1. **A clinician’s guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria** • EDITORIAL
   Pages 1-6
   Thomas G. Slama, Alpesh Amin, Stephen A. Brunton, Thomas M. File, Jr, Gary Milkovich, Keith A. Rodvold, Daniel F. Sahm, Joseph Varon, David Weiland *et al.*

2. **Rational antibiotic treatment of outpatient genitourinary infections in a changing environment** • ARTICLE
   Pages 7-13
   Richard D. David, Peter M.C. DeBlieux and Robert Press

3. **Appropriate antibiotic treatment of genitourinary infections in hospitalized patients** • ARTICLE
   Pages 14-20
   Hans Liu and S. Grant Mulholland

4. **Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting** • ARTICLE
   Pages 21-28
   John Segreti, Hans R. House and Robert E. Siegel

5. **Antimicrobial treatment of lower respiratory tract infections in the hospital setting** • ARTICLE
   Pages 29-38
   Ronald F. Grossman, John C. Rotschafer and James S. Tan

6. **Appropriate outpatient treatment of acute bacterial exacerbations of chronic bronchitis** • ARTICLE
   Pages 39-44
   Fernando J. Martinez and Antonio Anzueto

7. **Treatment of rhinosinusitis in the outpatient setting** • ARTICLE
   Pages 45-50
   Michael D. Poole and Louis G. Portugal
A clinician’s guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria

Thomas G. Slama, MD,a Alpesh Amin, MD, MBA,b Stephen A. Brunton, MD,c Thomas M. File, Jr, MD,d Gary Milkovich, RPh,e Keith A. Rodvold, PharmD,f Daniel F. Sahm, PhD,g Joseph Varon, MD,h David Weiland, Jr, MD,i for the Council for Appropriate and Rational Antibiotic Therapy (CARAT)

In response to the overuse and misuse of antibiotics, leading to increasing bacterial resistance and decreasing development of new antibiotics, the Council for Appropriate and Rational Antibiotic Therapy (CARAT) has developed criteria to guide appropriate and accurate antibiotic selection. The criteria, which are aimed at optimizing antibiotic therapy, include evidence-based results, therapeutic benefits, safety, optimal drug for the optimal duration, and cost-effectiveness.

Antibiotics were hailed as “miracle drugs” after their initial introduction in the 1940s. Their widespread availability and success led to such dramatic reductions in the morbidity and mortality caused by infectious diseases that in 1967 US Surgeon General William H. Stewart reportedly declared that it was time to “close the book” on infectious diseases.1,2 However, the subsequent emergence of new infectious diseases and the development of increasing antibiotic resistance among existing bacterial diseases underscore the continued importance of treating infectious diseases.

Although increased bacterial resistance to antibiotics has several causes, 2 key factors are the overuse and misuse of antibiotics.3–6 Antibiotics are frequently prescribed for indications in which their use is not warranted, or an incorrect or suboptimal antibiotic is prescribed. Although the population- and visit-based prescribing rates for antimicrobials in ambulatory care settings declined 23% and 25%, respectively, between 1992 and 2000 in the United States, many prescriptions for antibiotics in ambulatory patients are...
written to treat acute respiratory tract infections (RTIs), including the common cold, acute bronchitis, and acute uncomplicated rhinosinusitis.\textsuperscript{7–9}

The overuse and misuse of antibiotics has contributed to an increase in bacterial resistance patterns, which may differ by locality.\textsuperscript{8} In addition, antibiotics are now included in many animal feeds, which are given to promote growth in animals not otherwise known to be bacterially infected. Many of these antibiotics are then ingested by humans through consuming animal products. Taken together, these factors enhance the risk of developing strains of bacteria that are resistant to most common classes of antibiotics. Furthermore, the development of new antibiotics has stalled\textsuperscript{10,11} as a result of (1) fewer novel compounds in the pipelines of pharmaceutical companies and (2) decisions that have been made by the same companies to develop drugs for chronic conditions such as arthritis, depression, pain syndromes, lipid disorders, hypertension, and other disorders rather than infectious diseases because of the higher potential for profit.\textsuperscript{12} This may, in turn, lead to a situation in which it will be more difficult to combat bacterial infections. Consequently, approaches that preserve the efficacy of currently used antibiotics are needed.

The US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) are actively addressing the primary issues associated with the overuse and/or misuse of antibiotics. Less attention has been paid, however, to the accurate use of antibiotics, defined as choosing the correct drug at the correct dose for the correct duration of treatment. The available evidence suggests that, when antibiotic use is warranted, choosing the therapy most likely to achieve clinical cure and treating for the shortest length of time to achieve clinical and microbiologic efficacy will result in lower incidence of retreatment, as well as a lower incidence of antibiotic resistance.\textsuperscript{3,4,8}

### The Council for Appropriate and Rational Antibiotic Therapy

The Council for Appropriate and Rational Antibiotic Therapy (CARAT) is an independent, multidisciplinary panel of healthcare professionals, clinicians as well as scientists, established to advocate the appropriate and accurate use of antibiotics. CARAT has developed 5 criteria to assist healthcare providers in selecting the most appropriate and accurate treatment regimens (Table 1). These criteria are designed to help guide healthcare practitioners in using antibiotics where they are appropriately indicated. This article addresses issues of appropriate antibiotic therapy and offers guidelines for the accurate use of antibiotics. It also presents the rationale for treating infectious diseases with shorter-course therapy using optimal agents when antibiotic therapy is warranted, thus helping to reduce the development of antibiotic resistance and improve outcomes.

### Appropriate antibiotic therapy

The first consideration in choosing appropriate antibiotic therapy should be whether there is an indication for an antimicrobial agent. Indications for an antibiotic include the unambiguous demonstration or the strong suspicion that the etiologic agent is bacterial. In general, the latter should be based on the signs and symptoms of infection, as well as on other factors, including the age of the patient, the patient’s medical history, and the presence or absence of comorbidities. There are several guidelines and appropriate use statements in the literature that vary in this process.\textsuperscript{8,9,13–19} Once it is decided that an antibiotic is warranted, accurate use of the agent should be explored, including examining issues of resistance, benefits, safety, and cost.

Many of the same factors that go into determining whether or not an etiologic agent is bacterial should also be considered when selecting an antibiotic. Several groups have issued specific guidelines on the use of antimicrobials for certain disease states. According to guidelines on the treatment of community-acquired pneumonia (CAP) issued by the American Thoracic Society (ATS), factors that should be taken into account when choosing an antimicrobial include severity of illness, presence of comorbidities, presence of identified clinical risk factors for drug-resistant and unusual pathogens, place of therapy (e.g., outpatient vs. in hospital), and presence of risk factors for drug-resistant Streptococcus pneumoniae, among others.\textsuperscript{13}

In the 2000 update of their practice guidelines for the management of CAP, the Infectious Diseases Society of America (IDSA) recommended that, when an etiologic diagnosis is established or strongly suspected, the antimicrobial agent that is most cost-effective, least toxic, and most narrow in spectrum should be used. When etiologic diagnosis is not available and empiric antibiotic selection is required, severity of illness, pathogen probabilities, resistance patterns, and comorbid conditions should be considered.\textsuperscript{14}

The Sinus Allergy and Health Partnership, a group sponsored by the American Academy of Otolaryngology and Head and Neck Surgery, among others, has issued guidelines on the antimicrobial treatment of acute bacterial rhinosinusitis that recommend considering severity, rate of progression, and recent antibiotic exposure when selecting antibiotic therapy.\textsuperscript{16}

### Evidence-based results

In choosing an antibiotic, clinicians should consider the clinical evidence demonstrating that the drug is clinically and microbiologically appropriate, the efficacy of that drug in well-designed clinical trials, and the antibiotic resistance patterns of the local region. Clinicians should then use their professional judgment to choose the optimal antibiotic. Well-conducted, randomized, controlled clinical trials provide the highest quality information for making decisions.
Without it, providers may make decisions based on tradition and anecdotal experience.\textsuperscript{20}

Virtually all professional organizations have developed guidelines for evaluating clinical evidence. For example, in formulating guidelines for the treatment of CAP, the ATS applied a simplified 3-level grading system for the types of evidence used in evaluating medications (Table 2), a tool that has been gaining widespread professional acceptance.\textsuperscript{13} These guidelines are similar to those recommended by the IDSA.\textsuperscript{15}

**Therapeutic benefits**

The key to applying evidence-based results and making appropriate therapeutic choices for each patient involves determining the correct diagnosis and analyzing the therapeutic benefits of possible treatments. To maximize patient health and reduce unnecessary prescribing, the therapeutic benefits of each drug should be considered relative to the status of the patient’s infection. The clinician must consider any evidence that a particular antibiotic can result in a clinical and microbiologic cure, as well as the treatment failures associated with the absence of drug treatment. If possible, the clinician should identify the causative pathogen and use surveillance data on regional antibiotic resistance patterns in selecting the optimal therapeutic agent.

When evaluating potential therapeutic choices, data on regional antibiotic resistance patterns should be taken into consideration. Although antibacterial susceptibility patterns are based on the results of in vitro tests, they can be used as guidelines to minimize the chances of clinical failure. Therefore, regional resistance patterns should be used to help direct prescribing practices. If there is substantial resistance to a particular class of antibiotics in a particular geographic area, a different class of drug should be considered.\textsuperscript{8,14}

**Safety**

In treating patients with a particular drug, safety must be weighed against efficacy. Clinically applicable treatment

---

**Table 1** Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria for accurate use of antibiotic therapy

<table>
<thead>
<tr>
<th>Evidence-based results</th>
<th>Therapeutic benefits</th>
<th>Safety</th>
<th>Cost-effectiveness</th>
<th>Optimal drug dose and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Evidence-based results</td>
<td>● Therapeutic benefits</td>
<td>● Safety</td>
<td>● Cost-effectiveness</td>
<td>● Optimal drug dose and duration</td>
</tr>
<tr>
<td>● Evidence comes from well-conducted, randomized, controlled trials.</td>
<td>● Evidence comes from well-designed, controlled trials without randomization (including cohort, patient series, and case-control studies).</td>
<td>● Level II studies also include any large case series in which systematic analysis of disease patterns and/or microbial etiology was conducted, as well as reports of new therapies that were not collected in a randomized fashion.</td>
<td>● Evidence comes from case studies and expert opinion. In some instances, therapy recommendations come from antibiotic susceptibility data without clinical observations.</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Am J Respir Crit Care Med.\textsuperscript{13}

**Table 2** American Thoracic Society simplified grading system for ranking evidence in the treatment of community-acquired pneumonia

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I (high)</td>
<td>● Evidence comes from well-conducted, randomized, controlled trials.</td>
</tr>
<tr>
<td>Level II (moderate)</td>
<td>● Evidence comes from well-designed, controlled trials without randomization (including cohort, patient series, and case-control studies).</td>
</tr>
<tr>
<td></td>
<td>● Level II studies also include any large case series in which systematic analysis of disease patterns and/or microbial etiology was conducted, as well as reports of new therapies that were not collected in a randomized fashion.</td>
</tr>
<tr>
<td>Level III (low)</td>
<td>● Evidence comes from case studies and expert opinion. In some instances, therapy recommendations come from antibiotic susceptibility data without clinical observations.</td>
</tr>
</tbody>
</table>

Adapted from Am J Respir Crit Care Med.\textsuperscript{13}
strategies should be chosen to maximize efficacy while minimizing side effects.

Although antibiotics are generally considered safe and well tolerated, they have been associated with a wide range of adverse effects. Safety profiles vary for different classes of antibiotics, as well as for antibacterial agents within each class. In addition, it should be considered that the safety profiles of newer medications may not be as well established as those that have been in use for many years. In a study of the period between 1975 and 2000, 548 new chemical entities were approved for use in the United States; 45 of these (8.2%) acquired new black-box warnings and 16 (2.9%) were withdrawn from the market during this time. Of the 16 withdrawn from the market, 8 were withdrawn within 2 years after their introduction. For example, temafloxacin was withdrawn 0.3 years after introduction and grepafloxacin was withdrawn 2.0 years after introduction.21

In general, the selected antibiotic should be the one that satisfies all other criteria and has the lowest rate of known adverse events.

**Optimal drug for optimal duration**

Optimal drug selection requires finding the antimicrobial class and the specific member of that class that is best suited to treat a particular infection. Because empiric therapy is necessary in most cases, multiple factors have to be considered. Among these are whether the etiologic agent is likely to be gram-positive or gram-negative, whether a narrow or broad-spectrum agent should be chosen, the resistance patterns of the likely pathogen to this drug, both nationally and regionally, and the individual patient’s medical history, including recent antibiotic exposure. Several governing bodies, such as the ATS and the IDSA, have issued guidelines for the use of antimicrobial therapy in CAP. The IDSA guidelines for the treatment of outpatients with signs and symptoms of CAP suggest considering previous health, recent courses of antibiotic treatment, and comorbid conditions when determining a treatment.15 Previously healthy patients with no recent antibiotic therapy should be treated with a macrolide (erythromycin, azithromycin, or clarithromycin) or doxycycline, whereas previously healthy patients recently treated with an antibiotic should be treated with a broad-spectrum agent such as a respiratory fluoroquinolone alone or an advanced macrolide (azithromycin or clarithromycin) plus a narrow-spectrum agent such as a β-lactam. Outpatients with co-morbidities—including chronic obstructive pulmonary disease, renal or congestive heart failure, or a malignancy—should be treated with an advanced macrolide or a respiratory fluoroquinolone if they had no recent antibiotic therapy or a respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam if they had a recent course of antibiotic therapy.15

**Optimal duration** means prescribing the selected drug for the shortest amount of time required for clinical and microbiologic efficacy. There are many reasons for reducing antimicrobial therapy to the shortest appropriate duration. They include the potential for reduced occurrence of adverse effects, increased patient adherence, decreased promotion of resistance, and decreased costs.22

The rational use of medicines has been defined by the WHO as requiring that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements, for an adequate time, and at the lowest cost to them and their community.23 As part of its guidelines, the WHO has recognized that antimicrobial resistance has become a serious worldwide public health problem and has formulated a global strategy of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms.

**Cost-effectiveness**

Choosing inappropriate therapy is associated with increased costs, including the cost of the antibiotic and increases in overall costs of medical care because of treatment failures and adverse events. Upper RTIs, while usually mild and not life-threatening, are associated with significant healthcare costs. Treatment failure results in increased costs, particularly if hospitalization is required.24

Using an optimal course of antibiotics can have economic as well as clinical advantages. Outpatients may experience a faster return to their normal daily routine and an earlier return to work. In a study comparing 500-mg and 750-mg intravenous levofloxacin in 232 inpatients with CAP (intention-to-treat population), the higher dose of drug was associated with a more rapid intravenous-to-oral switch (2.35 vs. 2.75 days), fewer doses of oral antibiotic (4.08 vs. 8.59 doses), and lower cost of levofloxacin (US$115.47 vs. US$150.65).25 Other studies have also supported the efficacy of shorter courses of treatment in pneumonia.26–33 Similar results have also been found for short courses of therapy for bronchitis, sinusitis, and urinary tract infections.34–43

**Pharmacokinetic considerations**

Pharmacokinetic properties differentiate among classes of antibiotics, and even among antibiotics within the same class, in their ability to eradicate bacteria at drug concentrations attained during therapy.8 Among these properties are the time for which non–protein-bound serum concentration of drug exceeds its minimum inhibitory concentration (MIC); the ratio between peak serum concentration (Cmax) and MIC; and the ratio between drug exposure, measured as area under the serum 24-hour concentration-time curve (AUC24), and MIC (AUC24/MIC) ratio. These parameters have been shown to be coordinated with clinical outcome.44–46 For example, at a free-drug AUC24/MIC ratio >33.7, the microbiological response of *S pneumoniae* to fluoroquinolones is 100%.47 An AUC24/MIC ratio of >125 predicts an 85.4% microbiologic response to levofloxacin and an 81.5% response to ciprofloxacin.48
For several classes of antibiotics, including the β-lactams and macrolides, bacteriologic efficacy can be correlated with the time during which drug concentration exceeds MIC.46,50 Thus, for optimal reduction of bacterial load, these agents should be administered such that drug concentrations exceed the MIC for 40% of the dosing interval.

In contrast to the time-dependent efficacy of the β-lactams, macrolides, and lincosamides, the aminoglycosides, metronidazole, and fluoroquinolones exhibit concentration-dependent bactericidal activity. The efficacy of these drugs has been found to correlate with the Cmax–MIC and AUC24–MIC ratios.44–46,51 For example, an AUC24–MIC ratio of 25 to 40 is thought to predict optimal bactericidal activity for fluoroquinolones against S. pneumoniae.47,49,52–54 Thus, for this class of drug, administration of a maximum dose for a shorter time would be optimal in the absence of adverse effects resulting from high drug doses.

Summary

Infectious diseases are still a serious problem, compounded by the development of antibiotic resistance in many bacteria and the relative lack of newer antimicrobial agents to combat these multiresistant organisms. In choosing appropriate and accurate antibiotic therapy, the clinician should use the 5 criteria of CARAT described herein (evidence-based results, therapeutic benefits, safety, optimal drug for the optimal duration, and cost-effectiveness). Appropriate aggressive short-course treatment is recommended for ensuring clinical and microbiologic cure, optimal patient adherence, and minimal generation of antibiotic resistance. Ideally, institution of the 5 CARAT criteria will optimize safe and well-tolerated treatment regimens, curb unnecessary prescribing of antibiotics, decrease treatment costs, and increase adherence.

References

Rational antibiotic treatment of outpatient genitourinary infections in a changing environment

Richard D. David, MD,a Peter M.C. DeBlieux, MD,b Robert Press, MD, PhDc

aThe David Geffen School of Medicine at UCLA, University of California–Los Angeles, Los Angeles, California, USA; bLouisiana State University Health Sciences Center, New Orleans, Louisiana, USA; and cNew York University School of Medicine, New York, New York, USA.

In the outpatient setting, genitourinary infections (GUIs) remain costly to treat and are a significant cause of morbidity. Recent evidence supports more substantial roles for pathogens other than *Escherichia coli*, particularly gram-positive pathogens, in the pathogenesis of GUIs. Broad-spectrum agents should be considered in order to address this etiologic change appropriately. Criteria for antimicrobial selection set forth by the Council for Appropriate and Rational Antibiotic Therapy (CARAT) recommend using antibiotics that are supported by strong clinical evidence, have good susceptibility profiles, are safe, are cost-effective, and are used for the optimal duration. Evidence-based guidelines recommend considering local *E coli* resistance rates to trimethoprim-sulfamethoxazole and using fluoroquinolones as second-line therapy when resistance is high. Fluoroquinolones are recommended for the treatment of pyelonephritis and prostatitis. Among the fluoroquinolones, levofloxacin and gatifloxacin offer coverage for the gram-negative and gram-positive pathogens, which may make them preferable in treating urinary tract infections empirically in such patient groups. For the treatment of bacterial prostatitis, only trimethoprim and the fluoroquinolones possess both the appropriate bactericidal activity and the ability to diffuse into the prostate. Levofloxacin shows particularly good penetration into prostatic tissue. Safety issues to consider include imbalances in intestinal microflora caused by antimicrobial agents that may lead to overgrowth of vancomycin-resistant enterococci and *Clostridium difficile*–associated diarrhea. Once the optimal agent is identified, the optimal duration of treatment should be determined to maximize treatment success while minimizing the potential for resistance. Finally, cost considerations include the costs of treatment failure due to inappropriate therapy or nonadherence to the therapeutic regimen.

Choosing the right empiric treatment for genitourinary infections (GUIs) has been made more difficult in recent times due to increases in antimicrobial resistance, shifting and unpredictable regional resistance patterns, and changing etiologies. Even uncomplicated, community-acquired urinary tract infections (UTIs), generally considered easy to treat, are posing therapeutic challenges.1 It is therefore timely to reevaluate our treatment options for GUIs.

