiveness of such programs.

Formulary restrictions have been proven to impact antimicrobial use. One intervention at the University of Kentucky Chandler Medical Center in 1999 involved multiple aspects: (a) the removal of ceftazidime and cefotaxime from the formulary, (b) the restriction of ceftriaxone and carbapenem use to only approved indications, (c) the addition of cefepime to the formulary, (d) the replacement of ciprofloxacin with levofloxacin on the formulary, and (e) a 72-hour stop order on all vancomycin requests. Follow-up analysis evaluated antimicrobial use and resistance rates in selected organisms. In 2000, antimicrobial expenditures decreased by over $200,000 (despite an increase in inpatient days) and further declined by $600,000 as of 2002 (when compared to 1998 expenditures). Not surprisingly, ceftazidime, cefotaxime, and ceftriaxone use decreased by nearly 80% by 2002. Another benefit of the ASP has been a decrease in resistance rates of several important pathogens, including multidrug-resistant P. aeruginosa and methicillin-resistant Staphylococcus aureus (MRSA; Figures 1a and 1b). The benefits from implementing this program have shown to be persistent.

Prospective Audit With Intervention and Feedback. A strategy of prospective audit with intervention and feedback involves a daily review of targeted agents for appropriateness. Follow-up intervention, if necessary, involves contacting the prescriber to recommend alternative agents. This tactic requires an antimicrobial committee to develop guidelines for appropriate use of targeted agents, and personnel (usually clinical pharmacists) are needed to perform the reviews and follow-up communication on a daily basis. The advantage of this strategy is that prescribers do not experience any perceived loss of autonomy, particularly if suggested changes by the reviewers are voluntary. This tactic also allows opportunity for educating prescribers through follow-up.

When utilized in a medium-sized community teaching hospital in Boston, this strategy resulted in significant reductions in inappropriate use of broad-spectrum intravenous agents, particularly third-generation cephalosporins. An antimicrobial management team (consisting of an infectious diseases physician and an infectious diseases-trained pharmacist) reviewed antimicrobial orders for all patients receiving parenteral third-generation cephalosporins, aztreonam, parenteral fluoroquinolones, or imipenem. The recommendations of the antimicrobial management team were communicated to the prescribers via nonpermanent chart notes. Following the implementation of the program, parenteral antimicrobial use decreased steadily from
terns. However, it is important to note that antimicrobial selection is only one component of these recommendations. Diagnosis and testing, admission criteria, nursing care, conversion to oral medication, and discharge planning can also impact quality of care and resource utilization. One study that incorporated a critical pathway at 20 hospitals for patients with CAP showed an 18% decrease in admissions for low-risk patients and significantly lower LOS and duration of IV therapy when compared to conventional therapy, resulting in significant cost savings.

Antimicrobial order forms can be an effective tactic to decrease antimicrobial consumption by implementing automatic stop orders and/or requiring physicians to justify antimicrobial use. However, prescribers may view the process of filling out these forms as inconvenient and time consuming. The transition to computerized data entry systems at institutions may improve the use and convenience of such strategies.

Streamlining or de-escalation can decrease antimicrobial exposure and save costs when empiric therapy involves a combination of agents to ensure broad-spectrum coverage. Once culture results identify the pathogen, a planned removal of antimicrobials that are not necessary or that provide redundant coverage is initiated to provide more targeted therapy. For example, if vancomycin is initially included in the treatment regimen but culture results show an absence of MRSA, vancomycin can then be removed. This approach can lead to substantial cost savings without affecting clinical outcomes.

Dose optimization, an important part of antimicrobial stewardship, takes into account factors such as the pharmacokinetics and pharmacodynamics of the agent, patient and pathogen.

1994 to 1998 while costs of parenteral antimicrobials decreased by nearly 30% (Figure 2), despite a 15% increase in the Medicare Case Mix Index and a 56% increase in ICU patient-days. The effect of this strategy on resistance and nosocomial infections was less clear. The rate of *Clostridium difficile* infection showed an initial decrease in 1993 and remained fairly steady after this (Figures 3a and 3b). Similarly, the number of infections caused by ceftazidime-resistant Enterobacteriaceae decreased following implementation of the program, followed by a steady rate until 1996 and then a decrease again in 1997 and 1998. However, vancomycin-resistant enterococci (VRE) were first isolated in 1995 and their number grew dramatically in 1996. MRSA rates did not seem to be affected by the program and grew steadily.

