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, Alpesh Amin, MD, MBA, Stephen A. Brunton, MD, Thomas M. File, Jr, MD, Gary Milkovich, RPh, Keith A. Rodvold, PharmD, Daniel F. Sahm, PhD, Joseph Varon, MD, David Weiland, Jr, MD, 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.

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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. 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. 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.  

The overuse and misuse of antibiotics has contributed to an increase in bacterial resistance patterns, which may differ by locality. 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 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. 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.

### 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 variably discuss this process. 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.

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.

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.

### 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.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.13 These guidelines are similar to those recommended by the IDSA.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.8,14

### Safety

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

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

- Evidence-based results
- Therapeutic benefits
- Safety
- Cost-effectiveness
- Optimal drug dose and duration
  —Shorter-course, more aggressive therapy

**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>
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<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>
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<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>
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<tr>
<td></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>
<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>
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Adapted from Am J Respir Crit Care Med.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. 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. 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 macrolide (erythromycin, azithromycin, or clarithromycin) plus high-dose amoxicillin or high-dose amoxicillin-clavulanate. Outpatients with comorbidities—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.

*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.

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. 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.

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. $150.65). Other studies have also supported the efficacy of shorter courses of treatment in pneumonia. Similar results have also been found for short courses of therapy for bronchitis, sinusitis, and urinary tract infections.

**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. 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. For example, at a free-drug AUC24/MIC ratio >33.7, the microbiological response of *S pneumoniae* to fluoroquinolones is 100%. An AUC24/MIC ratio of >125 predicts an 85.4% microbiologic response to levofloxacin and an 81.5% response to ciprofloxacin.
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. 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. For example, an AUC24–MIC ratio of 25 to 40 is thought to predict optimal bactericidal activity for fluoroquinolones against S. pneumoniae. 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