**Epidemiology**

In the United States, UTIs account for 7 million office visits and 100,000 hospitalizations yearly, making them the most common bacterial infections in outpatient settings.2,3 Approximately 1 in 3 women will require antimicrobial treat-
ment for a UTI before age 24, and 40% to 50% of women will have a UTI during their lifetime. The estimated annual cost of UTIs is $1.6 billion for evaluation and treatment. Despite advances in antimicrobial therapy, UTIs remain a significant cause of morbidity.

Classification and diagnosis

UTIs are classified as uncomplicated or complicated. Uncomplicated UTIs occur in sexually active healthy female patients with structurally and functionally normal urinary tracts. Complicated UTIs are those that are associated with comorbid conditions that prolong the need for treatment or increase the chances for therapeutic failure. These conditions include abnormalities of the urinary tract that impede urine flow, the existence of a foreign body (e.g., indwelling catheter, stone), or infection with multidrug-resistant pathogens. UTIs in male patients are considered complicated. Despite involvement of the upper urinary tract, pyelonephritis can be considered uncomplicated pyelonephritis when it occurs in a healthy patient.

Women are significantly more susceptible than men to UTIs, although the pathogenic strains involved tend to be more virulent in men. Prostatitis is the most common urologic diagnosis in men ≥50 years of age, affecting about 50% of men during their lifetime. The true incidence of uncomplicated pyelonephritis is not known.

The diagnosis of a UTI largely relies on clinical symptoms and a limited number of laboratory findings (Table 1). Prostate-specific antigen (PSA) levels may be elevated in both acute and chronic bacterial prostatitis. Men who present with an elevated PSA level and findings of prostatitis should be given a course of antibiotics followed by a repeat PSA measurement before a biopsy is performed.

Risk factors

Because of the shorter length of their urethra, women, in general, are at greater risk than men of contracting UTIs. Other patients at increased risk of complications of UTIs include infants, pregnant women, and the elderly, as well as those with spinal cord injuries, indwelling catheters, diabetes mellitus, multiple sclerosis, human immunodeficiency virus or acquired immunodeficiency syndrome, underlying urologic abnormalities, or a prior history of UTI. Among premenopausal women, use of diaphragms, condoms, and/or spermicides for contraception are also risk factors for UTIs. The most important risk factor for complicated UTI is obstruction. Other factors associated with complicated UTIs or pyelonephritis include advanced age, diabetes, male sex, menopause, use of immunosuppressive drugs, and recent antibiotic use.

Etiology

*Escherichia coli* is generally considered the most common cause of UTIs, especially in uncomplicated infections. However, recent evidence supports more substantial roles for other pathogens. In 2 studies, the gram-positive pathogen *Enterococcus faecalis* was isolated more often than *E. coli* in patients with UTIs. Non–*E. coli* pathogens play substantial etiologic roles in complicated UTIs. A recent study found that among spinal cord injury patients, 30% of acute UTIs were caused by *Klebsiella* species, 22% by *Enterococcus* species, and only 22% by *E. coli*. This shift in the etiology of UTIs should be taken into account when choosing a therapy. Consideration of the use of broad-spectrum agents is warranted to address this etiologic change appropriately.

Treatment goals

Alleviation of symptoms and prevention of complications are short-term treatment goals for UTIs. Long-term goals include prevention of recurrent infection and improvement in rate of reinfection. Since the morbidity of uncomplicated UTIs seems to be limited to the symptoms caused by the infection, the primary goal of treatment is symptom alleviation. Convenience (including infrequent dosing intervals), safety, existing antibiotic resistance patterns, the generation of resistance, tolerability, and cost are considerations when choosing therapy.
Application of the Council for Appropriate and Rational Antibiotic Therapy criteria

In light of the changing etiology of UTIs as well as increasing antimicrobial resistance, a new paradigm is necessary to guide treatment choices. To aid in the selection of appropriate antimicrobial treatments for infectious diseases, the Council for Appropriate and Rational Antibiotic Therapy (CARAT) recommends determining whether a treatment choice is (1) supported by clinical evidence, (2) likely to provide therapeutic benefits, (3) safe, (4) the optimal drug for the optimal duration, and (5) cost-effective. This article will discuss how these criteria can be applied to the treatment of UTIs in the outpatient setting.

Evidence-based therapy

UTIs

Evidence-based guidelines are available that have been formulated from clinical trial data. These guidelines provide useful resources for practicing clinicians. In the treatment of acute uncomplicated UTIs, for example, the 2004 Sanford Guide to Antimicrobial Therapy notes that resistance of *E coli* to trimethoprim-sulfamethoxazole (TMP-SMX) is high (15% to 20%) and correlates with microbiologic and clinical failure. Therefore, in areas where local resistance is <20%, TMP-SMX is recommended; in areas where local resistance is >20%, a fluoroquinolone should be given.\(^\text{18}\)

The Infectious Diseases Society of America (IDSA) has proposed evidence-based guidelines for the management of UTIs.\(^\text{4}\) These guidelines, published in 1999, recommend the use of TMP-SMX for 3 days as standard care for uncomplicated bacterial cystitis, but only in regions where TMP-SMX resistance is below the range of 10% to 20%. In communities where uropathogen resistance to TMP-SMX is above the range of 10% to 20%, fluoroquinolones are recommended as the initial treatment for uncomplicated UTIs because they provide consistent broad-spectrum coverage.\(^\text{4}\) In recent years, resistance to TMP-SMX has increased dramatically while susceptibility to newer fluoroquinolones remains high (Figure 1).\(^\text{19}\)

The clinical studies supporting the IDSA recommendations revealed that treatment with TMP-SMX for 3 days yielded bacterial eradication rates comparable to 7- to 10-day treatment. However, with the short-duration regimen, an increased bacterial recurrence rate was noted by day 3 post-therapy. In patients with uncomplicated UTIs, 3-day and 7-day fluoroquinolone regimens were equally effective.\(^\text{5,20}\) After a decade of use in the management of uncomplicated UTIs, fluoroquinolones such as levofloxacin and ciprofloxacin have maintained consistent activity against *E coli* and other pathogens implicated in the etiology of UTIs, elevating the chances for therapeutic success (Table 2).\(^\text{1,21,22}\)

Pyelonephritis and prostatitis

The 2004 Sanford Guide to Antimicrobial Therapy recommends a fluoroquinolone as first-line therapy for acute uncomplicated pyelonephritis.\(^\text{18}\) For acute prostatitis in men ≤35 years of age, ofloxacin alone or ceftriaxone followed by doxycycline are recommended. In men aged ≥35 years, fluoroquinolones or TMP-SMX are recommended.\(^\text{18}\)
Recommendations for the treatment of acute pyelonephritis and bacterial prostatitis from the IDSA, the Association of Genitourinary Medicine, and others are summarized in Table 3. Fluoroquinolone treatment for 2 to 4 weeks has been reported to cure approximately 70% of the cases of bacterial prostatitis. However, older fluoroquinolones (including ciprofloxacin), although still effective against the gram-negative species such as *E. coli* that are the predominant pathogens in bacterial prostatitis, may be less effective against emerging gram-positive strains, such as *E. faecalis*, which are becoming a more common cause of UTIs. In some recent studies, gram-positive pathogens were more prevalent than *E. coli* (Figure 2). Based on this evidence, it is important to choose an agent that provides both gram-negative and gram-positive coverage. Together, these data provide evidence-based guidance for the optimal management of uncomplicated UTIs, as advocated by the CARAT criteria, and highlight the central role of fluoroquinolones in the treatment of UTIs.

To be effective for the treatment of bacterial prostatitis, an antibiotic must be able to attain sufficient concentrations in the prostatic fluid to achieve bactericidal levels. Only trimethoprim and the fluoroquinolones possess both the appropriate bactericidal activity and the ability to diffuse into the prostate. For example, ciprofloxacin attains a prostatic tissue-to-serum ratio of 1.86:1. Levofloxacin shows particularly good penetration into prostatic tissue, attaining a prostatic tissue-to-serum ratio of 2.96:1.

**Therapeutic benefits**

To stem future increases in resistance, clinicians must use their hospital-generated antibiogram to choose the antibiotic most likely to eradicate the infection as the first line of treatment. Treatment failure not only costs more money, it also drives future resistance. Therefore, it is critical for clinicians to know their own local resistance patterns and prescribe accordingly. It has been found that, despite increasing resistance to some commonly used antimicrobials, many clinicians do not consider antimicrobial resistance a problem in their own institution or practice.

### Table 2 Susceptibility of urinary tract infection isolates from girls and women (15–50 years of age)*

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Ampicillin</th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Nitrofurantoin</th>
<th>TMP-SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacter</em> spp</td>
<td>3</td>
<td>96</td>
<td>99</td>
<td>51</td>
<td>95</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp</td>
<td>98</td>
<td>67</td>
<td>83</td>
<td>98</td>
<td>NA</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>60</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>82</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp</td>
<td>1</td>
<td>99</td>
<td>99</td>
<td>57</td>
<td>92</td>
</tr>
<tr>
<td><em>Proteus</em> spp</td>
<td>92</td>
<td>99</td>
<td>98</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>NA</td>
<td>74</td>
<td>72</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td>29</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>16</td>
<td>90</td>
<td>95</td>
<td>99</td>
<td>97</td>
</tr>
</tbody>
</table>

NA = not available; TMP-SMX = trimethoprim sulfamethoxazole.

Adapted from *Am J Med* and *Clin Infect Dis*.

*In vitro results do not necessarily correlate with clinical results. In clinical trials, levofloxacin has demonstrated comparable efficacy to ciprofloxacin. No comparative clinical data are available for ampicillin, TMP-SMX, or nitrofurantoin.

### Table 3 Summary of evidence-base treatment recommendations

<table>
<thead>
<tr>
<th>UTI</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pyelonephritis</td>
<td>Young, nonpregnant women: fluoroquinolone, TMP-SMX, amoxicillin, or amoxicillin-clavulanate for 7–14 days 4</td>
</tr>
<tr>
<td>Bacterial prostatitis</td>
<td>Fluoroquinolone, TMP-SMX, or doxycycline for 28 days 10,23,24</td>
</tr>
</tbody>
</table>

TMP-SMX = trimethoprim-sulfamethoxazole; UTI = urinary tract infection.

Adapted from *Clin Infect Dis*, *Sex Transm Infect*, *Emerg Med Clin North Am*, and *Urology*.

10S The American Journal of Medicine, Vol 118 (7A), July 2005
at the forefront of treatment of uncomplicated UTI. *E coli* resistance to β-lactams (chiefly ampicillin) and first-generation cephalosporins has increased steadily over the last decade and now approaches 40%. Yet, the most notable and alarming shifts have occurred in resistance to TMP-SMX, one of the principal recommended treatments for uncomplicated UTIs. Indeed, nationwide, *E coli* resistance to TMP-SMX is now >20% in the United States and displays geographic variation, with the highest resistance rate (24%) occurring in Texas and Louisiana (Figure 1). In fact, 7.1% of *E coli* strains have shown multidrug resistance to ≥3 antimicrobials, such as combinations of ampicillin, cephalothin, ciprofloxacin, nitrofurantoin, and TMP-SMX. These multidrug-resistant *E coli* isolates were most resistant to TMP-SMX, ampicillin, or cephalothin (>80%) as individual agents and least resistant to ciprofloxacin and nitrofurantoin (38.8% and 7.7%, respectively). The most common multidrug-resistant phenotype (57.9%) was resistant to TMP-SMX, ampicillin, and cephalothin.

*E coli* resistance to fluoroquinolones has remained low, e.g., 3.1% for levofloxacin and 3.7% for ciprofloxacin. With continued high activity against *E coli*, the fluoroquinolones may offer the best opportunity to eradicate pathogens responsible for uncomplicated UTIs.

Although *E coli* is traditionally considered the most common cause of UTIs, investigators have recently highlighted the polymicrobial nature of acute UTIs, in some patient groups. For example, in patients with spinal cord injury, one third of infections were polymicrobial, sometimes with a mix of gram-negative as well as gram-positive strains (chiefly *Enterococcus* species). Thus, to optimize the therapeutic benefits of antimicrobial therapy in uncomplicated UTIs, the CARAT criteria would support the use of the optimal antimicrobial for the optimal duration, or the use of the most bacteriologically and clinically efficacious agent for the shortest time necessary to achieve clinical success and to prevent the increases in antimicrobial resistance that have been associated with treatment failure in UTIs. In the management of uncomplicated GUIs, antimicrobials with a broad spectrum of activity may provide the optimal treatment advocated by the CARAT criteria, because these agents offer the greatest opportunity for averting the spread of resistant organisms and treatment failure.

**Safety**

The safety and tolerability of antimicrobial treatments vary widely. Even among the fluoroquinolones, which are generally considered safe and effective, some safety issues warrant review. These issues, including damage to normal intestinal flora and *Clostridium difficile*–associated diarrhea, can be found in the article by Liu and Mulholland elsewhere in this supplement.

**Optimal drug for optimal duration**

The goal of choosing the optimal drug for the optimal duration is to provide the most targeted, effective therapy that will achieve clinical efficacy while preventing or minimizing increases in resistance. Short-course (3-day) therapy is generally considered the preferred treatment for uncomplicated UTIs. Short courses of therapy enhance tolerability and adherence, and reduce cost without decreasing efficacy. Short-course therapy may help prevent selection for resistant organisms.

**Preventing increases in resistance**

In the treatment of UTIs, the application of the CARAT criteria can optimize outcomes and may slow the spread of resistant bacterial strains. A principal goal of the CARAT criteria is to encourage the use of the optimal antimicrobial for the optimal duration, or the use of the most bacteriologically and clinically efficacious agent for the shortest time necessary to achieve clinical success and to prevent the increases in antimicrobial resistance that have been associated with treatment failure in UTIs. In the management of uncomplicated GUIs, antimicrobials with a broad spectrum of activity may provide the optimal treatment advocated by the CARAT criteria, because these agents offer the greatest opportunity for averting the spread of resistant organisms and treatment failure.

**Cost**

The true cost-effectiveness of an antimicrobial treatment is determined by many variables. Treatment failures result in
increased costs that may be due to a variety of factors, including antibiotic resistance or poor adherence. Factors that influence adherence to therapy include dose frequency and length of treatment, as well as side-effect profile and frequency. Because less frequent dosing has been associated with enhanced adherence, shorter courses of therapy with a reduced pill burden should address this problem in addition to reducing the risk of some adverse events.

The available treatment options offer different dosing regimens for each indication. Due to the influence of pill burden on adherence, the total pill burden should be considered for each treatment option. For uncomplicated UTI, levofloxacin and gatifloxacin are indicated for 3 days of treatment with 1 pill given each day. Ciprofloxacin, although also indicated for 3 days of treatment, needs to be taken twice a day, double the pill burden of levofloxacin and gatifloxacin, unless the extended-release preparation is used. Similarly, for complicated UTIs, levofloxacin and gatifloxacin are indicated for 10 days of therapy with 1 pill per day. Ciprofloxacin treatment requires 7 to 10 days of therapy, with 2 pills taken per day, so that patients may take up to 20 pills, unless the extended-release preparation is used. Finally, for bacterial prostatitis, levofloxacin is indicated for 28 days of treatment with 1 pill per day, whereas ciprofloxacin is indicated for 28 days of treatment with 2 pills per day, which is double the pill burden for levofloxacin.

Summary

The CARAT criteria provide a sound approach for adapting antimicrobial therapy to rapidly changing bacterial-resistance patterns. These criteria imply that optimal antimicrobial treatment for GUIs can be achieved with fluoroquinolones such as levofloxacin or ciprofloxacin that provide effective, well-tolerated, convenient antimicrobial treatment that can bolster adherence, possibly decreasing the need for retreatment and reducing the potential for resistance. In the case of levofloxacin, this can be given once daily, whereas for ciprofloxacin, twice-a-day therapy is necessary unless the extended-release preparation is used. The IDSA guidelines recommend fluoroquinolones as first-line therapy for uncomplicated UTIs when local uropathogen resistance to TMP-SMX exceeds 10% to 20%, an increasingly common occurrence that underscores the need for clinicians to be aware of resistance patterns in their community. Some fluoroquinolones, such as levofloxacin and gatifloxacin, display a broad spectrum of predictable activity against both the gram-negative and the emerging gram-positive species currently implicated in the etiology of UTIs. As a result, these agents may offer the best empiric therapeutic choice to optimize treatment for uncomplicated UTIs in a manner consistent with the CARAT criteria. Levofloxacin appears to be safer than gatifloxacin, especially in people with diabetes. Its predictable activity against the increasing number of resistant pathogens implicated in GUIs may avert the costs associated with treatment failures, disease progression, and return visits to physicians’ offices.

References

Appropriate antibiotic treatment of genitourinary infections in hospitalized patients

Hans Liu, MD, S. Grant Mulholland, MD

From the Jefferson Medical College, Philadelphia, Pennsylvania

KEYWORDS:
Antibiotic therapy; Bacterial prostatitis; Fluoroquinolones; Gram-positive organisms; Pyelonephritis; Urinary tract infections

The etiology of urinary tract infections (UTIs) that require hospitalization, whether they originate in the hospital or in the community, is changing, with increasing findings of gram-positive organisms. The Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria recommend evaluating treatment choices on the basis of sound clinical evidence, potential for therapeutic benefits, safety, optimal duration of treatment, and cost-efficacy in order to improve antibiotic treatment. Evidence-based guidelines recommend fluoroquinolones for the treatment of patients with cases of pyelonephritis or bacterial prostatitis severe enough to warrant hospitalization. For other serious UTIs, fluoroquinolones are usually recommended either when traditional agents have failed or when resistance to traditional agents is high. Even in the context of rapidly changing antimicrobial resistance patterns, the fluoroquinolones have maintained consistent, well-tolerated efficacy against many of the principal organisms responsible for UTIs, and are generally considered safe for most patients. To increase the likelihood of treatment success with first-line therapy, an antimicrobial agent must attain sufficient concentrations in the target tissue or in the urine for an appropriate amount of time. Both levofloxacin and gatifloxacin are excreted unchanged in the urine in concentrations that far exceed the minimum inhibitory concentration of most uropathogens. Factors that affect cost-effectiveness that should be considered include acquisition costs as well as treatment success and ease of use for hospital staff.

© 2005 Elsevier Inc. All rights reserved.

In recent years, studies have shown that the etiology of urinary tract infections (UTIs) is changing. Some studies have found that gram-positive organisms are more prevalent than *Escherichia coli*. This changing etiology may be due to the widespread use of antibiotics with limited efficacy against gram-positive pathogens, which may have allowed the proliferation of such pathogens. In this context, clinicians must reevaluate which agents are used to treat UTIs to ensure that the optimal agent is administered as first-line therapy. Ideally, antibiotic use should reduce or avoid treatment failures that can contribute to future increases in resistance.

Requests for reprints should be addressed to Hans Liu, MD, Bryn Mawr Medical Specialists, 933 Haverford Road, Bryn Mawr, Pennsylvania 19010.
E-mail address: liuliang@aol.com.

The Council for Appropriate and Rational Antibiotic Therapy (CARAT) has developed criteria for accurate use of antibiotics to aid clinicians in making treatment decisions. These are general guidelines that should be considered before choosing an antimicrobial treatment. The criteria suggest evaluating whether a treatment choice is (1) supported by sound clinical evidence, (2) likely to provide therapeutic benefits, (3) safe, (4) the optimal drug for the optimal duration, and (5) cost-effective. This article will discuss how these criteria can be applied to genitourinary infections (GUIs) treated in the hospital.

UTIs that require hospitalization, whether they originate in the hospital or in the community, have a major impact on morbidity and healthcare costs. It is estimated that >100,000 patients per year are admitted to hospitals because of UTIs. UTIs are also the most common nosocomial...
infections in the United States, accounting for 31% of all nosocomial infections. However, hospital-acquired UTIs remain underrecognized and undertreated, leading to complications such as renal and perinephric abscesses, urethritis, epididymitis, periurethral gland infections, and bacteremia. Complications increase morbidity, hospital stay, and, in turn, medical costs.\(^2\) Mortality from bacteremia secondary to hospital-acquired UTIs is reported to be as high as 15%.\(^2\) This is most common in patients of advanced age and with severe underlying disease.