**Supplemental Strategies.** Other supplemental strategies can also play a pivotal role in ASPs. These include education, guidelines and clinical pathways, antimicrobial order forms, streamlining or de-escalation, dose optimization, and IV-to-PO switch.

**Education** is essential for any program that is designed to influence prescribing behaviors. Programs are needed to disperse information in an accurate and timely fashion. Since personnel can change over time, it is also important that the message be repeated routinely. Effective implementation of ASPs will incorporate education along with active strategies, such as prospective audit and intervention.

**Guidelines and clinical pathways** can improve antimicrobial utilization by multidisciplinary development of evidence-based guidelines that incorporate local microbiology and resistance patterns. However, it is important to note that antimicrobial selection is only one component of these recommendations. Diagnosis and testing, admission criteria, nursing care, conversion to oral medication, and discharge planning can also impact quality of care and resource utilization. One study that incorporated a critical pathway at 20 hospitals for patients with CAP showed an 18% decrease in admissions for low-risk patients and significantly lower LOS and duration of IV therapy when compared to conventional therapy, resulting in significant cost savings.

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**Dose optimization,** an important part of antimicrobial stewardship, takes into account factors such as the pharmacokinetics and pharmacodynamics of the agent, patient and pathogen.
Stewardship tactics can be used at the various stages of managing a patient with an infectious disease (Figure 4). During patient evaluation, clinician education as well as management guidelines can aid in the proper diagnosis and the further actions needed (admission, laboratory testing, etc). Selecting the initial antimicrobial can also be impacted by education and the implementation of guidelines, as well as any formulary restriction and pre-authorization policies. Computer-assisted strategies can be useful during the stage of antimicrobial selection, while a review and feedback strategy can help provide additional educational opportunities to the prescriber and offer a chance to adjust therapy and amend prescribing practices.

Impact of ASPs

Though more data are needed to demonstrate the benefits of the programs, ASPs have the potential to reduce resistance, health care costs, and drug-related adverse events while improving clinical outcomes. The impact of ASPs on bacterial resistance can be difficult to assess due to the multiple factors that can influence resistance development and spread. Optimized antimicrobial use is thought to help reduce the emergence of resistance, though few prospective randomized trials have attempted to analyze this.32 Other studies that have attempted to assess various strategies to minimize resistance development usually have multiple confounding variables that can make it difficult to attribute any impact to one tactic. However, as discussed earlier, given an apparent association between antimicrobial use and the emergence of resistance, ASPs that reduce the inappropriate use of antimicrobials will decrease the selection pressure for the emergence of resistance.

The routine use of combination therapy is not recommended given a lack of data supporting its impact on preventing resistance development or improving outcomes.39 However, empiric combination therapy can be important when treating severely ill patients to ensure early adequate coverage of potential pathogens.30 Once culture results are available, de-escalation of therapy is recommended to provide targeted therapy and reduce antimicrobial exposure.39,30

Stewardship Tactics at Various Stages of Patient Management

Stewardship tactics can be used at the various stages of managing a patient with an infectious disease (Figure 4). During patient evaluation, clinician education as well as management guidelines can aid in the proper diagnosis and the further actions needed (admission, laboratory testing, etc). Selecting the initial antimicrobial can also be impacted by education and the implementation of guidelines, as well as any formulary restriction and pre-authorization policies. Computer-assisted strategies can be useful during the stage of antimicrobial selection, while a review and feedback strategy can help provide additional educational opportunities to the prescriber and offer a chance to adjust therapy and amend prescribing practices.

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The IDSA/SHEA guidelines report that comprehensive programs can lead to a reduction in antimicrobial use by 22%-36%, resulting in significant cost savings. The study by Martin et al.,
presented earlier, demonstrated how a policy of formulary restriction and pre-authorization can result in substantial pharmacy cost savings. These programs can provide substantial economic benefits irrespective of the size of the institution.

The impact of ASPs on clinical outcomes and adverse events can also be difficult to measure given the multifactorial nature of these issues. In one example of prospective audit and feedback, the rate of *C. difficile* infections decreased and remained stable after implementation of the program. ASPs that reduce overall antimicrobial usage by minimizing the inappropriate use of these agents will have the potential to decrease the risk of drug-related adverse events and unintended consequences.

**Implementing an ASP**

The rationale, design, and implementation of ASPs have been described extensively in the medical literature. Baseline information should be obtained pertaining to antimicrobial use, expenditure, and institutional bacterial susceptibilities derived from the hospital antibiogram. This can help identify recurrent problems with antimicrobial use at the institution, such as over-use of a particular class or failure to switch from IV-to-PO when appropriate. An antimicrobial management strategy should be formulated, and an antimicrobial stewardship team with well-defined responsibilities formed. A multidisciplinary approach should be considered when selecting the ASP team members. The IDSA/SHEA guidelines recommend that the 2 core members of the team should include an infectious diseases physician and a clinical pharmacist with infectious diseases training. Other critical members of the team can include a clinical microbiologist, a hospital epidemiologist, an infection control professional, and an information system specialist.

It is important to obtain support from the hospital administration as well as build relationships within the institution to help gain acceptance of the program once implemented. The hospital administration should give core team members the authority to enforce stewardship tactics. The ASP team members should also be fairly compensated for the additional time and effort needed to implement the ASP. One survey of infectious diseases consultants identified lack of compensation as a major barrier to implementing ASPs. Prior to implementation of a program, the ASP team should negotiate the expected outcomes with hospital administration, which should be measurable and attainable.

Physician acceptance is extremely important during the design and implementation of an ASP. Adherence to ASPs should be monitored on a regular basis in order to identify ways in which physicians may try to circumvent ASP policies. One study described the experience at the University of Pennsylvania, where requests for restricted antimicrobials from 8:00 a.m. to 10:00 p.m. must be approved by an infectious diseases-trained pharmacist or infectious diseases fellow. However, outside of these active ASP hours, restricted antimicrobials may be ordered without prior approval, though all orders still require approval by the ASP for continuation of treatment. The study evaluated whether prescribers were waiting until after the approval period ended (10:00 p.m.) for ordering restricted antimicrobials. Antimicrobial orders over a 3-month period were compared from one hour before (9:00-9:59 p.m.) and one hour after (10:00-10:59 p.m.) the ASP approval period. A greater proportion of antimicrobials ordered after the ASP approval period were for restricted antimicrobials (57% vs. 49.9%, *P* = 0.02). Furthermore, once the ASP evaluated new antimicrobial orders for continuation of therapy, a significantly higher percentage of orders made after the ASP approval period was discontinued. The difference was most profound for orders originating from the surgical unit. This study suggests that physicians were more likely to wait until after the ASP approval period ended to order restricted antimicrobials without prior approval. These orders were more often found to be in conflict with guidelines or were unnecessary and hence discontinued. Finally, prescribers should receive positive feedback on a regular basis, and audits should be conducted routinely to monitor the effectiveness of the program.

**Barriers to ASPs**

Despite the many benefits of ASPs in improving antimicrobial use and clinical outcomes while reducing costs, several barriers exist that may hinder their implementation. Foremost is finding the appropriate personnel who are willing to devote the extra time and effort towards developing and enforcing ASPs. This barrier is further exacerbated by the fact the few clinicians receive additional compensation for the added responsibility. A survey by the Emerging Infectious Diseases Network found that only 18% of respondents were compensated for added responsibility.

Hospital administration may be hesitant to fund such programs without a guarantee of future pharmacy savings.

Implementing tactics for an effective ASP will require funding to compensate those involved in the planning and monitoring of such programs. Further study is needed to understand the economic impact of ASPs as current reports are limited to single-center, longitudinal studies. However, these reports consistently show a decrease in antimicrobial use ranging from 22% to 36% and annual cost savings of $200,000 to $900,000 at both large academic medical centers and smaller community hospitals. These savings should be more than offset any additional cost in implementing an ASP.

Another barrier is that ASP team members may not want to antagonize colleagues in other specialties as this can damage relationships and the potential for future consultations. This barrier may be circumvented by using a prospective audit with feedback tactic that makes any recommendation voluntary rather than mandatory and allows for educational opportunities. Other barriers for acceptance of ASPs may include a loss of physician autonomy pertaining to clinical decision making, a shortage of infectious diseases-trained pharmacists, restriction policies that can be onerous to adopt, and the continued need to assess the success of a program in order to sustain efforts.