UTIs are classified as either complicated or uncomplicated. Complicated UTIs are infections that are associated with factors, both medical and surgical (anatomic), that increase the risk of treatment failure. These factors include functional or anatomic abnormalities of the urinary tract that compromise urine flow, the presence of foreign bodies (such as an indwelling catheter), and conditions or locations that compromise antibiotic delivery, such as prostatitis.\(^7\)\(^8\)

Acute, uncomplicated UTIs tend to be treated on an outpatient basis, except when associated with severe illness (marked by high fever, severe pain, and marked debility) or possible urosepsis (infection arising from the urinary tract), for which hospitalization is required.\(^7\) Patients with acute bacterial prostatitis should be admitted if they have comorbid illness, intractable vomiting, dehydration, urinary outflow obstruction, chronic indwelling urinary catheters, or sepsis (invasion of the bloodstream by microorganisms from the focus of infection).\(^9\) Patients with acute, uncomplicated pyelonephritis or complicated UTIs should be hospitalized if they have severe illness or possible urosepsis.\(^10\)

Although \textit{E coli} is the predominant pathogen in both uncomplicated and complicated UTIs, complicated UTIs are caused by more diverse pathogens.\(^11\) Studies have shown that up to 33% of infections may be polymicrobial and a significant proportion (23%) may be due to gram-positive \textit{Enterococcus} species.\(^12\)\(^13\) In fact, a recent study found equal rates (22%) of \textit{E coli} and \textit{Enterococcus} species in spinal cord injury patients with UTIs.\(^12\) \textit{E coli}, \textit{Proteus mirabilis}, \textit{Klebsiella pneumoniae}, and \textit{Staphylococcus saprophyticus} are characteristic pathogens in acute uncomplicated pyelonephritis cases, including those treated in both outpatient and inpatient settings.\(^7\) \textit{E coli} is the predominant pathogen in acute prostatitis, found in 64% of cultures, although other gram-negative rods are found in 12% of cultures.\(^9\)

The pathogens that cause hospital-acquired UTIs originate from the patient’s endogenous intestinal flora or, less commonly, from moist sites in the hospital environment.\(^14\) Similar to UTIs in general, the pathogens that cause nosocomial UTIs have undergone a shift in recent years away from gram-negative rods toward fungal and gram-positive organisms.\(^12\) Currently, \textit{E coli} accounts for only 17.5% of nosocomial UTIs, \textit{Candida albicans} 16%, \textit{Enterococcus} species 14%, \textit{Pseudomonas aeruginosa} 11%, and \textit{Enterobacter} species 5%. Other pathogens, chiefly coagulase-negative staphylococci and \textit{Staphylococcus aureus}, are implicated as primary pathogens in 30% of infections.\(^2\)

In light of the changing etiology of UTIs, treatment choices should be reevaluated. Both likely etiology and local resistance patterns should influence antimicrobial treatment decisions. This article focuses on applying the CARAT criteria to UTIs that are commonly treated on an inpatient basis.

**Evidence-based therapy**

A wealth of clinical trials and several evidence-based guidelines are available for review when selecting a treatment for UTIs in the hospital. The present section discusses 3 major categories of UTIs and their treatment options. It is critical that clinicians evaluate the existing evidence for treatment in a particular setting before choosing antimicrobial therapy.

**Treatment of pyelonephritis**

The Infectious Disease Society of America (IDSA) guidelines for the treatment of UTIs in women indicate that patients with cases of pyelonephritis severe enough to warrant hospitalization should be treated with a parenteral fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin (with or without an aminoglycoside). For gram-positive cocci, ampicillin-sulbactam (with or without an aminoglycoside) is recommended. As the patient improves, he or she can be switched to an oral antimicrobial agent.\(^3\)

**Treatment of complicated UTIs**

UTI episodes that involve structural or functional abnormalities of the genitourinary tract are categorized as complicated UTIs. All UTIs in men, including prostatitis, are considered complicated.\(^11\)\(^15\) Patients with acute bacterial prostatitis should be admitted to the hospital and given parenteral antibiotics if comorbid illness (such as cardiac disease or diabetes mellitus), intractable vomiting, dehydration, sepsis, or urinary outflow obstruction are present, or if the patient has an indwelling catheter. In such cases, fluoroquinolones are the treatment of choice.\(^9\)\(^16\)

For other serious UTIs, including acute complicated UTIs that require hospitalization, fluoroquinolones are usually recommended either when traditional agents—i.e., aminoglycosides, \(\beta\)-lactams, advanced-generation cephalosporins—have failed or when resistance to traditional agents is high.\(^10\)\(^11\) Because of the elevated risk of \textit{P aeruginosa} infection and, in turn, sepsis, in the hospital setting, an antipseudomonal antibiotic, such as ceftazidime, may be included in the treatment regimen.\(^11\)
Episodes of nosocomial infections related to an indwelling catheter are also classified as complicated UTIs. Conventional agents include aminoglycosides (gentamicin) and β-lactams. However, broad spectrum β-lactam antibiotics are less active against common nosocomial causative organisms. Fluoroquinolones have been shown to be as effective as aminoglycosides in treating complicated UTIs; they are generally associated with fewer adverse events, and they offer the advantage of being available in both IV and oral formulations. Orally administered ciprofloxacin was shown to provide a superior short-term microbiologic response, and similar long-term clinical response rates, compared with intravenously administered gentamicin.

Nursing home–associated UTIs

In elderly nursing home residents, complicated UTIs such as cystitis, pyelonephritis, and catheter-associated infections and symptomatic bacteriuria require antimicrobial therapy. Recommended treatments for pyelonephritis are parenteral trimethoprim-sulfamethoxazole (TMP-SMX) or fluoroquinolones, among which levofloxacin and ciprofloxacin are the preferred choices. Initial combination therapy with 2 agents that have different mechanisms of antibacterial activity is recommended to combat resistant organisms. The patient may be switched to an oral regimen when afebrile status is achieved. In the management of cystitis in women with symptoms for >1 week, recommended therapy is 7 to 10 days with oral fluoroquinolones or possibly TMP-SMX if local resistance patterns are not a problem. Catheter-associated infections that may be associated with bacteremia should be initially treated with broad-spectrum agents, and adjusted according to culture data.

Therapeutic benefits

Evaluating the potential therapeutic benefits of an antimicrobial in the treatment of UTI in hospitalized patients requires assessing local resistance patterns and choosing an agent with the highest activity against those pathogens. In vitro resistance data show increasing resistance to several agents among common pathogens. Many factors are thought to contribute to increased resistance, including inappropriate antibiotic use that leads to initial treatment failure.

Many clinicians consider antimicrobial resistance a problem that is more relevant on a national level than it is to their own practice or institution. However, the IDSA recommends that physicians be aware of local resistance patterns, and that regimens for empiric therapy reflect current susceptibility patterns. This is especially important in the hospital setting, where antimicrobial resistance is particularly common.

Recent research has demonstrated that in vitro resistance patterns predict the therapeutic efficacy of antimicrobials in UTIs.

In many regions, burgeoning resistance of uropathogens to conventional antibiotic treatment with agents such as TMP-SMX increases the risks for treatment failure. Among uropathogens isolated in the United States, TMP-SMX resistance now approaches 25%, and higher resistance rates have been noted elsewhere in the world. In the treatment of complicated UTIs, resistance to some β-lactams—ampicillin, for instance—now approaches 40%. In contrast, fluoroquinolones such as levofloxacin, ofloxacin, and ciprofloxacin still display uropathogen eradication and clinical cure rates of >90% with 7- to 10-day treatment.

Although ampicillin plus gentamicin, imipenem, and TMP-SMX are common initial treatments for complicated UTIs, fluoroquinolones are moving to the forefront as a preferred oral treatment due to their broad spectrum of activity against the shifting pattern of in-hospital uropathogens. In recent trials, gram-positive bacteria such as Enterococcus faecalis were found to be more prevalent than E coli (Table 2). Taking into consideration the changing etiology of UTIs toward gram-positive organisms, it should be noted that older fluoroquinolones, such as ciprofloxacin, have limited activity against some gram-positive bacteria.

Widespread administration of ciprofloxacin may result in increases in many gram-positive causative bacteria in either UTIs or respiratory infections. The newer fluoroquinolones, which have greater gram-positive activity, may be more effective in the treatment of UTIs. It should be noted, however, that fluoroquinolones have only modest in vitro activity against enterococci, which are among the most common gram-positive pathogens.
Safety

Fluoroquinolones are the most commonly recommended antimicrobials for serious UTIs. The safety profiles of available agents vary, however. The most common adverse effects with fluoroquinolones are usually transient and mild-to-moderate in severity, and involve the gastrointestinal tract and the central nervous system.33

To ensure safety and tolerability, antimicrobial treatment choices should take certain patient characteristics into consideration. For example, gatifloxacin is associated with a prolongation of the QTc interval as well as disturbances in glucose homeostasis. Therefore, use of gatifloxacin should be avoided in patients with known prolongation of the QTc interval, with uncorrected hypokalemia, or receiving class IA or III antiarrhythmic agents.33,34 Gatifloxacin should also be used with caution in patients with diabetes.34 Conversely, levofloxacin is generally well tolerated and common side effects are usually mild, with nausea and diarrhea the most frequent side effects.35 The remaining fluoroquinolones, moxifloxacin and gemifloxacin, are not indicated for treatment of UTIs.36,37

The properties of particular antimicrobials also should be considered. To reduce “collateral damage” to normal intestinal microflora, antibiotics that achieve only low concentrations in the feces should be used.35 Of the fluoroquinolones, relatively low percentages of gatifloxacin and levofloxacin are excreted unchanged in feces (5% and 4%, respectively).34,35 Destruction of normal intestinal flora, such as the anaerobe Bacteroides fragilis, may lead to overgrowth of vancomycin-resistant enterococci (VRE).38 Levofloxacin and ciprofloxacin, which have relatively high 90% minimum inhibitory concentration (MIC90) values against the B fragilis group (≥32 µg/mL for both), have been associated with decreases in VRE.38,39

Concerns regarding the incidence of Clostridium difficile–associated diarrhea (CDAD) have affected antibiotic choice in some healthcare settings. In a district general hospital in the United Kingdom, switching to ceftriaxone as a first-line therapy was associated with an increase in CDAD, whereas switching to levofloxacin was associated with a decrease in CDAD.40 Similarly, in a long-term care facility, a formulary change from levofloxacin to gatifloxacin was associated with an increase in CDAD cases, whereas the change back to levofloxacin was associated with a decrease in the incidence of CDAD (Figure 1).41 These data should be considered in light of evidence that the costs of treating hospitalized patients with CDAD are an average of 54% higher than in patients without CDAD.42

The length of time that an antibiotic has been on the market is also an important safety consideration. Of the drugs that enter the market, 20% acquire a black-box warning or are withdrawn. Only half of the withdrawals occur within 2 years, and only half of significant label changes occur within 7 years of introduction into the market.43 Therefore, the true incidence of adverse events associated with antibiotics that have recently entered the market, such as gatifloxacin, will not be known for some time.

Optimal drug for optimal duration

When considering treatment options, it is critical to choose the agent that is most likely to produce clinical success as a first-line therapy. Optimal antibiotic selection is based on characteristics such as appropriate spectrum (coverage), potency, clinical efficacy, and pharmacokinetic/pharmacodynamic profile.

To achieve microbiologic and therapeutic efficacy, an antimicrobial agent must attain sufficient concentrations in the target tissue or in the urine for an appropriate amount of time. For patients with complicated UTIs, appropriate antimicrobials must achieve high concentrations in the urine. Among the fluoroquinolones, both levofloxacin and gatifloxacin are excreted unchanged in the urine in concentrations that far exceed the MIC of most uropathogens (83% and 76%, respectively).44

Figure 1 Gatifloxacin is associated with Clostridium difficile outbreaks. A formulary change from levofloxacin to gatifloxacin revealed that gatifloxacin was associated with a higher incidence of C difficile–associated diarrhea (CDAD). When the formulary was changed back to levofloxacin, the incidence of CDAD decreased. (Reprinted from Clin Infect Dis.41)
In the treatment of bacterial prostatitis, the agent of choice must be able to penetrate into prostatic tissue. Both ciprofloxacin and levofloxacin, which are indicated for prostatitis, achieve greater concentrations in prostatic tissue than in plasma. Ciprofloxacin attains nearly 2-fold higher concentrations in the prostate than in the plasma, whereas levofloxacin attains levels in the prostate that are approximately 3 times higher than in the plasma.

In addition to adequate penetration into the relevant tissue, the appropriate duration of treatment is also necessary to achieve efficacy. Therapy that is insufficient in duration will result in treatment failure, whereas treatment past the optimal duration can contribute to the development of antibiotic resistance in the patients' normal microbial flora. In patients with serious UTIs—defined as acute, complicated UTIs that require initial IV antimicrobial therapy and/or hospitalization—the total duration of therapy should be 7 to 14 days. For patients with acute pyelonephritis who are sufficiently ill to be admitted to the hospital, IDSA guidelines recommend IV antimicrobial treatment until clinical improvement (resolution of fever) is achieved. At that point, the patient should be switched to an oral antibiotic.

Cost efficacy

Treatment failure is a main driver of treatment cost, because the costs of both the failed therapy and the new treatment must be taken into account. Determining the most appropriate antibiotic to use as first-line therapy should reduce treatment failures and significantly contribute to reduction of costs. For certain fluoroquinolones, such as levofloxacin and gatifloxacin, the IV and oral formulations display same-dose bioequivalence. This permits convenient step-down therapy and thus maintains consistent broad-spectrum activity, as well as obviating the need to switch antibiotics during UTI therapy. Finally, switching to a single-fluoroquinolone formulary may provide cost savings. The University of Kentucky Hospital switched to a single-fluoroquinolone formulary in May 2001, choosing levofloxacin based on its range of indications, safety profile, susceptibility profile, cost, and dosing convenience, including once-a-day dosing and IV-to-oral switch. The hospital found that *P aeruginosa* and *S aureus* susceptibility to levofloxacin were maintained or increased, as shown in Figure 2 and Figure 3.

Furthermore, substantial cost savings were realized, with
a 42% reduction in drug acquisition costs in the fluoroquinolone budget for the hospital (Figure 4). Costs of other factors, including adverse events, drug interactions, and treatment failures, were not assessed in this study.

Summary

Optimizing the management of UTIs in the hospital setting demands effective infection control procedures, particularly those related to catheterization. When choosing a course of treatment, the CARAT criteria recommend that clinicians consider antimicrobials with established, robust activity against the uropathogens implicated either locally or in a specific patient. Considering the increasing prevalence of gram-positive pathogens in the etiology of UTIs, clinicians should consider increasing the use of agents with more broad-spectrum coverage and decreasing the use of agents with poor gram-positive coverage. Even in the context of rapidly changing antimicrobial resistance patterns, the fluoroquinolones have maintained consistent, well-tolerated efficacy against many of the principal organisms responsible for UTIs. In addition, key properties of this class of antimicrobials can foster treatment adherence, sustaining broad-spectrum antimicrobial activity through the entire course of therapy—features that optimize outcomes and hinder the spread of resistant pathogens. Moreover, because of bioequivalent IV and oral formulations, these agents offer the opportunity for cost-effective, step-down therapy with the same agent, an important issue for many patients with UTIs that require hospitalization. Cost-effective, step-down therapy obviates the time-consuming and costly reserving demands associated with initiating a different course of oral antibiotic therapy after IV treatment. In the treatment of hospital-acquired UTIs, the fluoroquinolones, especially agents such as levofloxacin, meet the criteria set by CARAT for optimal drug therapy for the optimal duration in a well-tolerated, cost-effective manner.

References

Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting

John Segreti, MD, Hans R. House, MD, Robert E. Siegel, MD

Department of Internal Medicine, Section of Infectious Diseases, Rush Medical College, Rush University Medical Center, Chicago, Illinois, USA; Department of Emergency Medicine, University of Iowa, Iowa City, Iowa, USA; and Critical Care Center, Bronx Veterans Affairs Medical Center, Mount Sinai School of Medicine, New York, New York, USA.

Community-acquired pneumonia (CAP) is a common illness with high rates of morbidity and mortality. Nearly 80% of the treatment for this condition is provided in the outpatient setting. Among the etiologic agents associated with bacterial CAP, the predominant pathogen is *Streptococcus pneumoniae*. Treatment of CAP for the most part is empirical; therefore, any antibiotic treatment should cover both typical and atypical pathogens. The β-lactams have historically been considered standard therapy for the treatment of CAP. However, the impact of rising resistance rates is now a primary concern facing physicians. For patients with comorbidities or recent antibiotic therapy, current guidelines recommend either combination therapy with a β-lactam and a macrolide or an antipneumococcal fluoroquinolone alone. Fluoroquinolones are broad-spectrum antibiotics that exhibit high levels of penetration into the lungs and low levels of resistance. Evidence from clinical trials indicates clinical success rates of >90% for moxifloxacin, gatifloxacin, and levofloxacin in the treatment of CAP due to *S pneumoniae*. Data from comparative clinical trials suggest fluoroquinolone monotherapy is as efficacious as β-lactam–macrolide combination therapy in the treatment of CAP patients. The respiratory fluoroquinolone levofloxacin has also been shown to be effective in CAP patients for the treatment of macrolide-resistant *S pneumoniae*. The use of azithromycin, telithromycin, and fluoroquinolones in short-course regimens has been shown to be efficacious, safe, and tolerable in patients with CAP. Based on clinical evidence, high-dose, short-course therapies may represent a significant advance in the management of CAP.

© 2005 Elsevier Inc. All rights reserved.

KEYWORDS:
Antibiotics; Community-acquired pneumonia; Fluoroquinolones; Short-course therapy

Each year, there are 2 to 3 million cases of community-acquired pneumonia (CAP) in the United States, resulting in approximately 10 million physician visits.¹ Up to 80% of treatment for the condition is provided in the outpatient setting.² Although CAP is the leading cause of death from infection and the sixth-leading cause of death overall in the United States, mortality from CAP among outpatients is estimated at <1%.³

Etiology of community-acquired pneumonia

The etiology of CAP among outpatients has not been well studied.² Furthermore, no etiologic agent is found in as many as 50% of cases, even when extensive diagnostic testing is performed.³ In those cases in which an etiologic agent is identified, *Streptococcus pneumoniae* accounts for approxi-
Antimicrobial management of community-acquired pneumonia

A diagnosis of CAP is often made based on clinical signs and symptoms as well as laboratory and radiographic tests. Signs and symptoms that are indicative of CAP include fever, new cough, purulent tracheobronchial secretions, and focal respiratory abnormalities (i.e., decreased/altered breath sounds and/or crackles). Other tests include chest radiograph, sputum Gram stain and culture, and blood cultures. Using signs, symptoms, and tests is well accepted in the diagnosis of CAP; however, little evidence exists to determine the utility of these criteria individually.

Physicians generally treat outpatient CAP empirically. Empiric treatment requires the consideration of many patient and clinical variables. Therefore, a set of treatment criteria would be useful in helping clinicians choose an effective initial treatment that would prevent the need for retreatment for a wide range of possible pathogens. The Council for Appropriate and Rational Antibiotic Therapy (CARAT) emphasizes evidence-based results, therapeutic benefits, safety and tolerability, optimal drug for optimal duration, and cost-effectiveness as criteria for evaluating treatment options.

Evidence-based results

The CARAT criteria recommend prescribing an antibiotic based on established guidelines and clinical evidence. Guidelines published by the Infectious Diseases Society of America (IDSA) and recommendations published by the Texas Academy of Family Physicians recommend a macrolide or doxycycline to treat infections caused by pneumococcal and atypical pathogens only for patients who have not had recent antibiotic therapy and who do not have comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, renal failure, congestive heart failure, or malignancy. Fluoroquinolones or combination therapy are recommended for patients with any of these comorbid medical conditions and for penicillin-resistant pneumococci and gram-negative pathogens. These recommendations are outlined in Table 1.

Similarly, joint guidelines from the Canadian Infectious Disease Society (CIDS) and the Canadian Thoracic Society (CTS) recommend respiratory fluoroquinolones as a first choice for outpatients who have had antibiotics within 3 months or corticosteroid treatment, as well as those who have modifying factors such as COPD or *H influenzae* or in whom enteric gram-negative rods are implicated. American Thoracic Society (ATS) guidelines recommend either a β-lactam–macrolide combination or monotherapy with an antipseudomococcal fluoroquinolone for more complex outpatients with modifying factors such as cardiopulmonary disease.

Although guidelines are an excellent resource for evidence-based recommendations, clinical evidence should also be taken into account. For the treatment of CAP, the effectiveness of the fluoroquinolone moxifloxacin (400 mg once daily) was compared with that of standard therapy with amoxicillin (1 g given 3 times daily) or clarithromycin (500 mg twice daily) alone or in combination in a randomized, double-blind, controlled trial (N = 564). Clinical success rates were similar for moxifloxacin and standard therapy (93.5% vs. 93.9%, respectively). Recent trials also support the use of gatifloxacin to treat CAP, particularly when it is caused by *S pneumoniae*. In an open-label, noncomparative trial (N = 136) of oral gatifloxacin (400 mg daily for 7 to 14 days), clinical benefit was achieved in 95.3% of evaluable patients. The same dosage regimen of gatifloxacin was evaluated in a prospective, single-arm, open-label, noncomparative study of patients with confirmed or suspected CAP (N = 1,488). Clinical benefit occurred in 91%, 94%, and 92% of patients diagnosed with *S pneumoniae*, *H influenzae*, and *M catarrhalis*, respectively.

For CAP, there is significant evidence to support the use of monotherapy with a fluoroquinolone rather than combination therapies (e.g., with a β-lactam and a macrolide). Intravenous or oral levofloxacin monotherapy (500 mg) was compared with combination therapy with parenteral ceftriaxone (1 to 2 g once or twice daily) and/or oral cefuroxime axetil (500 mg twice daily), with erythromycin or doxycycline added at the investigator’s discretion in a prospective, multicenter, randomized trial (N = 456). Clinical success rates were significantly higher in the levofloxacin-treated group (levofloxacin vs. comparator, 96% vs. 90%; 95% confidence interval [CI], −10.7 to −1.3). Two other randomized, multicenter trials comparing monotherapy with combination therapy in hospitalized CAP patients found comparable results and are described in the article by Grossman and colleagues in this supplement.

Accumulating data support the use of shorter courses of antibiotics at higher doses to increase efficacy and decrease the chance for inducing further resistance. Azithromycin, given in 3- or 5-day courses, for the treatment of nonsevere pneumonia in children was assessed in a randomized, double-blind, placebo-controlled trial (N = 2,188). Cure rates were equivalent between the groups (89.5% vs. 89.9%, P = not reported). Short-course, high-dose amoxicillin therapy has also been shown to prevent increases in carriage of penicillin-nonsusceptible *S pneumoniae* (PNSP) in children.
with respiratory tract infections. In an open-label, randomized study of 40 patients, a short course of azithromycin (5 days) was found to be as effective as a longer course of erythromycin (10 days) in the treatment of nonpneumococcal CAP (79% vs. 76%, \( P \leq 0.05 \).

Finally, a short course of telithromycin (800 mg daily for 5 or 7 days) was compared with a longer course of clarithromycin (500 mg daily for 10 days) in a study of 575 patients with CAP. Clinical cure rates were statistically equivalent in all 3 (telithromycin 5-day, telithromycin 7-day, and clarithromycin 10-day) groups (89.3%, 88.8%, and 91.8%, respectively).

Although \( S \) pneumoniae is the most common cause of CAP, atypical pathogens account for a significant proportion of the pathogens isolated from patients with this disease. Furthermore, it has been found in patients with pneumonia requiring hospitalization that using treatment regimens covering both typical and atypical pathogens results in lower mortality rates. These regimens include a nonpseudomonal third-generation cephalosporin plus a macrolide, a second-generation cephalosporin plus a macrolide, or a fluoroquinolone alone. Therefore, when choosing a treatment for CAP empirically, initial antibiotic therapy should cover both typical and atypical pathogens.

Dunbar and coworkers reported a subgroup analysis of a randomized controlled trial of levofloxacin at doses of 500 mg or 750 mg for patients with CAP. This subgroup included 149 patients diagnosed with Legionella pneumophila, \( C \) pneumoniae, or \( M \) pneumoniae, and found that levofloxacin was highly effective against atypical pathogens, with clinical success rates of 95.5% for the 750-mg group and 96.5% for the 500-mg group. In addition, a significantly greater proportion of patients treated with 750 mg of levofloxacin experienced resolution of fever by day 3 of treatment (\( P = 0.031 \)). Other agents effective against atypical pathogens are the advanced-generation macrolides such as azithromycin and clarithromycin; therefore, the ATS guidelines also recommend these drugs for outpatient treatment of CAP patients without cardiopulmonary disease. Doxycycline therapy is recommended in patients who are intolerant of macrolides.

### Therapeutic benefits

Local resistance patterns should be taken into account when evaluating the potential efficacy of antimicrobial therapy. Clinicians, however, tend to consider resistance a national issue, rather than one that affects their own practices and institutions. Although 70% of pathogens in US hospitals have developed resistance to \( \geq 1 \) antimicrobial, many clinicians do not perceive the extent of the problem in their practices. Physicians must therefore become more knowledgeable about resistance patterns in their own communities in order to help control the rise in microbial resistance.

National resistance trends vary among the common CAP pathogens. According to the 2002–2003 Tracking Resistance in the US Today (TRUST) 7 Study, \( S \) pneumoniae susceptibility was 96.1% for ceftriaxone, 93.4% for amoxicillin-clavulanate, 72.2% for azithromycin, and 99.1% for levofloxacin. In the 2003–2004 TRUST 8 data, susceptibilities were similar to these values. Susceptibilities of \( S \) pneumoniae were 96.7% for ceftriaxone, 91.7% for amoxicillin-clavulanate, and 72.2% for azithromycin.
cillin-clavulanate, 73.8% for azithromycin, and 98.7% for levofloxacin.\textsuperscript{26} Antimicrobial resistance in \textit{S pneumoniae} has been sustained over the last 2 years for some agents; azithromycin resistance, for example, was 27.6% in 2002, 27.6% in 2003, and 25.4% in 2004 (Table 2).\textsuperscript{26,27} In the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin United States (PROTEKT US) Study, the emergence and spread of antimicrobial resistance among isolates of \textit{S pneumoniae}, \textit{S pyogenes}, and \textit{H influenzae} were tracked across the country. This study found that 1% of the \textit{S pneumoniae} were resistant to levofloxacin. The \textit{H influenzae} isolates were 99.7% susceptible to the respiratory fluoroquinolones levofloxacin, moxifloxacin, and gatifloxacin compared with 96.3% for telithromycin.\textsuperscript{28}

Resistance varies considerably among geographic regions of the United States. In TRUST 7, regional \textit{S pneumoniae} azithromycin resistance rates ranged from 15.2% to 40.6%; the highest regional resistance rates for levofloxacin were 1.7%.\textsuperscript{25} TRUST 8 data show a continuation in regional variation.\textsuperscript{26}

According to TRUST 8 data, resistance to \(\beta\)-lactams and first-generation cephalosporins is high for \textit{H influenzae} and \textit{M catarrhalis} (Tables 3 and 4).\textsuperscript{26} Fluoroquinolone resistance for these microbes is low, however.\textsuperscript{26} Short-course, higher-dose therapies can help to address the growing concern of microbial resistance by reducing selection pressure on pathogens and increasing adherence.\textsuperscript{29}

These national resistance levels, as well as local resistance patterns, should be taken into account when choosing antibiotic treatment for CAP. When high levels of resistance are present, the appropriate treatment choice is the one that is effective in patients who have resistant pathogens or in those at risk for resistant pathogens. Levofloxacin was shown to be effective in the treatment of patients with CAP who were infected with macrolide-resistant \textit{S pneumoniae} in an analysis of data from 7 phase 3 and 4 clinical trials.\textsuperscript{30} The percentage of patients who achieved a clinical cure or improvement was 96.9% in patients with macrolide-resistant \textit{S pneumoniae} compared with 95.1% of the general population of patients. Results for microbiologic eradication were similar (96.9% eradication for patients with macrolide-resistant \textit{S pneumoniae} and 93.5% eradication for all patients). These data indicate that levofloxacin is an appropriate choice in the treatment of CAP when macrolide-resistant \textit{S pneumoniae} is present in the community.\textsuperscript{30}

### Table 2

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>18.4</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>27.6</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>26.0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1.6*</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.9</td>
</tr>
<tr>
<td>No. of institutions</td>
<td>260</td>
</tr>
<tr>
<td>No. of isolates</td>
<td>7,671</td>
</tr>
</tbody>
</table>

\textit{TMP-SMX} = trimethoprim/sulfamethoxazole; TRUST = Tracking Resistance in the US Today.

Data presented at the TRUST 8 Investigators meeting.\textsuperscript{26} *Ceftriaxone (nonmeningitis) National Committee for Clinical Laboratory Standards breakpoints: susceptible, \(\leq 1 \text{ mg/mL}\); intermediate, \(2-4 \text{ mg/mL}\); resistant, \(>4 \text{ mg/mL}\).\textsuperscript{27}

### Table 3

<table>
<thead>
<tr>
<th>% Resistant ((\beta)-Lactamase–positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Ampicillin</td>
</tr>
<tr>
<td>TMP-SMX</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
</tr>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Cefuroxime</td>
</tr>
<tr>
<td>Azithromycin*</td>
</tr>
<tr>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Levofloxacin*</td>
</tr>
</tbody>
</table>

\textit{NT} = not tested; \textit{TMP-SMX} = trimethoprim-sulfamethoxazole; TRUST = Tracking Resistance in the US Today.

Data presented at the TRUST 8 Investigators meeting.\textsuperscript{26} *Shown as percent nonsusceptible.
Increases in resistance are a major concern for healthcare providers. The prevalence of fluoroquinolone resistance and nonsusceptibility in *S. pneumoniae* increased 2-fold between 1999–2000 and 2001–2002 for ciprofloxacin resistance (from 1.2% to 2.7%) as well as for levofloxacin nonsusceptibility (from 0.6% to 1.3%). Although resistance to these agents has doubled, it is still extremely low. In addition, the introduction and use of more potent respiratory fluoroquinolones with high pneumococcal activity has been speculated to minimize the emergence of fluoroquinolone resistance.

Three major antibiotic-resistant pathogens include extended-spectrum β-lactamase (ESBL)—producing gram-negative bacteria, vancomycin-resistant enterococci (VRE) such as *Enterococcus faecalis*, and methicillin-resistant *S. aureus* (MRSA). The third-generation extended-spectrum cephalosporin ceftazidime has been associated with increased ESBL production in *Klebsiella* and *Enterobacter* species. Ciprofloxacin may also increase the prevalence of highly resistant VRE, and ciprofloxacin or ceftazidime use has been associated with increases in MRSA. This evidence emphasizes that use of any antibiotic may be associated with potential selection for resistance, although it has been argued that not all antibiotics select for resistance.

Identifying those patients who are more likely to have resistant pathogens can also help achieve treatment goals and reduce resistance pressure. Patient groups with increased risk for developing resistant pneumococcal infections include those with recent antibiotic treatment, malignancies, human immunodeficiency virus infection, and sickle-cell disease, or other significant comorbidities.

### Safety and tolerability

The prominent antibiotic therapies for CAP are the advanced macrolides and respiratory fluoroquinolones. The safety profiles of available agents vary, however. Fluoroquinolones have demonstrated landmark safety profiles while their concentration-dependent adverse effects differ, which may limit the clinical use of higher doses and longer duration of therapy with some drugs in this class.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of antimicrobial resistance in <em>Moraxella catarrhalis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;, µg/mL (β-Lactamase–positive)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>8</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>0.25</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.03</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.25</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>0.25</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.06</td>
</tr>
</tbody>
</table>

NT = not tested; TMP-SMX = trimethoprim-sulfamethoxazole; TRUST = Tracking Resistance in the US Today. Data presented at the TRUST 8 Investigators meeting.

The most common adverse effects with fluoroquinolones involve the gastrointestinal tract and the central nervous system, and they are usually transient and mild to moderate in severity. Exceptions include trovafloxacin, which can cause serious hepatic toxicity that has led to restrictive use in the United States, and temafloxacin and grepafloxacin, which have been withdrawn from markets worldwide.

Additionally, although short-course, higher-dose therapy for CAP has benefits, only antibiotics that are safe at standard doses and have been shown to possess favorable safety profiles at higher doses should be considered appropriate for higher-dose therapy. Levofloxacin is generally well tolerated, and common adverse effects are usually mild, with nausea and diarrhea being the most frequent side effects. Furthermore, levofloxacin exhibits comparable rates of drug-related adverse effects regardless of whether patients with CAP are treated with once-daily dosing regimens of either levofloxacin 500 mg for 10 days or 750 mg for 5 days (Table 5).

### Table 5 | Safety data for 2 levofloxacin regimens for treatment of community-acquired pneumonia (CAP)

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>Levofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg</td>
<td>750 mg</td>
</tr>
<tr>
<td>10 days</td>
<td>5 days</td>
</tr>
<tr>
<td>≥1 Treatment-emergent AE</td>
<td>59.6</td>
</tr>
<tr>
<td>≥1 Drug-related AE*</td>
<td>5.7</td>
</tr>
<tr>
<td>≥1 Serious AE†</td>
<td>14.0</td>
</tr>
<tr>
<td>Discontinuation of therapy</td>
<td>8.3</td>
</tr>
<tr>
<td>Death</td>
<td>3.4</td>
</tr>
</tbody>
</table>

AE = adverse event. Reprinted with permission from *Clin Cornerstone.*

*The most common drug-related AEs for the 500-mg group were rash, insomnia, and diarrhea; and for the 750-mg group they were nausea, rash, and aggravation of CAP symptoms.

†Worsening of CAP was the most frequently reported serious AE (3.4% for 500-mg group and 3.5% for 750-mg group).
fear—occurring with similar frequency among the agents.\textsuperscript{37} Incidence of \textit{C difficile}-associated diarrhea (CDAD) is particularly correlated with use of cefotaxime, ceftriaxone, and ceftazidime.\textsuperscript{38} In a district general hospital in the United Kingdom, ceftriaxone as a first-line therapy was associated with increased CDAD, whereas switching to levofloxacin was associated with a reduced incidence of CDAD.\textsuperscript{39} In addition to third-generation cephalosporins, use of gatifloxacin has also been associated with CDAD. A study in a long-term care facility showed CDAD rates associated with gatifloxacin were higher than for levofloxacin (34\% vs. 17\%, respectively).\textsuperscript{40} This is attributed to the broader anaerobic activity of gatifloxacin. Further information concerning safety and tolerability of antibiotic therapies is given by Grossman and colleagues.\textsuperscript{12}

**Optimal drug for optimal duration**

The CARAT criteria, as well as the World Health Organization (WHO) recommendations, emphasize the importance of choosing the optimal drug for the optimal duration to prevent the further emergence of resistant bacterial strains.\textsuperscript{41} Both scientific principles and recent clinical data indicate that the optimal dose to achieve the highest potential for efficacy is a higher-dose regimen. Data also suggest that with appropriate antibiotic selection, based on appropriate spectrum, potency, and pharmacokinetic/pharmacodynamic profile, lower respiratory tract infections in outpatients can be successfully treated in $\leq 7$ days rather than the 7 to 14 days currently recommended.\textsuperscript{29}

A shorter course of therapy may reduce the selection pressure for the treated pathogen and may also decrease the impact on endogenous flora.\textsuperscript{29} Additionally, high cure rates may be achieved when a short-course, higher-dose therapy with a potent, rapidly acting agent is used.\textsuperscript{42} Other potential benefits of a short-course, higher-dose therapy include less total drug exposure, avoidance of adverse effects, enhanced patient and healthcare worker convenience and adherence, and improved cost-effectiveness.\textsuperscript{42}

Short-course, higher-dose regimens therefore have the potential to reduce the emergence of antibacterial resistance in the pathogen as well as other commensal flora, in both the patient being treated and the wider population.\textsuperscript{42} Some studies have found reduced carriage of, or infection with, resistant organisms in patients treated with either short-course, or short-course, higher-dose regimens.\textsuperscript{15,43} Although it is not yet clear that short-course, higher-dose therapy can reduce resistance, there is ample evidence that low-dose, long-duration therapy promotes resistance. Studies indicate that a low daily dose and a long duration of treatment with an oral $\beta$-lactam contribute to selective pressure in promoting penicillin-resistant \textit{S pneumoniae} (PRSP).\textsuperscript{44} Additionally, use of $\beta$-lactams, sulfonamides, and macrolides is associated with PRSP. Both short-term and long-term $\beta$-lactam use significantly increases the risk of penicillin-resistant infection.\textsuperscript{45}

A reduced exposure to total drug amount may also increase patient tolerability and adherence.\textsuperscript{29,42} In one study, adherence was better among children who received a 3-day regimen of amoxicillin compared with those who received a 5-day regimen.\textsuperscript{29} Additionally, a review of 76 studies determined that adherence is significantly improved with once-daily dosing as compared with 3 or 4 daily doses.\textsuperscript{29} Overall, short-course therapy for CAP is more convenient for the patient, improves adherence, decreases adverse effects, and may significantly help to slow the emergence of antimicrobial resistance.\textsuperscript{29} A complete discussion of the pharmacokinetic principles behind high-dose, short-course antimicrobial treatment can be found in the accompanying article by Poole and Portugal.\textsuperscript{46}

A number of studies have demonstrated the comparable or superior effectiveness of short-course, high-dose regimens.\textsuperscript{42} Higher-dose, short courses of levofloxacin (750 mg for 5 days) have been found effective in eradicating \textit{S pneumoniae} and inducing remission.\textsuperscript{13} Increasing the dose of levofloxacin from 500 mg to 750 mg increases peak drug concentration and allows for a shorter course of treatment without diminishing therapeutic benefit. In a multicenter, randomized, double-blind investigation of 530 patients with mild-to-severe CAP, levofloxacin 750 mg daily for 5 days was compared with levofloxacin 500 mg daily for 10 days.\textsuperscript{13} In the clinically evaluable population, the clinical success rates were comparable in both groups, at 92.4\% for the 750-mg group and 91.1\% for the 500-mg group (95\% CI, 7.0 to 4.4). At the posttherapy visit, eradication rates for common pathogens were similar for both groups. In addition, at day 3, 67.4\% of patients in the 750-mg group reported resolution of fever, compared with 54.6\% of patients in the 500-mg group ($P = 0.006$).\textsuperscript{13}

The 750-mg course of levofloxacin also offers an effective tool for the management of CAP caused by atypical pathogens.\textsuperscript{21} Levofloxacin is effective against intracellular atypical agents, such as \textit{L pneumophila} and \textit{C pneumoniae}, whereas penicillin and cephalosporins are not. In addition, \textit{M pneumoniae} is not susceptible to $\beta$-lactams.\textsuperscript{20} For atypical pneumonia, macrolides, doxycycline, and fluoroquinolones are recommended.\textsuperscript{21}

**Cost-effectiveness**

Antibiotic efficacy is a prime factor in cost-effectiveness and in preventing the high costs of retreatment, particularly hospitalization. Decreased patient adherence increases costs as well, and simpler, less-frequent dosing regimens result in better compliance. For several therapeutic classes, patient adherence has been shown to decrease proportionally as the number of daily doses increases. For medications in general, adherence is significantly higher for once-daily versus 3- or 4-times daily dosing.\textsuperscript{47}

Clinical success and patient adherence factors also drive the increase in microbial resistance. Initial treatment of CAP with a therapy that is well tolerated, active against the
In addition to increasing patient adherence, evidence from clinical trials supports the use of critical pathways to improve patient outcomes and decrease costs in the treatment of CAP. The Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin (CAPITAL) study found that using critical pathways can reduce the use of institutional resources and cost without an increase in adverse outcomes. A significantly greater percentage of low-risk patients presenting to hospitals that used critical pathways were treated as outpatients without an increase in adverse clinical outcomes (Figure 1), indicating that critical pathways can be used to identify patients who can be safely treated on an outpatient basis. In addition, the levofloxacin-treated patients were more likely to receive treatment with a single class of antibiotic compared with patients treated with conventional management (64% and 27%, respectively; \( P < 0.001 \)).