**Future Direction of Antimicrobial Stewardship**

The IDSA/SHEA guidelines provide institutions with information needed when considering implementing an ASP. With more and more institutions implementing ASPs, it is anticipated that a growing number of studies will become available to better assess their impact—particularly, how the appropriate use of antimicrobials may impact the emergence of bacterial resistance. With the growing use of computerized order-entry and decision-support systems, ASPs may also become easier to implement and enforce while still providing opportunities to discuss with clinicians the appropriate use of antimicrobials. The greatest challenge may be in finding qualified personnel willing and able to direct such programs at each institution.
DISCLOSURES

Richard H. Drew serves as a consultant to Merck, Theravance, Ortho-McNeil, and Schering-Plough. He receives research support from Schering-Plough, NeuTec, and Cubist and has received honoraria as a speaker from Schering-Plough, Ortho-McNeil, Enzon, sanofi-aventis, Wyeth-Ayerst, and Astellas Pharma. Drew is on the Development Team for CustomID.

Marco Ciocio, PhD, of Venoco 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


A n integral and critical component of the START educational program was discussion pertaining to regional and local issues related to community-acquired pneumonia (CAP) and antimicrobial stewardship. Below are some of the frequently asked questions during the START educational program.

**Question 1: Sending samples to an outside laboratory for pathogen identification results in a much lower rate of *S. pneumoniae* than what is expected based on published reports. Is this accurate? How useful are sputum samples in determining the causative pathogen in CAP patients?**

**Response:** *S. pneumoniae* is the most common causative pathogen associated with mild and severe cases of CAP. 

It is not a robust organism and does not survive for prolonged periods of time under inhospitable conditions. Sending culture samples to an outside microbiology laboratory, which may involve overnight shipment and extreme temperature variations, can result in complete or nearly complete die-off of the *S. pneumoniae* in that sample. This can lead to inaccurate results. For example, shipping a sample that may contain 10^6 cells of *S. pneumoniae* along with only a few cells of a more robust organism, such as *Staphylococcus aureus* or *Escherichia coli*, may lead to a culture result that only shows the more robust organism though this may be due to contamination of the sample. Therefore, an on-site laboratory should always be preferred in order to limit the delay in culture testing. Rapid methods of detecting organisms in sputum samples, such as polymerase chain reaction (PCR), can be used as a diagnostic tool or to confirm microbiological results.

**Question 2: How effective is the pneumococcal vaccine in preventing infection?**

**Response:** Currently, the 2 commonly used pneumococcal vaccines are the 7-valent vaccine administered to children and the 23-valent vaccine administered to adults. Both vaccines work well in preventing invasive infections, such as bacteremia and meningitis, caused by strains covered in the vaccine. Recent reports have also shown a benefit of the vaccine in reducing the incidence of noninvasive infections, such as pneumococcal pneumonia, in children and older adults.

As a consequence of the use of the pneumococcal vaccine, there has been an apparent shift in the predominant genotypes of *S. pneumoniae* strains, such as serotype 19A. The prevalence of strains that are covered in the vaccine and were previously major causes of infection has reportedly decreased, while strains not covered in the vaccine have become more common. As a result, the pneumococcal vaccine will need to be updated periodically to ensure that the predominant strains causing infection are covered.

**Question 3: As a result of the passage of the Pharmacist Immunization Bill in the New York State, how many community pharmacists will actually be involved in immunizing patients against influenza?**

**Response:** With the passage of the Pharmacist Immunization Bill, New York joins 48 other states that allow pharmacists to adminis-ter influenza and pneumococcal vaccines. This can help alleviate the strain on primary care facilities and hospitals particularly at the start of the flu season when the demand for these vaccinations is very high. States that allow pharmacists to administer vaccinations have seen an increase in influenza vaccination rates. One study compared influenza vaccination rates in states that allow pharmacists to administer vaccinations versus states that do not. Where pharmacists were allowed to administer vaccinations, the vaccination rate increased from 58% in 1995 to 68% in 1999, compared to an increase of 61% to 65% in states that do not allow pharmacists to administer vaccines. However, due to the legal implications of pharmacists administering injections, many community pharmacy chains may not allow their pharmacists to actually perform the vaccinations but may hire qualified nurses to perform this duty.