### Summary

When choosing an antimicrobial, effective treatment depends on proper patient evaluation and the identification of numerous factors, such as recent antibiotic exposure, diabetes, or COPD. Although patients without these conditions may be treated effectively with a macrolide, for example, for patients who have these conditions and have used antibiotics or oral steroids within the past 3 months, a fluoroquinolone is recommended.

Fluoroquinolones meet the recommendations outlined in the CARAT criteria and in general offer the optimal drug at the optimal dosage for antibiotic treatment of patients with CAP. Higher-dose, short-course fluoroquinolone treatment may represent a significant advance in the management of CAP. Short courses of a fluoroquinolone may also decrease the emergence of resistant strains, as well as minimizing therapeutic failures and the need for retreatment.

### References

10. Fogarty C, Siami G, Kohler R, et al. Multicenter, open-label, randomized study to compare the safety and efficacy of levofloxacin versus...


Antimicrobial treatment of lower respiratory tract infections in the hospital setting

Ronald F. Grossman, MD, a John C. Rotschafer, PharmD, b James S. Tan, MD c

a University of Toronto, Toronto, Ontario, Canada; b University of Minnesota, Minneapolis, Minnesota, USA; and c Northeastern Ohio Universities College of Medicine, Akron, Ohio, USA.

KEYWORDS: Antimicrobial treatment of lower respiratory tract infections in the hospital setting

Respiratory tract infections (RTIs) that may require hospitalization include acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP), and hospital-acquired pneumonia (HAP), which includes ventilator-associated pneumonia (VAP). Healthcare-associated pneumonia (HCAP) is treated similar to HAP and may be considered with HAP. For CAP requiring hospitalization, the current guidelines for the treatments of RTIs generally recommend either a β-lactam and macrolide combination or a fluoroquinolone. The respiratory fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin, and gemifloxin) are excellent antibiotics due to high levels of susceptibility among gram-negative, gram-positive, and atypical pathogens. The fluoroquinolones are active against >98% of Streptococcus pneumoniae, including penicillin-resistant strains. Fluoroquinolones are also recommended for AECB requiring hospitalization. Evidence from clinical trials suggests that levofloxacin monotherapy is as efficacious as combination ceftriaxone-erythromycin therapy in the treatment of patients hospitalized with CAP. For early-onset HAP, VAP, and HCAP without the risk of multidrug resistance, ceftriaxone, ampicillin-sulbactam, ertapenem, or one of the fluoroquinolones is recommended. High-dose, short-course therapy regimens may offer improved treatment due to higher drug concentrations, more rapid killing, increased adherence, and the potential to reduce development of resistance. Recent studies have shown that short-course therapy with levofloxacin, azithromycin, or telithromycin in patients with CAP was effective, safe, and tolerable and may control the rate of resistance.

Lower respiratory tract infections (RTIs) are the main cause of death due to infectious disease in the United States. RTIs treated in the hospital include severe cases of acute exacerbations of chronic bronchitis (AECB) and community-acquired pneumonia (CAP) as well as hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP). Pneumonia alone is the sixth most common cause of death, with 2 to 3 million cases of CAP and 45,000 deaths occurring each year. About 300,000 cases of HAP occur annually, and HAP has an attributable mortality rate of approximately 33% to 50%. Chronic obstructive pulmonary disease (COPD), which is characterized by AECB, results in approximately 119,000 deaths per year in the United States.

Direct costs of RTIs such as AECB are estimated to cost US$1.2 billion for patients aged ≥65 years and $419 million for patients <65 years. The cost of care for CAP is estimated between $8.4 billion and $9.7 billion dollars annually. Finally, HAP results in $2 billion of direct costs annually. In total, these add up to over $12 billion annually. In 1997 the cost to US employers of patients with respira-
tory infections was $112 billion, including direct costs of medical treatment and indirect costs of time lost from work.6

The decision to admit a patient with either CAP or AECB to the hospital is based on the severity of symptoms. For patients with CAP, the American Thoracic Society (ATS) and the Texas Academy of Family Physicians recommend using the Patient Outcomes Research Team (PORT) Severity Index (PSI) as a guideline to stratify patients.7,8 The index uses demographic factors, coexisting conditions, and physician and laboratory findings to divide patients into 5 risk classes. It is recommended that patients in the fourth and fifth classes (i.e., those with the most severe illness) be hospitalized.7 ATS guidelines note that the PSI should be used in conjunction with good clinical judgment, taking into consideration risk factors for a complicated course as well as potential nonmedical reasons for admission.8 However, the PORT approach may oversimplify the process of risk stratification of individual patients even when their severity of illness is profoundly different.8 Additionally, it gives heavy emphasis on age as a variable, requiring physicians to collect more data for younger patients to categorize them in a risk group. Finally, PORT scores do not include rare clinical conditions such as severe neuromuscular disease as factors in the prediction rules, thus affecting final scores.8 PORT scores also are cumbersome to obtain and difficult to use.

The validity of the PSI system to determine treatment in outpatient care versus hospitalization was confirmed in a low-risk subset of CAP patients.9 For selected patients, outpatient care was as safe and effective as hospitalization. Further support for the use of PSI in guiding the admission decision for low risk CAP patients was seen in separate studies in hospitals in Canada and the United States, which resulted in admission of fewer low-risk patients without compromising the effectiveness of treatment or well-being of the outpatients.10,11

The decision to admit a patient with COPD who is experiencing an AECB is based on the number of symptoms and risk factors. Symptoms include shortness of breath, increased sputum production, and increased sputum purulence. Risk factors for hospitalization include percentage of predicted forced expiratory volume in 1 minute (FEV1), ischemic heart disease, and mucous hypersecretion.7 Inappropriate antibiotic therapy, or overuse and/or misuse of antibiotics, is a common occurrence that may increase a patient’s duration of stay in the hospital, and may predispose patients to increased resistance to a class of antibiotics.12,13 A study in the United States on excessive antibiotic use in acute respiratory infections involving the upper and lower respiratory tract showed that 55% of the total prescriptions in 1998 were prescribed in excess.12 Additionally, inappropriate initial antibiotic therapy may increase hospital mortality rates for patients in hospital intensive care units (ICUs). For example, a retrospective study in France for the outcomes of VAP patients between 1992 and 1997 found initial antibiotic therapy was appropriate in 49.5% of patients (N = 111). The study concluded that, in comparison with appropriate initial antibiotic treatment, inappropriate initial antibiotic treatment could increase the duration of stay and the crude hospital mortality in VAP patients for patients with equal severity of illness at the time of VAP diagnosis.13

As described below, major recommendations set forth by various healthcare groups aim at avoiding unnecessary and inappropriate therapy, particularly when selecting initial antibiotic treatment options for a patient admitted with an RTI.

The Council for Appropriate and Rational Antibiotic Therapy Criteria

A number of health organizations, including the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), are currently spearheading efforts to reduce the incidence of antibiotic resistance.14–16 The WHO emphasizes the importance of choosing the correct drug at the correct dose for the correct duration of treatment to control resistance. In today’s environment, many treatment options are available. The Council for Appropriate and Rational Antibiotic Therapy (CARAT) has defined the following 5 core criteria to assist clinicians in determining the right drug, right dose, and right duration of treatment to improve outcomes and decrease the risk of future resistance: (1) evidence-based results; (2) therapeutic benefits; (3) safety; (4) optimal drug for optimal duration; and (5) cost-effectiveness. This article discusses the application of these criteria to the management of CAP and AECB due to bacteria, or acute bacterial exacerbations of chronic bronchitis (ABECB), in the hospital setting.

Evidence-based results

Management of CAP in the hospital setting

The importance of appropriate treatment is underlined by the data: each year in the United States there are 45,000 deaths, 10 million physician visits, and 500,000 hospitalizations due to CAP. Among hospitalized patients with CAP, the average mortality is approximately 14%.1,17 However, better management may help to improve patient care.

Despite efforts to control antibiotic resistance, which is believed to be caused mainly by the overuse and misuse of antibiotics, patients with RTIs are frequently treated with antibiotics that are incorrect, suboptimal, or unwarranted.18 The CARAT guidelines recommend determining a need for antimicrobial treatment before prescribing antibiotics.

A number of established guidelines provide evidence-based recommendations for treatment (Table 1).1,8,19,20 The ATS, the British Thoracic Society (BTS), and the Infectious Diseases Society of America (IDSA) all recom-
mend that inpatients with CAP receive prompt antibiotic treatment.1,18–20 The 2003 IDSA guidelines for CAP note that initial therapy of patients within 4 hours after arrival at the hospital was associated with improved outcomes and reduced mortality in the hospital.20,21

Guidelines delineate a role for fluoroquinolones for both non-ICU and ICU patients (see Table 1), either as first-line monotherapy or as part of combination therapy.1,8,19,20 The ATS recommends respiratory fluoroquinolones, such as levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin, for their ability to cover gram-negative, gram-positive, and atypical pathogens, generally with once-daily therapy.8 These newer fluoroquinolones show greater in vitro activity against respiratory pathogens, particularly *Streptococcus pneumoniae*, regardless of susceptibility to penicillin.19 Despite >20 years of clinical use, fluoroquinolones are active against >98% of *S pneumoniae* strains in the United States, including penicillin-resistant strains.20 This may give respiratory fluoroquinolones a more prominent role in the future if bacterial resistance to penicillin and macrolides continues to increase.19 The respiratory fluoroquinolones are also active against *Haemophilus influenzae*, atypical pathogens and *Legionella* species.19

ATS guidelines also recommend starting patients on intravenous (IV) therapy but switching to oral therapy when possible. Switch therapy may be either sequential or step-down. When an agent attains the same serum levels when dosed either by IV or orally may allow for some moderately severe patients to be treated outside of the hospital and may also allow for a more rapid IV-to-oral switch and subsequent discharge.8

Treatment with a β-lactam and macrolide combination is often recommended for CAP requiring hospitalization. Generally, combination therapy requires more complicated dosing regimens, which may decrease patient compliance. Additionally, combination therapy is associated with the adverse event profiles of the individual agents, such that there is increased risk of adverse events as well as greater chances of drug-drug interactions. A meta-analysis of all prospective randomized trials compared β-lactam with β-lactam and aminoglycoside in patients with sepsis, 1200 of whom were infected with either HAP or CAP. The study found a significantly higher rate of nephrotoxicity with β-lactam and aminoglycoside combination therapy than with β-lactam monotherapy.22

In addition, there is a great deal of evidence suggesting monotherapy with a fluoroquinolone is as effective and safe as combination therapy. A randomized, multicenter, phase 4 comparative trial (N = 269) demonstrated that levofloxacin monotherapy is as efficacious as combination β-lactam and macrolide (ceftriaxone-erythromycin) therapy in the treatment of serious CAP. The results are shown in Table 2.23 In the clinically evaluable population, 89.5% of patients achieved clinical success in the levofloxacin group compared with 83.1% of patients in the comparator group (95% confidence interval [CI], –16.8 to 4.2).23

Another study that compared levofloxacin monotherapy with combination therapy was a phase 4, multicenter, open-label, randomized trial that compared levofloxacin monotherapy with azithromycin-ceftriaxone in the treatment of moderate-to-severe CAP. In the clinically evaluable population, the clinical success rate (including both cured and

### Table 1 Community-acquired pneumonia treatment guidelines for inpatients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IDSA</th>
<th>ATS</th>
<th>BTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early treatment</td>
<td>Prompt treatment; 8-hr delay associated with increased mortality</td>
<td>First dose within 8 hr of admission</td>
<td>Within 2 hr; immediate treatment if life-threatening or if admission is delayed</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>FQ preferred, or a cephalosporin-macrolide</td>
<td>IV macrolide if no risk of DRSP, gram negative, or aspiration; if risk exists, β-lactam–macrolide or FQ alone</td>
<td>β-Lactam–macrolide; FQ in patients intolerant of penicillin or macrolides; levofloxacin combined with another agent active against <em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>ICU</td>
<td>If <em>Pseudomonas</em> not an issue, β-lactam–macrolide or FQ; if <em>Pseudomonas</em> an issue, antipseudomonal agent + ciprofloxacin, or an aminoglycoside + FQ or macrolide</td>
<td>β-Lactam–macrolide or quinolone + 2 antipseudomonal in at-risk patients</td>
<td>β-Lactam–macrolide or cefuroxime, cefotaxime, or ceftriaxone, plus erythromycin or clarithromycin; alternatively, FQ with enhanced antipseudomoccal agent, e.g., benzylpenicillin (all IV)</td>
</tr>
</tbody>
</table>

ATS = American Thoracic Society; BTS = British Thoracic Society; DRSP = drug-resistant *S pneumoniae*; FQ = fluoroquinolone; ICU = intensive care unit; IDSA = Infectious Diseases Society of America; IV = intravenous.

Adapted from Clin Infect Dis,1,20 Am J Respir Crit Care Med,8 and Thorax.19

---

**Table 2**

<table>
<thead>
<tr>
<th>Treatment IDSA</th>
<th>ATS</th>
<th>BTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early treatment</td>
<td>Prompt treatment; 8-hr delay associated with increased mortality</td>
<td>First dose within 8 hr of admission</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>FQ preferred, or a cephalosporin-macrolide</td>
<td>IV macrolide if no risk of DRSP, gram negative, or aspiration; if risk exists, β-lactam–macrolide or FQ alone</td>
</tr>
<tr>
<td>ICU</td>
<td>If <em>Pseudomonas</em> not an issue, β-lactam–macrolide or FQ; if <em>Pseudomonas</em> an issue, antipseudomonal agent + ciprofloxacin, or an aminoglycoside + FQ or macrolide</td>
<td>β-Lactam–macrolide or quinolone + 2 antipseudomonal in at-risk patients</td>
</tr>
</tbody>
</table>

ATS = American Thoracic Society; BTS = British Thoracic Society; DRSP = drug-resistant *S pneumoniae*; FQ = fluoroquinolone; ICU = intensive care unit; IDSA = Infectious Diseases Society of America; IV = intravenous.

Adapted from Clin Infect Dis,1,20 Am J Respir Crit Care Med,8 and Thorax.19
improved patients) was 94.1% in the levofloxacin-treated group compared with 92.3% in the azithromycin-ceftriaxone-treated group. Microbiologic eradication rates were 89.5% in the levofloxacin-treated group and 92.3% in the azithromycin-ceftriaxone-treated group. In addition to clinical data, levofloxacin provides more pathogen coverage than either ceftriaxone or azithromycin alone, and is also indicated by the US Food and Drug Administration (FDA) for penicillin-resistant *S. pneumoniae* (PRSP); neither ceftriaxone nor azithromycin has received this indication.

A prospective, observational study of hospitalized CAP patients (*N* = 459) compared monotherapy with levofloxacin (500 mg every 24 hours) with combination therapy (ceftriaxone 2 g every 24 hours plus clarithromycin 500 mg every 12 hours). The percentage of patients who developed acute respiratory failure due to extension of pneumonia after admission was significantly lower in the levofloxacin group than in the ceftriaxone-clarithromycin group (6.0% vs. 12.4%, respectively; *P* = 0.02). Decompensation of baseline disease was seen more frequently in the ceftriaxone-clarithromycin group than in the levofloxacin group (combination therapy vs levofloxacin, 4.8% vs 3.2%; *P* = 0.038). Median total treatment duration was 10 days in the levofloxacin group and 12 days in the ceftriaxone-clarithromycin group (*P* = 0.06). No significant differences were identified in rate of pleural effusion, acute respiratory failure, heart failure, severe sepsis, or renal failure. In all, 12% of patients in the ceftriaxone-clarithromycin group died compared with 6% of patients in the levofloxacin-treated group (*P* = 0.024). The authors did not discuss cause of death, however, so differences in mortality cannot be attributed to drug treatment.

Comparisons among fluoroquinolones have also been made. Levofloxacin 500 mg qd monotherapy was compared with moxifloxacin 400 mg qd monotherapy in 2 studies. In a recent CAP study in elderly patients (≥65 years), the clinical cure rates of those treated with levofloxacin compared with patients who received moxifloxacin were equivalent (88% vs 93%, respectively; 95% CI, −1.9% to 11.9%). Another CAP study not restricted to elderly patients reported similar results, with 86% clinical success in the levofloxacin group and 74% in the moxifloxacin group.

Guidelines vary in recommending an optimal duration of treatment for CAP. ATS guidelines state that traditional treatment has been for 7 to 14 days, but recognize the lack of existing data on treatment duration, as well as new data indicating that shorter treatment can be as effective as longer treatment. In addition, the WHO has recognized the potential benefits of shorter courses of therapy, including decreasing the disruption of the normal flora, decreasing selection pressure (which favors the development of drug-resistant organisms), and encouraging patient adherence to treatment.

Several recent studies have shown that short-course therapy in patients with CAP of varying severity, including severe CAP, can be effective, safe, and tolerable, and may help control the rate of resistance. For example, in hospitalized patients, a short course of azithromycin (5 days) was found to be as effective as a longer course of erythromycin (10 days) in the treatment of nonpneumococcal CAP. In addition, a short course of telithromycin (5 or 7 days) was shown as effective as a longer course of clarithromycin (10 days) in a group that included both outpatients and inpatients.

In the treatment of mild-to-severe CAP in a population that included both hospitalized and nonhospitalized patients, 750 mg/day of levofloxacin for 5 days was as effective as 500 mg/day for 10 days in patients in PSI classes I to IV. Too few patients in PSI class V were included to generalize the results of this study to that population. The 750-mg dose increases the area under the curve (AUC)/minimum inhibitory concentration (MIC) and peak concentration (*C*<sub>max</sub>/MIC by increasing peak antibiotic concentrations, which may reduce the risk of selection of resistant organisms. The incidence of adverse events was similar for the 2 groups, indicating that the higher-dosage, shorter-duration therapy is as safe and tolerable as the lower-dosage, longer-duration therapy. Both regimens are well tolerated. The shorter course reduced total antimicrobial exposure by 25%, resolved fever significantly faster, and may reduce costs.

### Table 2 Clinical success rates by treatment group

<table>
<thead>
<tr>
<th>Population, Clinical Outcome</th>
<th>Levofoxacin Group</th>
<th>Ceftriaxone Group</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to treat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>96 (72.7)</td>
<td>88 (64.2)</td>
<td>−19.9 to 2.9</td>
</tr>
<tr>
<td>Failure</td>
<td>14 (10.6)</td>
<td>19 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Unable to evaluate</td>
<td>22 (16.7)</td>
<td>30 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>132 (100)</td>
<td>137 (100)</td>
<td></td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>85 (89.5)</td>
<td>74 (83.1)</td>
<td>−16.8 to 4.2</td>
</tr>
<tr>
<td>Failure</td>
<td>10 (10.5)</td>
<td>15 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>95 (100)</td>
<td>89 (100)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.

Reprinted with permission from *Clin Infect Dis.*

### Treatment of HAP, VAP, and HCAP

Appropriate therapy for treatment of HAP, VAP, and HCAP should follow the guidelines from the ATS as well as the principles of the CARAT criteria for the accurate use of antibiotics. Compared with patients with CAP, those with HAP are often at greater risk for colonization and infection with a wider variety of multidrug-resistant (MDR) bacterial pathogens. The major clinical strategies for HAP, VAP, and HCAP include initial management of the disease on the basis of time of onset and risk for MDR pathogens, adequate
dosing during empiric therapy for MDR pathogens, and broad-spectrum initial antibiotic therapy followed by appropriate antibiotic de-escalation to limit development of resistance. These approaches are consistent with the CARAT criteria, which support initial broad-spectrum therapy with optimal antibiotic dosage to achieve appropriate pharmacodynamic parameters. Once the pathogen is identified, therapy can be streamlined to limit collateral damage from antibiotic therapy.