**Question 4: There has been a growing concern regarding methicillin-resistant *S. aureus* (MRSA) infections over the past few years. Is MRSA implicated in CAP or is it predominantly associated with skin and soft tissue infections?**

**Response:** Sixty percent of *S. aureus* isolates in the hospitals are methicillin-resistant, but this percentage can vary greatly depending on geographic location or the institution. Historically, MRSA has been confined to the hospital setting as a major cause of nosocomial infections, particularly skin and soft tissue infections and ventilator-associated pneumonia. However, we are now seeing more patients who acquire a MRSA infection in the community. Earlier, the isolates responsible for hospital-acquired MRSA infections and community-acquired MRSA infections could be differentiated based on their genetic elements, patient characteristics, and antimicrobial resistance profiles. However, this is no longer the case as hospitalized patients are being identified with MRSA strains that are typically associated with community-acquired infections, and vice versa. This has complicated diagnoses and hence appropriate therapy. Among CAP patients, MRSA is not a predominant cause of infection. However, as the prevalence of MRSA increases in the community, we may see an increase in the incidence of necrotizing pneumonia due to MRSA.

**Question 5: What are the risk factors for CAP due to MRSA?**

**Response:** Providing pathogen-directed therapy upfront is important, therefore, recognizing risk factors for potential pathogens is critical. The 3 major risk factors for CA-MRSA pneumonia are (a) positive Gram stain, (b) influenza-like symptoms, and (c) previous antimicrobial use. In cases of pneumonia caused by MRSA, vancomycin or linezolid are the currently recommended agents. Linezolid is preferred to vancomycin by some clinicians, particularly in areas where the minimum inhibitory concentration (MIC) of *S. aureus* strains is >1 μg per mL for vancomycin as infections due to these strains have been associated with a greater risk of failure when treated with vancomycin.

**Question 6: What are the contraindications for moxifloxacin and other fluoroquinolones?**

**Response:** The contraindications, listed on the package insert,
include hypersensitivity to moxifloxacin or any other fluoroquinolone. Also, recently, concern associated with QTc interval prolongation with fluoroquinolone use, particularly IV moxifloxacin, has come to the forefront. Patients with heart disorders, cardiac arrhythmias, or taking other medications that may prolong the QTc interval should be prescribed fluoroquinolones with caution. The package insert of all fluoroquinolones has also recently been changed to reflect the risk of tendinitis and tendon rupture with fluoroquinolone use, and clinicians should be made aware of this.

Question 7: As an antimicrobial stewardship tactic, how is antimicrobial pre-authorization implemented at a hospital?
Response: There are various approaches to implementing an antimicrobial pre-authorization program at a hospital. One approach involves the antimicrobial stewardship program (ASP) team deciding the agents that should be restricted and the approved uses for those agents. A qualified member of the ASP team must be available to respond when an order for a restricted antimicrobial is submitted to the pharmacy. When an order for a restricted drug is submitted to the pharmacy, the pharmacist on duty would contact the ASP personnel and provide details of the patient. The ASP personnel would then approve or disapprove the order. If the order is not approved, the prescribing physician would be contacted immediately for a discussion regarding the decision-making process and the reasons for inappropriateness of the agent requested and the alternative agents. All attempts should be made to come to a consensus regarding the antimicrobial to be used. In cases where an agreement cannot be reached, the infectious disease consult service should be approached and asked to determine the authorization of the requested antimicrobial. In cases where the ASP team is not available 24 hours a day, any drug should be released for the first 24-hour treatment, but the use of a restricted drug should be reviewed at the earliest opportunity and must be approved by the ASP team for continuation.

Question 8: In the current ATS/IDSA CAP guidelines, for patients in the ICU not at risk of infection due to Pseudomonas, it seems that double gram-negative coverage is recommended with a β-lactam plus a fluoroquinolone. Is this necessary?
Response: The ATS/IDSA guidelines do not promote double gram-negative coverage as a means to provide synergy or attack the pathogen via multiple routes. ICU patients are extremely ill and may not be able to survive if given antimicrobials with initial inadequate coverage within the first 24 hours. The combination therapy with double gram-negative coverage is to ensure adequate coverage early during the infection and before culture results are available. Once the pathogen has been identified and susceptibility results obtained, it may be possible to de-escalate therapy in order to limit overuse of antimicrobials and to reduce the risk of the emergence of resistance. However, it can be difficult to convince clinicians to change the course of therapy while a patient is doing well, though evidence shows that de-escalation does not impact clinical outcomes and decreases the risk of resistance development.