Choosing the initial, appropriate IV antibiotic regimen has become more difficult due to the rapid emergence of different types of MDR pathogens such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*. Joint guidelines from ATS and IDSA for the treatment of HAP, VAP, and HCAP have been published recently. Recommendations for initial empiric treatment are summarized in Table 3, and dosing recommendations for HAP are listed in Table 4. These recommendations are consistent with the CARAT principles and should provide safe and well-tolerated regimens, prevent unnecessary prescribing of antibiotics, decrease treatment costs, and increase adherence. It is recommended that patients without MDR risk factors and early-onset HAP or VAP initially be treated with ceftiraxone, ampicillin-sulbactam, ertapenem, or one of the fluoroquinolones (moxifloxacin, ciprofloxacin, or levofloxacin), with the exception of gatifloxacin. Because the frequency of both penicillin resistance and MDR is increasing among *S pneumoniae*, levofloxacin or moxifloxacin are preferred compared with ciprofloxacin. levofloxacin may be used to treat several RTIs in which the major pathogens are gram-negative bacteria, as evidenced by several in vitro studies that demonstrate the large spectrum of gram-negative antimicrobial activity. A comparison of in vitro susceptibility of levofloxacin, ciprofloxacin, and moxifloxacin against several gram-negative clinical isolates demonstrated that susceptibility rates for ciprofloxacin and levofloxacin were >85% for *Escherichia coli*, *Enterobacter cloacae*, *Enterobacter aerogenes*, and *K pneumoniae*, and 80% for *Serratia* and *Acinetobacter* species.

Patients with late-onset HAP, VAP, or HCAP or those with known risk factors for MDR pathogens should be treated with an antipseudomonal cephalosporin (cefepime or ceftazidime), an antipseudomonal carbapenem (imipenem or meropenem), or a piperacillin-tazobactam. An antipseudomonal fluoroquinolone or an aminoglycoside should also be given. Linezolid or vancomycin should be given if there are risk factors for methicillin-resistant *S aureus* (MRSA) present, including a high local incidence of MRSA. Levofloxacin and ciprofloxacin are considered to have comparable antipseudomonal activity on the basis of in vitro activity and therefore either may be used as an antipseudomonal fluoroquinolone.

### Table 3: American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) treatment guidelines for initial empiric treatment of hospital-acquired pneumonia

<table>
<thead>
<tr>
<th>MDR = multidrug resistant. Adapted from Am J Respir Crit Care Med.</th>
<th>Table 3: American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) treatment guidelines for initial empiric treatment of hospital-acquired pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-Onset with No Known Risk Factors for MDR Pathogens</td>
<td>Late-Onset or Risk Factors for MDR Pathogens Present</td>
</tr>
<tr>
<td>• Third-generation cephalosporin — Ceftriaxone</td>
<td>• Antipseudomonal cephalosporin — Cefepime, ceftazidime</td>
</tr>
<tr>
<td>• Extended-spectrum fluoroquinolone — Levofoxacin, moxifloxacin, ciprofloxacin*</td>
<td>• Antipseudomonal carbapenem — Imipenem, meropenem</td>
</tr>
<tr>
<td>• Amino-penicillin — Ampicillin-sulbactam</td>
<td>• Antipseudomonal penicillin — Piperacillin-tazobactam</td>
</tr>
<tr>
<td>• Narrow-spectrum carbapenem — Ertapenem</td>
<td>• Antipseudomonal fluoroquinolone — Ciprofloxacin or levofloxacin</td>
</tr>
<tr>
<td>• Aminoglycoside — Amikacin, gentamicin, tobramycin</td>
<td><strong>Antipseudomonal quinolones</strong></td>
</tr>
<tr>
<td></td>
<td>Levofloxacin 750 mg every day</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin 400 mg every 8 hr</td>
</tr>
<tr>
<td></td>
<td>Vancomycin 15 mg/kg every 12 hr‡</td>
</tr>
<tr>
<td></td>
<td>Linezolid 600 mg every 12 hr</td>
</tr>
</tbody>
</table>

*The frequency of penicillin-resistant *Streptococcus pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin.

### Table 4: American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) treatment guidelines for initial empiric treatment of hospital-acquired pneumonia

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipseudomonal cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>1–2 g every 8–12 hr</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2 g every 8 hr</td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>500 mg every 6 hr or 1 g every 8 hr</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g every 8 hr</td>
</tr>
<tr>
<td>β-Lactam/β-lactamase inhibitor</td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>4.5 g every 6 hr</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7 mg/kg per day†</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>7 mg/kg per day†</td>
</tr>
<tr>
<td>Amikacin</td>
<td>20 mg/kg per day†</td>
</tr>
<tr>
<td>Antipseudomonal quinolones</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750 mg every day</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg every 8 hr</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg every 12 hr‡</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg every 12 hr</td>
</tr>
</tbody>
</table>

*Dosages are based on normal renal and hepatic function. †Trough levels for gentamicin and tobramycin should be <1 μg/mL; for amikacin they should be <4–5 μg/mL. ‡Trough levels for vancomycin should be 15–20 μg/mL.
The efficacy of the fluoroquinolones for the treatment of nosocomial pneumonia is comparable to antibiotics that have been more commonly used. In a clinical trial including 438 adult patients with nosocomial pneumonia, 220 patients were treated with levofloxacin 750 mg qd IV and then orally for 7 to 15 days, and 218 were treated with imipenem-cilastatin 500 to 1,000 mg IV every 6 to 8 hours, followed by oral ciprofloxacin 750 mg every 12 hours for 7 to 15 days. Patients with documented or suspected *P aeruginosa* or MRSA also received adjunctive therapy as required by the study protocol. Clinical success was comparable in patients evaluable for microbiologic efficacy (58.1% vs. 60.6%), as was eradication (66.7% vs. 60.6%). In the subgroup of patients with VAP, 111 of whom were treated with levofloxacin and 111 with imipenem-cilastatin, the clinical success rates were 58.6% and 63.1%, respectively. Microbiologic success and 28-day mortality rates were also comparable. Together, these studies indicate that levofloxacin is as effective and well tolerated as imipenem-cilastatin in patients with HAP.

It should be noted that nosocomial pneumonia therapy in the ICU often involves excessive antibiotic use, mainly due to the associated high mortality. An operational approach to reducing the amount and duration of antibiotic use in the ICU is reevaluation of patients after initiation of therapy, using an operational criterion such as the clinical pulmonary infection score (CPIS). Reevaluation with the CPIS has been shown to successfully identify patients for whom short-course therapy would be appropriate. This resulted in shorter durations of antibiotic treatment and significantly reduced costs of treatment.

Management of severe ABECB associated with COPD in the hospital setting

Severe exacerbations of COPD generally require hospitalization. Risk factors for hospitalization include ischemic heart disease, other cardiopulmonary disease, >3 COPD admissions in the past year, and poor underlying lung function (indicated by FEV1 percent predicted). In addition, patients with significant compromise of lung function may develop respiratory failure as a consequence of an acute exacerbation, and up to 60% of these patients will require mechanical ventilation. Hospital mortality rates from severe AECB range from 10% to 30% for patients with significant compromise of lung function.

In those patients most likely to be hospitalized, current guidelines recommend treatment with medications such as fluoroquinolones to provide coverage for resistant organisms. In patients with FEV1 <35% of predicted, treatment should be targeted to the identified pathogen. *P aeruginosa* and *Enterobacteriaceae* species are common, so the agent chosen should have activity against these pathogens.

**Therapeutic benefits**

Susceptibility patterns can be used as guidelines to minimize the chances of clinical failure. In vitro resistance of the pathogen has been shown to correlate with clinical failure. Therefore, if a substantial percentage of patients in a particular geographic area demonstrate resistance to a particular class of antibiotics, a different class of drug should be considered in that area.

**Therapeutic benefits in the treatment of CAP**

In hospitalized patients, *S pneumoniae* is the most common pathogen responsible for CAP, occurring in up to 60% of episodes of culture-positive pneumonias. Other likely pathogens are *Haemophilus influenzae*, *S aureus*, enteric gram-negatives, *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and viruses. *P aeruginosa* has been recovered in some patients with severe CAP. In 20% to 70% of cases, however, no etiologic agent is identified.

A goal of the CARAT criteria is to encourage use of the optimal drug for the optimal duration in order to improve patient outcomes and reduce the incidence of resistance. Antimicrobial resistance is a global problem resulting in high hospitalization rates, mortality, and costs. According to data gathered by the Tracking Resistance in the US Today (TRUST) program, a comprehensive surveillance of the resistance patterns of *S pneumoniae*, *H influenzae*, and *M catarrhalis*, resistance of *S pneumoniae* to penicillin and macrolides is high in the United States. In other parts of the world, such as in France, Spain, and several Asian countries, the resistance among clinical *S pneumoniae* isolates is even higher. The Asian Network for Surveillance of Resistant Pathogens (ANSORP) study found very high erythromycin resistance among *S pneumoniae* isolates in France and Spain (58% and 57%, respectively), whereas in many Asian countries >70% of isolates were erythromycin resistant. Fluoroquinolones, however, have the lowest resistance rates of all commonly used respiratory antibiotics. A study of resistance in *S pneumoniae* found that 99% of isolates remain susceptible to fluoroquinolones, whereas resistance is >20% for macrolides and >10% for all other agents tested except vancomycin and ceftiraxone.

In an investigation of RTI isolates of *S pneumoniae*, penicillin-intermediate and penicillin-resistant rates were 15% and 6%, respectively. Nonsusceptibility rates were 11% for tetracycline, 8% to 9% for macrolides, and only 0.3% for fluoroquinolones.

These data emphasize regional differences in antimicrobial resistance. Local resistance patterns should be used as guidelines to minimize the chances of clinical failure, as clinical failure is a major risk factor for increases in resistance.
and levofloxacin are active against the QTc interval to varying degrees. Moxifloxacin and general fluoroquinolones are associated with prolongation of the QTc interval and should be avoided in patients receiving class IA or class III antiarrhythmic agents.55 Finally, telithromycin, similar to the macrolides from which it is derived, also has been shown to cause prolonged QTc intervals in some patients.56

Safety and tolerability of therapies

Safety and tolerability vary among agents. Gatifloxacin and moxifloxacin, for example, have been linked to problems with glucose hemostasis in patients with diabetes.52,53 Several fluoroquinolones are associated with prolongation of the QTc interval and should be avoided in patients receiving class IA or class III antiarrhythmic agents.52–54 The package insert for gatifloxacin warns that it should also be avoided in patients with uncorrected hypokalemia.52 Gemifloxacin may also prolong the QTc interval in some patients and should be avoided in individuals with uncorrected electrolyte disorders and those receiving class IA or class III antiarrhythmic agents.55 Finally, telithromycin, similar to the macrolides from which it is derived, also has been shown to cause prolonged QTc intervals in some patients.56

The safety of newer agents is an unknown. In fact, 8% of all newly approved drugs received ≥1 black-box warnings, a marker of serious adverse reactions, from 1975 to 2000.57 In the same period, another 3% were removed from the market.57 It is known that telithromycin, for example, can cause visual disturbances, severe in some cases, and interacts with certain statins, including simvastatin, lovastatin, and atorvastatin. Therapy with these statins should be stopped during the course of treatment with telithromycin.56,58 Gemifloxacin has been associated with a rash that is most common in female patients aged <40 years old.53,54 The true presence or incidence of other adverse events, especially those that are rare, will not be known until these agents have been on the market for some time.

In recent years, some agents with a long history of use have shown severe drug–drug interactions. Erythromycin and the coadministration of strong inhibitors of CYP3A enzyme such as nitroimidazole antifungal agents, diltiazem, verapamil, or troleandomycin increase the risk of sudden death from cardiac causes and therefore should be avoided in concurrent use in clinical practice.59 Case studies with clarithromycin also deserve attention and should be judged critically for select patient groups. In patients with type 2 diabetes taking sulfonylurea medications, clarithromycin coadministration may lead to severe hypoglycemia.60 Additionally, clarithromycin should be used with caution in patients stabilized on digoxin therapy because of a significant risk of bradycardia resulting from digoxin toxicity.61,62

These safety issues are important when determining the potential of an antimicrobial for higher-dose, short-course therapy. For example, gatifloxacin should probably not be used for higher-dose therapy due to its concentration-dependent effects on glucose homeostasis, and high-dose therapy with moxifloxacin is also not recommended due to its dose-dependent effects on the QTc interval.53 Levofloxacin and ciprofloxacin, however, have comparable safety profiles at higher and lower doses and are therefore good candidates for higher-dose, short-course therapy.53

### Table 5 Proposed classification of patients with acute bacterial exacerbations of chronic bronchitis (ABECB)

<table>
<thead>
<tr>
<th>Classification of ABECB</th>
<th>Clinical Status</th>
<th>Pathogens</th>
</tr>
</thead>
</table>
| Mild to moderate        | Simple chronic bronchitis     | *Haemophilus influenzae*  
|                         |                               | *Moraxella catarrhalis*  
|                         |                               | *Streptococcus pneumoniae* (possible β-lactam resistance)  
| Moderate                | Complicated chronic bronchitis| *Haemophilus influenzae*  
|                         |                               | *Moraxella catarrhalis*  
|                         |                               | *Streptococcus pneumoniae* (resistance to β-lactam common)  
| Severe                  | Chronic bronchial infection   | *Enterobacteriaceae*  
|                         |                               | *Haemophilus influenzae*  
|                         |                               | *Moraxella catarrhalis*  
|                         |                               | *Streptococcus pneumoniae*  

Adapted with permission from Chest.42,50
The optimal drug for the optimal duration

Clinical evidence increasingly supports the idea that optimal antibiotic therapy may consist of higher doses for shorter durations of treatment. When the initial antibiotic therapy is appropriate, there is evidence to support the contention that clinical effectiveness of short-term antibacterial therapy is comparable to a longer-term therapy and may provide the advantage of reduction in emergence of bacterial resistance. The optimal duration of treatment for ICU patients with VAP was examined in a large randomized double-blind trial comparing 8-day and 15-day antibiotic therapy. ATS guidelines were followed, with initial empirical combination therapy consisting of an aminoglycoside or a fluoroquinolone and a broad-spectrum β-lactam, followed by narrow-spectrum therapy based on laboratory results. Patients in the 8-day group consumed less antibiotic compared with the 15-day group, but did not exhibit higher mortality than the 15-day group (18.8% vs. 17.2%, respectively [1.6% difference]; 90% CI, −3.7% to 6.9%). Further, no increases in pulmonary infection-recurrence were found in the 8-day group, demonstrating no added benefit of prolonged 15-day treatment as well as noninferiority of 8-day treatment.

Clinical evidence also supports the idea that the optimal duration of therapy is one that is short term at high doses. These regimens may reduce the risk of resistance by providing faster, more complete bacterial killing while providing the added benefits of improving tolerability and patient adherence. Conversely, long-term, low-dose antibiotic treatment may increase resistance.

The pharmacodynamic and pharmacokinetic properties of fluoroquinolones support high-dose, short-course therapy regimens. Fluoroquinolones exhibit concentration-dependent killing; therefore, higher concentrations in key tissue spaces should enhance efficacy. Higher Cmax and AUC/MIC values with higher doses lead to increased bactericidal activity, and eradication of difficult pathogens. A full discussion is presented elsewhere in this supplement by Poole and colleagues and Martinez and associates.

Cost-effective choices for treating community-acquired pneumonia

Cost-effectiveness is the final CARAT criterion in choosing optimal therapy. Some factors that affect cost-effectiveness are treatment failures, patient adherence, efficacy, duration of therapy, hospital versus outpatient treatment, and, for patients treated in the hospital, length of stay. Acquisition costs for antibiotics constitute almost 6% of the total cost of treatment per patient.

The largest treatment cost is treatment failure, which incurs both the cost of the failed treatment and the cost of retreatment. Agents that maximize the success of first-line therapy reduce costs by decreasing the high costs of treatment failure, illustrating the need to ensure that the first treatment is effective.

In the hospital, the timing of step-down therapy from intravenous to oral treatment is often dependent on clinical signs and symptoms, and a faster switch can facilitate the change to outpatient treatment. Therapy with higher-doses can result in faster symptom resolution. For example, in the treatment of mild to severe CAP, administration of 750-mg levofloxacin (once daily for 5 days IV or orally) resulted in resolution of fever on day 3 in 67.4% of patients compared with 54.6%, in patients treated with 500-mg levofloxacin (once daily for 10 days IV or orally) (P = 0.006 by 2-sample McNemar test). Therefore, in patients admitted with severe CAP, faster symptom resolution may allow for early discharge and shortened hospital stay.

Antimicrobial agents with both intravenous and oral formulations can also facilitate step-down therapy. Agents with high bioavailability that achieve similar serum levels with intravenous or oral therapy, including levofloxacin, moxifloxacin, and gatifloxacin, may allow some patients who are normally hospitalized to be treated on an outpatient basis, and also may allow earlier discharge of hospitalized patients due to a faster switch from IV to oral treatment.

Implementing a critical pathway that provides specific criteria for admission, as well as the implementation of step-down therapy, has been associated with more low-risk patients being appropriately treated on an outpatient basis, as well as a reduction in length of stay for hospitalized patients. Both of these outcomes would be expected to produce significant cost savings. Another method of reducing the cost of treating hospitalized patients may be for hospital formularies to choose a single fluoroquinolone. At the University of Kentucky Hospital, levofloxacin was chosen over ciprofloxacin and gatifloxacin as the sole fluoroquinolone for the drug formulary. The change saved the hospital $100,000 in the first 12 months.

Summary

Higher-dose, short-course regimens provide additional benefits, including faster symptom resolution with no compromise of safety. Short-course, higher-dose therapy allows antimicrobial agents to achieve higher Cmax levels, leading to more rapid and complete bacterial killing. Furthermore, patients are exposed to less total antibiotic, which, in combination with more rapid and complete killing, can potentially prevent increases in resistance. Finally, shorter courses are likely to result in better patient adherence, reducing treatment failures. Short-course, higher-dose therapy fulfills WHO recommendations and is in accordance with the CARAT criteria.

Evidence from clinical trials of levofloxacin indicates that fluoroquinolone monotherapy provides clinical efficacy for hospitalized CAP, and supports the use of high-dose levofloxacin (750 mg) for nosocomial pneumonia. Current ATS/IDSA guidelines for the treatment of HAP recommend levofloxacin, moxifloxacin, or ciprofloxacin for early-onset
HAP and levofloxacin or ciprofloxacin for late-onset HAP. Therefore, levofloxacin and ciprofloxacin are the only fluoroquinolones recommended for patients with or without risk factors for MDR pathogens, and for both early- and late-onset HAP. Of the 2 drugs, levofloxacin is preferred to ciprofloxacin for patients with early-onset HAP.

References


Appropriate outpatient treatment of acute bacterial exacerbations of chronic bronchitis

Fernando J. Martinez, MD, a Antonio Anzueto, MD b

aUniversity of Michigan Health System; and the
bUniversity of Texas Health Science Center, San Antonio, Texas, USA.

KEYWORDS:
Acute exacerbations of chronic bronchitis; Antibiotics; Chronic obstructive pulmonary disease; Fluoroquinolones; Resistance; Short-course therapy

Acute exacerbations of chronic bronchitis (AECB), which are characteristic of chronic obstructive pulmonary disease (COPD), contribute to morbidity and decreased quality of life for patients with COPD. A significant proportion of these exacerbations are due to bacterial infections. The Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria provide guidance for choosing the optimal drug at its optimal dose and duration for antimicrobial treatment of AECB due to bacterial infection. Evidence-based guidelines recommend stratifying patients according to risk factors to improve selection of targeted antimicrobial therapy. With increasing rates of resistance to some antimicrobials, resistance is also an important consideration for reducing treatment failures and decreasing the need for further pharmacologic treatment. Fluoroquinolones are recommended as first-line therapy for patients with chronic bronchitis who have risk factors; gatifloxacin, gemifloxacin, and levofloxacin are highly active against commonly encountered pathogens. Safety profiles are an important consideration because adverse events and poor tolerability can reduce patient adherence rates, which in turn can lead to poorer outcomes. Safety profiles also become an important consideration as shorter-course, higher-dose therapies become more prevalent. First-line therapy with a well-tolerated antibiotic that is active against the predominant pathogens, combined with low resistance rates and a convenient once-a-day dosing regimen, may reduce overall costs. Fluoroquinolones exhibit low resistance, good activity levels, and high respiratory penetration, and they are particularly well suited for shorter-course, higher-dose regimens in selected patients. Shorter-course, higher-dose regimens, in turn, may be more effective, cost-efficient, and appropriate for controlling the rise of resistance than standard regimens.