Question 9: What is the role of infection control in antimicrobial stewardship programs?
Response: The focus on responsible use of antimicrobials has traditionally been in order to preserve their utility and reduce the emergence of resistance. Today, the appropriate use of antimicrobials has also become necessary, since antimicrobial use is a major risk factor for Clostridium difficile infection (CDI)—a major problem in many hospitals and associated with severe morbidity and high mortality. In the province of Ontario, Canada, where C. difficile has become a serious threat, a new policy requires mandatory reporting of all CDI cases. As a result, hospitals will need to ensure that not only are antimicrobials used responsibly but also infection control, including environmental cleaning, is effective in reducing the spread of this pathogen.

An antimicrobial stewardship program that promotes the appropriate use of antimicrobials along with effective infection control can be critical in protecting patients from CDI and other nosocomial infections. When implementing an antimicrobial stewardship program at an institution, it is therefore helpful to include an infection control officer for important insight and support—a recommendation of the IDSA/SHEA antimicrobial stewardship guidelines.

Question 10: Is routine surveillance of hospital personnel recommended as a tactic to reduce the risk of spreading nosocomial pathogens?
Response: Surveillance of personnel may be useful only in isolated instances where there is a cluster of infections at a particular institution or medical ward caused by the same strain, such as MRSA. The medical literature has reports of serious infections inadvertently caused by health care personnel. One investigation of a MRSA outbreak in pediatric and neonatal intensive care units found a high carriage rate of MRSA among health care personnel. A policy of strict handwashing and monitoring, as well as periodic and routine active surveillance of cultures as part of infection control measures was suggested in this case. In the absence of sporadic clusters of infection in hospital wards, it may not be useful to perform routine testing of personnel.

Question 11: Should reducing adverse events be a more prominent goal of antimicrobial stewardship and what methods should be used for detecting or accounting for these events?
Response: Adverse events, beyond antimicrobial resistance, are an important aspect of therapy that should be better quantified. There is a lack of a good source that illustrates the prevalence of adverse events in addition to what is reported on product information sheets. Many of the adverse events associated with antimicrobials are due to dosing and allergic reactions—majority of these are preventable, and clinicians should work to minimize such risks. Computer-assisted programs instituted at hospitals may help reduce the incidence of adverse events related to antimicrobial use.

DISCLOSURES
Keith A. Rodvold serves as a consultant to Johnson & Johnson, Astellas, GlaxoSmithKline, Theravance, Targanta, and Intranasal Therapeutics. He is on the advisory committees of Johnson & Johnson, Targanta, Baxter, and Pfizer and is a member of the speakers’ bureaus for Johnson & Johnson, Wyeth, 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.
START (Stewardship Tactics for Antimicrobial Resistance Trends)

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Release Date: March 1, 2009
Expiration Date: March 1, 2010

Type of Activity: Knowledge-based

Instructions for Credit

To receive CE credit for this educational activity, the learner must:

Read the supplement in its entirety, and either:
(a) complete the Self-Assessment, Evaluation, and Credit Application for this activity (“START [Stewardship Tactics for Antimicrobial Resistance Trends]” online through the AMCP CE/CME Center at: http://www.amcp.org [CE/CME Center]; or
(b) mail the completed Self-Assessment, Evaluation, and Credit Application to Vemco MedEd, 245 US Highway 22, Suite 304, Bridgewater, NJ 08807, or fax it to: 908.235.4222. Documentation of credit will be mailed within 4 weeks of receipt of the completed Self-Assessment, Evaluation, and Credit Application.

There is no fee to participate in this educational activity. To receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the Self-Assessment.

Self-Assessment Questions: START (Stewardship Tactics for Antimicrobial Resistance Trends)

1. The overall mortality rate among patients with CAP who are admitted to the hospital is:
   a. 2%
   b. 6%
   c. 12%
   d. 20%

2. The mortality prediction tool that does not require laboratory analysis is:
   a. PORT
   b. Pneumonia Severity Index (PSI)
   c. CURB-65
   d. CRB-65

3. The most common cause of severe CAP is:
   a. Streptococcus pneumoniae
   b. Staphylococcus aureus
   c. Pseudomonas aeruginosa
   d. Legionella pneumophila

4. Surveillance data from 2005-2006 estimate the S. pneumoniae resistance rate to macrolides in the United States to be approximately:
   a. 15%
   b. 24%
   c. 34%
   d. 45%

5. According to the IDSA/ATS guidelines, empiric treatment for patients with CAP admitted to the general medical ward can include all of the following EXCEPT:
   a. Ciprofloxacin
   b. Moxifloxacin
   c. Ceftriaxone plus azithromycin
   d. Celegom plus clarithromycin

6. For patients with CAP who are hospitalized, antimicrobial therapy is what percentage of their overall health care cost?
   a. <5%
   b. 10%
   c. 15%
   d. 25%

To complete this activity online, go to www.amcp.org (CE/CME Center) to access the posttest and evaluation form.
7. Which of the following antimicrobial classes does NOT exhibit time-dependent bacterial killing?
   a. Carbapenems
   b. Aminoglycosides
   c. Penicillins
   d. Cephalosporins

8. When dosing an intravenous β-lactam, all of the following strategies will increase the T > MIC EXCEPT:
   a. Administration through continuous infusion
   b. Administration through prolonged infusion
   c. Reducing the dosing interval
   d. Increasing the dosing interval

9. According to a study by Davis et al., which IV-to-PO conversion strategy resulted in the greatest percentage of patients switched to oral therapy?
   a. Step-down therapy
   b. Sequential therapy
   c. Switch therapy
   d. Switch therapy with step-down

10. According to the IDSA/SHEA antimicrobial stewardship guidelines, core stewardship strategies include prospective audit with feedback and:
    a. Education
    b. IV-to-PO switch therapy
    c. Formulary restriction and pre-authorization
    d. Streamlining therapy

11. The supplemental antimicrobial stewardship tactic not recommended by the IDSA/SHEA antimicrobial stewardship guidelines is:
    a. De-escalation of therapy
    b. Antimicrobial cycling
    c. Clinical pathways
    d. Antimicrobial order forms

12. According to the IDSA/SHEA antimicrobial stewardship guidelines, the 2 core members of the antimicrobial stewardship team should be:
    a. Infectious diseases (ID) physician and hospital epidemiologist
    b. ID physician and clinical pharmacist with ID training
    c. Infection control director and microbiologist
    d. Clinical pharmacist and hospital epidemiologist
Self-Assessment and Evaluation

Your evaluation and suggestions will help improve the quality of future continuing education activities. Please answer the following general questions, provide written comments, and evaluate the individual authors. Additional space for your comments and suggestions is available in this form. Thank you for your cooperation.

ANSWERS TO SELF-ASSESSMENT QUESTIONS


<table>
<thead>
<tr>
<th>LEARNING OBJECTIVES</th>
<th>Yes</th>
<th>Somewhat</th>
<th>No</th>
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<tbody>
<tr>
<td>After reading this supplement, are you able to</td>
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<tr>
<td>1. State the national guidelines for the empiric treatment of CAP</td>
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<td>2. List the common pathogens observed in the treatment of CAP and gain knowledge of national and regional resistance trends</td>
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<td>3. Assess the importance of PK and PD as factors in appropriate selection of empiric antimicrobial therapy</td>
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<td>4. Weigh cost-containment strategies for appropriate antimicrobial therapies</td>
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<td>5. Discuss the goals of antimicrobial stewardship and roles of key team members in running a stewardship initiative</td>
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<tr>
<th>AUTHORS</th>
<th>Excellent</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<tr>
<td>Evaluate the knowledge and expertise of the authors in the subject.</td>
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<tr>
<td>Richard Drew, PharmD, MS, BCPS</td>
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<td>Thomas M. File, Jr., MD, MSc</td>
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<td>David P. Nicolau, PharmD</td>
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<td>Keith A. Rodvold, PharmD</td>
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<tr>
<th>OVERALL EVALUATION</th>
<th>Yes</th>
<th>Somewhat</th>
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<tr>
<td>1. This supplement met my expectations.</td>
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<td>2. The content was relevant to my practice.</td>
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<td>3. This supplement was fair and balanced.</td>
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<td>4. This supplement was without commercial bias.</td>
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If you answered “No” to 3 or 4, please explain.

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<th>PRACTICE APPLICATION</th>
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<tbody>
<tr>
<td>1. What aspects of this supplement were most relevant to your practice?</td>
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<td>2. Please list at least one strategy to minimize the risk of resistance development during the treatment of CAP that you learned from this supplement?</td>
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<td>3. Do you intend to make changes to your practice based on this supplement? If yes, please specify.</td>
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<td>4. What aspects of managing CAP do you need to learn more about to improve your practice performance?</td>
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