© 2005 Elsevier Inc. All rights reserved.

Chronic obstructive pulmonary disease (COPD) is a disabling, preventable, and treatable disease state characterized by airflow limitation that is not fully reversible. COPD is also characterized by episodes of acute exacerbations of chronic bronchitis (AECB). These intermittent episodes contribute to morbidity and decreased quality of life and lead to approximately 14 million physician visits per year in the United States. Estimates for the cost of AECB in the United States range from $200 million each year to $1.2 billion for patients aged ≥65 years and $419 million for patients <65 years.

The clinical definition of AECB is an acute change, beyond day-to-day variability, in a patient’s baseline dyspnea, cough, and/or sputum sufficient to warrant a change in therapy. An operational classification of severity has been suggested, which denotes severity as ambulatory (level I), requiring hospitalization (level II), or acute respiratory failure (level III). Respiratory symptoms of AECB include...
increases in sputum production, sputum purulence, dyspnea, wheeze, cough, and fluid retention. Systemic symptoms include increased body temperature and heart rate as well as impaired mental status. Cardiopulmonary disease, ischemic heart disease, chronic malnutrition, and long duration of COPD are some of the factors that increase the risk of treatment failure or the need for hospitalization when associated with AECB.

**Etiology**

Risk factors for exacerbation include an infectious process (viral, bacterial, or atypical pathogen), environmental conditions, air pollution exposure, lack of adherence to long-term oxygen therapy, and failure to participate in pulmonary rehabilitation. Infection of the lower respiratory tract has been suggested to account for up to 80% of AECB episodes. There are 3 classes of pathogens that are commonly implicated in exacerbations: (1) Respiratory viruses, with or without a superimposed bacterial infection, are associated with 30% of cases. Significant viral pathogens include influenza, parainfluenza, and rhinoviruses. (2) Atypical bacteria, mostly *Chlamydia pneumoniae*, are implicated in <10% of cases. (3) Aerobic gram-positive and gram-negative bacteria occur in approximately 40% to 60% of cases. New sampling techniques, including protected specimen sampling, have found *Pseudomonas aeruginosa* and other gram-negative bacilli in a high percentage of patients—28% in 1 study. Studies using these techniques also support a pathogenic role of bacteria in a proportion of AECB cases. AECB that are due to bacterial infection are known as acute bacterial exacerbations of chronic bronchitis (ABECB).

**Application of the Council for Appropriate and Rational Antibiotic Therapy criteria**

Antibiotic therapy has been shown to be beneficial in patients with AECB, producing significantly earlier resolution of symptoms. Determining the optimal antibiotic therapy is the primary goal of the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria. Applying these criteria to the treatment of mild ABECB can help improve outcomes, prevent treatment failures, reduce healthcare costs, and decrease the spread of resistance.

**Evidence-based therapy**

AECB have negative effects on the health status of patients, and the impact is likely to increase with more frequent episodes. COPD is characterized by an accelerated decline in lung function as well as periods of acute exacerbation. The frequency of acute exacerbations has been demonstrated to have a significant impact in the decline of lung function. The Lung Health Study (LHS) data showed that smokers with frequent self-reported lower respiratory tract illnesses resulting in physician visits had significant increases in the rate of decline of forced expiratory volume in 1 second (FEV₁). Similarly, Donaldson and colleagues reported that patients with frequent exacerbations had a significantly faster decline in FEV₁ (∼40.1 mL/year; n = 16) and in peak expiratory flow (PEF) (∼2.9 L/min per year; n = 46) compared with infrequent exacerbators, in whom FEV₁ changed by ∼32.1 mL/year (n = 16) and PEF by ∼0.7 L/min per year (n = 63). Patients with frequent exacerbations also had a greater decline in FEV₁ if allowance was made for smoking status. This study has shown that exacerbation frequency is an important determinant of decline in lung function in COPD. Strategies for preventing COPD exacerbations may have an important impact on the natural course of this disease and on the morbidity and mortality of these patients.

Treatment for AECB is intended to provide symptomatic relief and prevent loss of respiratory function. Reducing the severity, duration, and number of AECB episodes is a primary goal of antibiotic therapy. Optimal treatment should lead to rapid resolution of symptoms, eradication of the causative pathogen, and a decreased likelihood of recurrence.

The CARAT criteria recommend that antibiotic treatment choices be supported with strong clinical evidence. The strongest evidence comes from randomized, double-blind, controlled multicenter trials. Clinical guidelines synthesize clinical trial data and provide useful, evidence-based treatment recommendations.

Guidelines for the treatment of AECB recommend stratifying patients according to risk factors. The aim of this stratification is to reduce treatment failure and increase the disease-free interval by identifying patients’ various risk factors, including an increased risk of infection with organisms not covered by standard antibiotic regimens. Two recent studies have confirmed a differential response between antimicrobial classes in impacting disease-free interval, whereas 1 study has not supported this concept. The differences between the studies may relate to differences in baseline characteristics between the study groups.

Stratification of patients with ABECB into risk categories allows physicians to identify patients at risk of treatment failure and can improve selection of targeted antimicrobial therapy. Such individualization of treatment can lead to improved outcomes. Because the spectrum of underlying disease is broad and the causes of bronchitis are diverse, the optimal initial therapy may differ among patient groups and by region (depending on local resistance patterns). The most effective treatment may include a broad-spectrum antibiotic.

Because there is no rapid, reliable way to identify the pathogen, physicians must rely on clinical judgment and epidemiologic factors to predict the most likely cause. For example, under the current recommendations, macrolides are recommended as a first-line treatment in AECB patients...
with chronic bronchitis without risk factors (Table 1). Risk factors include FEV₁ <50% of predicted, >4 exacerbations per year, and comorbid conditions such as cardiac disease. A number of guidelines and clinical studies support the use of fluoroquinolones for AECB treatment in some patients owing to low rates of resistance to fluoroquinolones or because of their broad spectrum of coverage. Furthermore, some clinical trial data have shown increases in the disease-free interval and faster resolution of symptoms with fluoroquinolone treatment. Fluoroquinolones exhibit low resistance, good activity levels, and high respiratory penetration. In addition, fluoroquinolones are particularly well suited for shorter courses of therapy at higher doses, because they are concentration-dependent agents. In contrast, β-lactams exhibit time-dependent killing, and their efficacy depends on multiple doses. The Canadian Thoracic Society (CTS) and the Canadian Infectious Disease Society (CIDS) guidelines recommend fluoroquinolones as a potential first-line therapy for patients with AECB who have chronic bronchitis and who also have risk factors (Table 1).

According to CTS/CIDS guidelines, early studies on antibiotic effectiveness for ABECB were inconclusive, but more recent, well-designed studies conclude that antibiotic therapy is effective, particularly within a patient risk-stratification framework. The guidelines state that the use of antibiotics is associated with improved clinical outcomes and hastened recovery, both clinical and physiologic. Further, treatment directed toward resistant pathogens with potent antimicrobial drugs, using patient stratification, may improve clinical outcomes and lower costs. The evidence suggests that fluoroquinolones are recommended for CTS/CIDS group II patients, who are defined by poor underlying lung function (≤50% FEV₁) or moderate impairment (50% to 60% FEV₁) with significant comorbidity and/or ≥4 exacerbations per year.

In addition to patient symptoms and risk factors, previous antibiotic use should be considered when choosing antimicrobial therapy. Patients who have been exposed to a particular class of antibiotics are more likely to have pathogens resistant to that class, and they may be better treated with alternative agents. CTS/CIDS guidelines for

**Table 1** Initial empiric therapy in outpatients with acute bacterial exacerbations of chronic bronchitis

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Basic Clinical State</th>
<th>Symptoms and Risk Factors</th>
<th>Probable Pathogens</th>
<th>First Choice</th>
<th>Alternatives for Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Acute tracheobronchitis</td>
<td>Cough and sputum without previous pulmonary disease</td>
<td>Usually viral</td>
<td>None unless symptoms persist for &gt;10–14 days</td>
<td>Macrolide or tetracycline</td>
</tr>
<tr>
<td>I</td>
<td>Chronic bronchitis without risk factors (simple)</td>
<td>Increased cough and sputum, sputum purulence, and increased dyspnea</td>
<td><em>Haemophilus influenzae</em>, <em>Haemophilus spp.</em> Moraxella catarrhalis, Streptococcus pneumoniae</td>
<td>2nd-generation macrolide, 2nd or 3rd-generation cephalosporin, amoxicillin, doxycycline, TMP-SMX</td>
<td>Fluoroquinolone, β-lactam/β-lactamase inhibitor</td>
</tr>
<tr>
<td>II</td>
<td>Chronic bronchitis with risk factors (complicated)</td>
<td>As in group I plus ≥1 of the following: ● FEV₁ &lt;50% predicted ● &gt;4 exacerbations/yr ● Cardiac disease ● Use of home oxygen ● Chronic oral steroid use ● Antibiotic use in the past 3 mo</td>
<td>As in group I plus <em>Klebsiella</em> spp + other gram-negative pathogens Increased probability of β-lactam resistance</td>
<td>Fluoroquinolone or β-lactam/β-lactamase inhibitor</td>
<td>May require parenteral therapy Consider referral to a specialist or hospital</td>
</tr>
<tr>
<td>III</td>
<td>Chronic supplicative bronchitis</td>
<td>As in group II with constant purulent sputum ● Some have bronchiectasis ● FEV₁ &lt;35% predicted ● Multiple risk factors (e.g., frequent exacerbations and FEV₁ &lt;50% predicted)</td>
<td>As in group II plus <em>Pseudomonas aeruginosa</em> and multiresistant Enterobacteriaceae</td>
<td>Ambulatory patients: tailor treatment to airway pathogen <em>P. aeruginosa</em> common (ciprofloxacin) Hospitalized patients: parenteral therapy usually required</td>
<td>—</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in 1 second; TMP-SMX = trimethoprim-sulfamethoxazole. Reproduced with permission from *Can Respir J.*
Antimicrobial resistance is a potential threat to effective treatment of AECB. In the CARAT criteria for choosing a therapeutic agent, resistance is an important consideration for reducing treatment failures and decreasing the need for further pharmacologic treatment. Unfortunately, clinicians are more likely to perceive resistance as a national issue rather than one that affects their individual practices or institutions. Physicians should become more knowledgeable about resistance overall as well as resistance patterns in their own communities. The process of choosing an antibiotic for ABECB should include knowledge of the frequencies of pathogen resistance.

Choosing the wrong antibiotic increases the chances of treatment failure and the risk of future resistance. The published relapse rates for ABECB patients range from 17% to 32%, and some research suggests that a major risk factor for relapse is lack of appropriate antibiotic therapy. In this particular study, patients treated with amoxicillin experienced a 54% relapse rate compared with only a 13% rate for patients treated with other antibiotics.

Resistance rates among community-acquired respiratory pathogens in the United States have risen steadily overall. Surveillance studies indicate that resistance to penicillin and macrolides among Streptococcus pneumoniae exceeds that seen in previous studies (Table 2). Approximately 10% of pneumococci are highly resistant to both penicillin and macrolides. Patterns vary among geographic regions in the United States, with S pneumoniae resistance to azithromycin ranging from 15.2% in New England to 40.6% in the South Central region. In general, high levels of resistance are seen across geographic regions for penicillin and macrolides. A more in-depth discussion of resistance rates can be found in the article by Segreti and colleagues elsewhere in this supplement.

Fluoroquinolones tend to have low rates of antimicrobial resistance. Gatifloxacin and levofloxacin are highly effective against S pneumoniae, regardless of geographic region. Furthermore, surveillance of ABECB pathogen susceptibility patterns shows that fluoroquinolones are highly active against cultured isolates, with 99% of all S pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis strains susceptible to gatifloxacin and levofloxacin. It is notable that quinolone resistance has been associated with exposure to a quinolone in the previous 3 months, current residence in a nursing home, and nosocomial acquisition of pneumococcal infection.

H influenzae resistance rates show a stable trend over the last 10 years, with 30% showing resistance to amoxicillin. β-lactamase production is evident in 40% of H influenzae and >95% of M catarrhalis isolates. In the United States, H influenzae resistance to amoxicillin ranges from 19% in New England to 31% in the East South Central, Middle Atlantic, and South Atlantic regions. Gatifloxacin and levofloxacin, however, are highly active against H influenzae, regardless of geographic region. Importantly, rare cases of quinolone-resistant H influenzae isolates have been reported from a long-term care facility.

M catarrhalis resistance rates for amoxicillin appear to have stabilized at 92%. However, M catarrhalis shows virtually no resistance to levofloxacin or amoxicillin-clavulanate. Gatifloxacin and levofloxacin are both highly effective against M catarrhalis, regardless of geographic region.

### Table 2: Respiratory Surveillance Program, 1999–2000: Resistance of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis to commonly used agents in acute exacerbation of chronic bronchitis

<table>
<thead>
<tr>
<th>Organism (No. Tested) by Antimicrobial Agent</th>
<th>% Susceptible/Resistant*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S pneumoniae (881)</em></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>64/15†</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>95/3</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>64/35</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>87/13</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>99/1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>99/1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>76/24</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>63/28</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100‡</td>
</tr>
<tr>
<td><em>H influenzae (1,863)</em></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>71/26</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>100/0</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>97/1</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>99†</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>63/7</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>100†</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>100‡</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>100‡</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>99/1</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>83/14</td>
</tr>
<tr>
<td><em>M catarrhalis (1,981)</em></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>7/93</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>100/0</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>99/0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>85/2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>100/0</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>100/0</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>100/0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>99/1</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>83/10</td>
</tr>
</tbody>
</table>

†Second percentage is for high-level resistance (≥2 μg/mL). When percentages do not total 100%, strains with intermediate resistance account for the difference.

 TMP-SMX = trimethoprim-sulfamethoxazole.

Reprinted with permission from Am J Med. *Percentages are rounded to the nearest whole number.

Interpretive criteria are those published for gram-negative bacilli, such as the Enterobacteriaceae.

and >95% of *M catarrhalis* isolates. In the United States, *H influenzae* resistance to amoxicillin ranges from 19% in New England to 31% in the East South Central, Middle Atlantic, and South Atlantic regions. Gatifloxacin and levofloxacin, however, are highly active against *H influenzae*, regardless of geographic region. Importantly, rare cases of quinolone-resistant *H influenzae* isolates have been reported from a long-term care facility.

*M catarrhalis* resistance rates for amoxicillin appear to have stabilized at 92%. However, *M catarrhalis* shows virtually no resistance to levofloxacin or amoxicillin-clavulanate. Gatifloxacin and levofloxacin are both highly effective against *M catarrhalis*, regardless of geographic region.
Other studies show that β-lactamase–mediated amoxicillin resistance is found in 20% to 40% of *H influenzae* strains and in almost 100% of *M catarrhalis* strains in North America and Europe.3

**Safety**

The published literature indicates that antimicrobials are not equal in their safety profiles. Adverse events and poor tolerability can reduce patient adherence rates, which in turn can lead to poorer outcomes. Safety concerns may also limit the number of antibiotics that are appropriate for high-dose, short-course therapy. Further details concerning the safety and tolerability of antimicrobial treatments for ABECB, including glucose homeostasis and QTc prolongation issues, are available in the articles by Grossman and associates33 and Segreti and colleagues31 in this supplement.

**Optimal drug for optimal duration**

The CARAT criteria call for use of the optimal drug for the optimal duration. Choosing the right therapy for the appropriate duration as a first treatment choice is crucial for decreasing treatment failures, which are costly and can increase the incidence of resistance.

In appropriate patients, short-course, higher-dose therapy for ABECB may be more effective, cost-efficient, and appropriate for controlling the rise of resistance. Longer exposure to less potent agents increases selection for resistance among bacteria; therefore, shorter-term therapies may reduce the rise of resistance among common respiratory pathogens. Long-term use is also associated with poorer patient adherence and a higher risk of adverse events.34 Higher-dose, short-course regimens, on the other hand, may improve convenience and increase cost-effectiveness.35

Pharmacokinetic/pharmacodynamic (PK/PD) principles provide the rationale for higher-dose, short-course therapy.30,36–38 Both peak to minimal inhibitory concentration (MIC) ratios and area under the concentration curve (AUC) to MIC ratios have an important impact on clinical outcomes for concentration-dependent agents such as fluoroquinolones.39 Once the AUC to MIC ratios fall below 30:1, the likelihood of eradication of *S pneumoniae* is diminished.39 In a study of treatment for *S pneumoniae*, the 750-mg dose of levofloxacin achieved increased peak levels compared with the 500-mg dose. This property makes high-dose levofloxacin an attractive treatment appropriate for *S pneumoniae* infections.37 Levofloxacin is also more extensively distributed into intrapulmonary compartments and achieves higher steady-state concentrations in plasma and epithelial lining fluid than ciprofloxacin.36 The pharmacodynamics of ciprofloxacin are more variable and bacterial killing rates are consistently slower than levofloxacin in the in vitro pharmacokinetic models.38

If treatment duration is too short, there is a risk of treatment failure; however, if treatment duration is too long, there is a risk of increasing resistance. Therefore, one of the benefits of short-course therapy is the reduction of resistance through more complete, faster bacterial killing.

**Cost**

Meeting the CARAT criterion for cost-effectiveness entails selecting the optimal initial treatment. Acquisition costs are only a small proportion of the total costs of ABECB treatment.40 The main factor in reducing treatment costs for ABECB is antibiotic effectiveness, particularly when the need for hospitalization is reduced.40 For patients with moderate to severe chronic bronchitis and at least 4 exacerbations in the previous year, ciprofloxacin offered substantial clinical and economic benefit over usual antibiotic treatments.41 Fluoroquinolones may be the preferred initial treatment in these patients.

Treatment failures are prime drivers of costs.42 Decreased patient adherence lessens overall efficacy, increasing the risk of treatment failure and the development of resistance. First-line therapy with a well-tolerated antibiotic that is active against the predominant pathogens, combined with low resistance rates and a convenient once-a-day dosing regimen, may reduce overall costs.40 A higher dose of levofloxacin (750 mg) has the added advantage of optimal PK/PD parameters, which increase the probability of bacterial eradication within a shorter course of treatment.37

**Summary**

The CARAT criteria provide guidance for choosing the optimal drug at the optimal dose and duration for antimicrobial treatment of ABECB. Depending on patient type, different agents meet these criteria. As empiric therapy for ABECB is selected, the CARAT criteria can be used to aid in selecting the correct first-line treatment for ABECB. The optimal first-line treatment will vary depending on patient profile (outlined in Table 1) and knowledge of local resistance patterns. The increasing number of controlled clinical trials provides physicians with a solid foundation for determining optimal treatment.

Clinical evidence demonstrates that fluoroquinolones are therapeutically effective and potent agents against the pathogens most often responsible for ABECB, including gram-negative and gram-positive bacteria. Overall, rates of resistance for fluoroquinolones are very low while safety and tolerability rates are generally good. Safety concerns may exclude some fluoroquinolones from use for high-dose, short-course therapy; however, others are ideal candidates due to their PK/PD properties and favorable safety profiles. Future research should focus on confirming the safety and efficacy of short-course, higher-dose therapeutic regimens for ABECB.
Rhinosinusitis is one of the most common respiratory tract conditions seen by primary care physicians. Each year approximately 20 million cases of acute bacterial rhinosinusitis (ABRS) occur in the United States. Since diagnosis of ABRS relies on clinical evaluation, treatments are usually empirical and include an antibiotic treatment that covers the common bacteria associated with ABRS infection, *Streptococcus pneumoniae* and *Haemophilus influenzae*. The Council for Appropriate and Rational Antibiotic Therapy (CARAT) recommends that antimicrobial therapy for rhinosinusitis should combine high susceptibility, clinical effectiveness, safety, and tolerability. The most efficacious antibiotics for ABRS include the respiratory fluoroquinolones gatifloxacin, levofloxacin, and moxifloxacin, as well as ceftriaxone and amoxicillin-clavulanate. The use of fluoroquinolones or high-dose amoxicillin-clavulanate is recommended for patients with mild disease who have had recent antimicrobial therapy or for patients with moderate disease. These drugs are generally well tolerated with mild adverse effects. Resistance to fluoroquinolones in *S pneumoniae* and *H influenzae* has remained low in spite of their increased use. Recent studies indicate that short-course, high-dose treatment regimens may reduce total drug use, improve tolerability and adherence, prevent increases in resistance, and increase efficacy. The use of fluoroquinolones or amoxicillin-clavulanate in a short-course, high-dose regimen may represent an exciting new protocol in the treatment of rhinosinusitis.

© 2005 Elsevier Inc. All rights reserved.

**KEYWORDS:**
Antibiotic resistance;
Antibiotic therapy;
Fluoroquinolone;
Macrolide;
Rhinosinusitis

Sinusitis is one of the most common conditions treated by primary care physicians in the United States. Approximately 1 billion cases of viral rhinosinusitis occur each year, complicated by 20 million cases of acute bacterial rhinosinusitis (ABRS). If one also counts situations in which sinusitis includes bacterial overgrowth in sinuses other than the maxillary sinus and into the nasopharynx, the number of cases of bacterial rhinosinusitis may be much higher. The healthcare costs of sinusitis total $3.5 billion annually. Sinusitis and bronchitis, together, account for >30 million missed workdays each year.

Diagnosing and managing ABRS is a continuing challenge for physicians, in part because the paranasal sinuses are accessible only with invasive sampling. Physicians must, therefore, often rely on clinical evaluation to treat ABRS.

**Etiology of rhinosinusitis**

Sinus disease is an inherent part of the common cold; 87% of patients with a cold have sinus cavity disease. The common cold is therefore a form of viral rhinosinusitis, and not simply a type rhinitis as traditionally thought. The term *acute sinusitis* is used to identify what is considered a bacterial infection; nonetheless, most acute bacterial infections of the sinuses are a complication of viral rhinosinusitis.

Bacterial sinusitis patterns correlate with those of the common cold throughout the year. Bacterial sinusitis is also
commonly associated with allergy, swimming, nasal polyps, foreign bodies, and tumors.\(^2\) *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most important pathogens in bacterial sinusitis, jointly accounting for approximately 50% of bacterial cases.\(^3\,\,5\) Moraxella catarrhalis, other streptococcal species (including *Streptococcus pyogenes*, *Streptococcus intermedius*, and other \(\alpha\)-hemolytic streptococci), *Staphylococcus aureus*, and anaerobic bacteria each account for a small proportion of cases.\(^2\)

### Antimicrobial management of rhinosinusitis

Sinusitis is the fifth most common diagnosis for which an antibiotic is prescribed.\(^3\) When not treated promptly with an appropriate agent, sinus infections may spread to neighboring structures and may further cause infection of the orbital area or intracranial structures, leading to periorbital or orbital cellulites, subperiosteal abscess, brain abscesses, and meningitis. Sinusitis is the primary source of infection in up to 66% of intracranial abscesses and 5% of community-acquired bacterial meningitis cases.\(^1\) Use of the appropriate antibiotic is crucial for reducing morbidity and related costs, as well as the risk of complications. To aid healthcare providers in selecting the appropriate antimicrobial treatment for infectious diseases, the Council for Appropriate and Rational Antimicrobial Therapy (CARAT) recommends consideration of evidence-based results, potential therapeutic benefits, relative safety profiles, and cost-effectiveness to evaluate treatment options and determine the optimal drug for the optimal duration. These criteria can be effectively applied to the treatment of rhinosinusitis to improve outcomes and reduce complications.

### Evidence-based results

CARAT recommends following evidence from well-designed clinical studies and established evidence-based treatment guidelines to manage infectious disease. The Sinus and Allergy Health Partnership (SAHP), an organization created by the American Academy of Otolaryngic Allergy, the American Academy of Otolaryngology–Head and Neck Surgery, and the American Rhinologic Society, issued guidelines for treatment of ABRS in 2000 that were updated in 2004.\(^3\) The guidelines note that, in general, a diagnosis of ABRS is appropriate in patients who have had symptoms of viral upper respiratory infection that have not improved after 10 days or worsen after 5 to 7 days.\(^3\)

The guidelines recommend any of the following as initial therapy in adults with mild disease who have not received antibiotics in the previous 4 to 6 weeks: amoxicillin-clavulanate, amoxicillin, cefpodoxime proxetil, cefuroxime axetil, or cefdinir. Fluoroquinolones or high-dose amoxicillin-clavulanate are recommended as first-line therapy for patients with mild disease who have had recent antimicrobial therapy or for those with moderate disease.\(^3\) The SAHP also ranks antibiotics commonly used to treat ABRS by clinical efficacy (Table 1).\(^3\)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory fluoroquinolones</td>
<td>90–92</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>90–92</td>
</tr>
<tr>
<td>High-dose amoxicillin-clavulanate</td>
<td>90–92</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>90–92</td>
</tr>
<tr>
<td>High-dose amoxicillin</td>
<td>83–88</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>83–88</td>
</tr>
<tr>
<td>Cefpodoxime proxtetil</td>
<td>83–88</td>
</tr>
<tr>
<td>Cefixime</td>
<td>83–88</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>83–88</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>83–88</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>83–88</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>77–81</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>77–81</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>77–81</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>77–81</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>77–81</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>77–81</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>65–66</td>
</tr>
<tr>
<td>Loracarbef</td>
<td>65–66</td>
</tr>
</tbody>
</table>

Adapted from *Otolaryngol Head Neck Surg.*\(^3\).
Increasingly, clinical trials have been evaluating the efficacy of higher doses of some antimicrobials for shorter durations of therapy. The evidence so far supports the use of these treatment regimens as safe and effective, and studies are currently underway that examine the efficacy of other antimicrobials at higher doses and for shorter durations of treatment.

**Therapeutic benefits**

Choosing the most appropriate antibiotic can improve patient outcomes and reduce the risk of resistance, which is a significant threat to the effective treatment of ABRS. Evidence suggests a relation between treatment failure and antimicrobial resistance. Patients who have previously failed treatment with a macrolide or β-lactam are more likely to be infected with a resistant strain of *S. pneumoniae.*

Despite these findings, clinicians are likely to perceive resistance as a national problem that does not affect their own practices or institutions. Intuitively, this naïveté is more likely in practices where clinicians treat a large number of simple uncomplicated viral infections with antibiotics, thus reducing their ability to discriminate between agents with wide variations in antibacterial activity. Because ABRS is treated empirically, physicians must choose antimicrobial treatment in the appropriate dose to cover both *S. pneumoniae* and *H. influenzae,* taking the potential for resistance into account. Physicians must therefore become more knowledgeable about resistance patterns, particularly for *S. pneumoniae* and *H. influenzae,* in their own communities; they also should be aware that resistance rates to certain antimicrobials are increasing for both *S. pneumoniae* and *H. influenzae.*

Surveillance studies from 1994 to 1995 found that 23.6% of *S. pneumoniae* strains were not susceptible to penicillin, although resistance rates varied considerably by geographic area. Surveillance conducted from 1996 to 1997 revealed even lower susceptibility, with 33.5% of *S. pneumoniae* isolates not susceptible to penicillin. In the Tracking Resistance in the United States Today (TRUST) studies conducted from 1997 to 1998, 17.3% of *S. pneumoniae* isolates were resistant to penicillin and 16.4% showed intermediate resistance to penicillin. TRUST data from 2000 indicated that penicillin-resistant *S. pneumoniae* (PRSP) isolates ranged from 8.3% to 24.8%, based on geographic region. In 2002 to 2003 studies, resistance to penicillin was high for *S. pneumoniae.* Data from TRUST 8, conducted from 2003 to 2004, indicate susceptibility rates of *S. pneumoniae* to penicillin as 65.3%.

Similar to penicillin resistance, resistance to azithromycin is also increasing. From 1994 to 1995, 10% of *S. pneumoniae* strains were not susceptible to azithromycin. In the 1997 to 1998 TRUST study, 21% of *S. pneumoniae* isolates and 0.1% of *H. influenzae* isolates were resistant to azithromycin. Of known PRSP strains, 66.1% were resistant to azithromycin as well. TRUST data from 2000 indicate 23.4% resistance to azithromycin among *S. pneumoniae* and 0.3% resistance to *H. influenzae.* In 2002 to 2003 studies, resistance to azithromycin was 27.6% for *S. pneumoniae* and 0.2% for *H. influenzae.* TRUST 8 data indicate azithromycin resistance rates for *S. pneumoniae* as 25.4% and for *H. influenzae* as 0.1%.

In a US surveillance study of antimicrobial susceptibilities as part of the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT US) study, which analyzed minimum inhibitory concentration (MIC), the most active antimicrobials against PRSP, according to the MIC90, were gatifloxacin, telithromycin, and levofloxacin. The susceptibility of PRSP to gatifloxacin, telithromycin, and levofloxacin was 98.1%, 99.4%, and 97.8%, respectively.

The MIC50 for the newer agent telithromycin against *H. influenzae* is 2.0 µg/mL and the MIC90 is 4.0 µg/mL, resulting in efficacy that is poor to fair, because the maximum concentration that reflects the drug’s ability to meet pharmacokinetically derived targets for effectiveness (area under the concentration curve [AUC] of 30 µg/mL/24hr) is only 0.5 µg/mL. Surveillance conducted from 1996 to 1997 revealed that levofloxacin was most active against *S. pneumoniae,* with 97.3% activity. In the TRUST studies conducted the following year, fluoroquinolones remained highly active. For example, *S. pneumoniae* susceptibility was 99.1% and *H. influenzae* susceptibility was 100% for levofloxacin. Surveillance conducted from 1996 to 1997 revealed that levofloxacin was most active against *S. pneumoniae,* with 97.3% activity. In the TRUST studies conducted the following year, fluoroquinolones remained highly active. For example, *S. pneumoniae* susceptibility was 99.1% and *H. influenzae* susceptibility was 100% for levofloxacin. TRUST data from 2000 indicated that levofloxacin susceptibility nationwide was 99.4% for *S. pneumoniae* and 100% for *H. influenzae* in the 2002 to 2003 studies. *S. pneumoniae* susceptibility to levofloxacin, gatifloxacin, and moxifloxacin was ≥99%. *H. influenzae* resistance in 2002 to 2003 was 0.0%. TRUST 8 data indicate susceptibility rates for *S. pneumoniae* as high as 98.7% for levofloxacin.

The incidence of multidrug-resistant *S. pneumoniae* is also increasing. In 2002 data, penicillin resistance closely predicted resistance to other β-lactams, macrolides, and trimethoprim-sulfamethoxazole. Multidrug resistance
Safety and tolerability

Adverse events and poor tolerability not only reduce the quality of outcomes and increase costs, but they can also reduce patient adherence rates, which in turn can further affect outcomes and increase costs. As their time on the market increases, newer antibiotics with limited clinical-use histories will have to be evaluated before true safety profiles are known. In addition, antibiotics with existing adverse-event profiles at standard doses may well be inappropriate for higher-dose, short-course therapy.

Fluoroquinolones are generally well tolerated, with adverse effects that are usually mild. Adverse effects associated with fluoroquinolones generally involve the gastrointestinal tract and central nervous system, and are usually transient and of mild-to-moderate severity. Detailed discussion of side effects can be found in the accompanying article by Grossman and colleagues.

Significantly, the US Food and Drug Administration (FDA) ordered 1 or more black-box warnings added to the prescribing information of 8.2% of all new drugs from 1975 to 2000, and 2.9% of new drugs were removed from the market during the same period. Half of withdrawals occurred within 2 years of FDA approval. These statistics underline the potential risk associated with all new medicines and the fact that the safety profiles of new agents, such as gemifloxacin and telithromycin, cannot be known with certainty for years.

Optimal drug for the optimal duration

Evidence suggests that shorter courses of therapy with higher doses have several advantages. Increasing the dose will provide higher peak concentrations in serum and key tissue spaces, providing more rapid and complete killing of pathogens. This may decrease the emergence of resistance, as well as allow shortening of treatment duration without compromising efficacy. Shorter courses of treatment may lead to decreased overall drug exposure, better adherence, and faster symptom resolution. Other benefits of a higher-dose, short-course therapy include improved patient and healthcare worker convenience as well as increased cost-effectiveness owing to reductions in treatment failures.

Principles of short-course, higher-dose therapy

Pharmacodynamic/pharmacokinetic principles and efficacy studies support the use of higher-dose, short-course fluoroquinolone therapy. Efficacy is based on achieving optimal pharmacodynamic parameters for each antimicrobial agent. Both peak/MIC ratios and AUC/MIC ratios have an important impact on clinical outcomes for fluoroquinolones. Evidence shows that fluoroquinolone AUC/MIC ratios of ≥30 can be sufficient for eradication of pneumococci from in vitro pharmacokinetic models. In vitro, a higher-dose levofloxacin (750 mg) achieved increased peak levels and showed better activity against ciprofloxacin-resistant *S. pneumoniae*, compared with a lower dose (500 mg); the investigator concluded that the rapid killing and eradication of pneumococci with the 750-mg dose warrant the clinical evaluation of this new dosing regimen in the treatment of pneumococcal infections. Another in vitro study showed that the pharmacodynamics of levofloxacin are less variable than those of ciprofloxacin, and the bacterial killing rates are consistently more rapid against *S. pneumoniae*.

The bioavailability of oral levofloxacin approaches 100% and is not significantly affected by the administration of food. It is widely distributed throughout the body and penetrates well into body tissues and fluids, and concentrations of levofloxacin in these body tissues and fluids are similar to or higher than those in plasma. High concentration/MIC ratios are achieved against both gram-positive and gram-negative organisms.

Short-course therapy has the potential to improve efficacy and safety, and minimize the evolution of resistance in the patient being treated and in the wider population. Although it is not yet certain that higher-dose, short-duration treatment prevents increases in resistance, it is clear that

| Table 2 | Susceptibilities of most common isolates to antibiotics commonly prescribed for sinusitis* |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Streptococcus pneumoniae | Haemophilus influenzae | Moraxella catarrhalis | Staphylococcus aureus |
| % S/I/R (N = 618) | % S/I/R, (N = 1,189) | % S/I/R, (N = 1,588) | % S/I/R, (N = 983) |
| Penicillin | 64/20/16 (2) | Not done | 8.5/0/91.5 (1) | 10.8/0/89.2 (6) |
| Gatifloxacin | 99.8/0.2/0 (2) | 100/0/0 (3) | 100/0/0 (7) | 97/1.1/2.0 (6) |
| Erythromycin | 68/0.3/32 (2) | Not done | 85/13/2 (7) | 39/32/29 (7) |
| Azithromycin | 64.7/0.6/34.7 (264) | 99.4/0/0.6 (3) | 100/0/0 (324) | 31.2/18.7/50.1 (448) |
| Clarithromycin | 65/0/0.5 (264) | 64/31/5 (3) | 100/0/0 (324) | 68.8/2.1/29.2 (448) |
| Levofloxacin | 99.8/0/0.2 (2) | 100/0/0 (3) | 100/0/0 (7) | 95.1/1/6/3.3 (6) |

1 = intermediate susceptibility; R = resistant; S = susceptible.
*Values in parentheses indicate number not tested.

Reprinted with permission from *Am J Med.*

varied considerably by geographic region. In 2002 to 2003, multidrug resistance was identified in 13.1% of all *S. pneumoniae* and in 19.2% of all sinus isolates. TRUST 8 data showed that the levofloxacin susceptibility rate among multidrug-resistant *S. pneumoniae* is >98%.
long durations of treatment, particularly with low doses of antimicrobials, can increase resistance.\(^6\) Low-dose, long-duration treatment with oral \(\beta\)-lactams, for example, contributes to selective pressure promoting pharyngeal penicillin-resistant \(S.\) pneumoniae.\(^36\)

Short-course therapy is also more convenient for patients and improves adherence, a key determinant of therapeutic success or failure.\(^30\) Compliance decreased among children who received a 5-day regimen of amoxicillin compared with those who received a 3-day regimen.\(^37\) Furthermore, a review of 76 studies determined that adherence significantly improves with once-daily dosing, compared with 3- or 4-times-a-day dosing.\(^38\) Indirectly, poor patient adherence due to daily multidosing and the increased risk of adverse events may diminish the efficacy of long-term antimicrobial use.\(^30\)

### Evidence for efficacy of short-course therapy

Increasing evidence supports the use of short-course therapy in the treatment of rhinosinusitis. Studies of short courses of gatifloxacin and telithromycin have shown clinical efficacy and tolerability that are comparable to standard courses of treatment.\(^7–11\) Levofloxacin, which is approved for short-course, higher-dose therapy (750 mg/day) for community-acquired pneumonia, is also being investigated for short-course, higher-dose treatment of bacterial rhinosinusitis.\(^5\)

### Cost-effectiveness

The factors that have the most impact on cost are those that affect clinical outcomes, including patient adherence, tolerability of the drug regimen, and rates of treatment failure. Patient adherence can be improved with a reduced pill burden and a tolerable side-effects profile.\(^30,38\) Shorter courses of therapy with a reduced pill burden should also enhance adherence in addition to reducing the risk of some adverse events.\(^30,38\) Levofloxacin, gatifloxacin, moxifloxacin, and telithromycin all provide once-daily dosing, whereas ciprofloxacin must be taken twice per day.\(^25,39–42\)

Treatment failure, whether due to patient nonadherence or a lack of clinical efficacy, is the most costly outcome, because these patients incur the costs of the initial treatment regimen and a second treatment regimen, as well as additional healthcare costs (i.e., office visits and occasional hospitalization). Treatment failure, however, can be reduced by using the optimal drug initially.

To optimize patient satisfaction with treatment, patient expectations must be aligned with expected clinical outcomes. Patients should be counseled that, in many cases, short-course therapy may end before symptoms of the original antecedent viral infection resolve. Such counseling may reduce patient requests for additional treatment, and microbiologic eradication will be achieved.

### Summary

Suboptimal treatment of ABRS can lead to clinical failure and the need for retreatment, promoting drug resistance and a higher potential for the development of chronic disease. The CARAT criteria can help clinicians identify optimal treatment for ABRS patients. Recently, fluoroquinolones have been recommended as first-line therapy for patients with moderate ABRS or those with mild disease who have had recent antimicrobial therapy.\(^3\) According to CARAT criteria, the optimal antimicrobial for rhinosinusitis is one that combines high susceptibilities and clinical effectiveness with safety and tolerability. Studies are examining the ability of short-course, higher-dose treatment to reduce pill burden and total drug use, improve tolerability and adherence, prevent increases in resistance, and increase efficacy. Short-course, higher-dose therapies may represent an exciting new protocol in the treatment of rhinosinusitis in the future.

### References

12. Iannini PB, Paladino JA, Adelman MH, Forrest A, Schentag JJ. Macrolide failure in Streptococcus pneumoniae infections is an identifiable clinical event. Presented at the 42nd Annual Meeting of the Infectious
17. Thornsberry C, Jones ME, Hickey ML, Mauriz Y, Kahn J, Sahm DF.
18. Low DE, Felmingham D, Brown SD, Rangaraju M, Nusrat R. Activity
19. Sao DK, Weaver MK, Flamm RK, Jones M, Evangelista AT, Thorns-
20. Doern GV, Brueggemann A, Holley HP Jr, Rauch AM. Antimicrobial