Optimal Use of Modern Antibiotics: Emerging Trends

Ron Polk

Development of new antimicrobial drugs is an essential component in the effort to remain ahead of emerging microbial resistance. However, when new antibiotics are used with unrestrained enthusiasm, a predictable consequence is the further expansion of resistance. This problem is well known to the infectious diseases specialist and is increasingly appreciated by the nonspecialist and the public. A far more sensible strategy is to identify new ways to use these drugs to increase the duration of their usefulness. New methods to optimize antibiotic selection, dose, and duration of therapy are being investigated, and application of some of these strategies has been shown to have a favorable impact on resistance. Much of the classic thinking of how to use antibiotics is changing, and these newer strategies may result in prolongation of the era of the “antibiotic miracle.”

The emergence of pathogens with increased resistance to available antibacterials has historically been followed by development of “modern” antibiotics with improved activity for these resistant isolates. After a variable period, resistance frequently emerges to these new antibiotics, which then leads to development of even more modern antibiotics, and the cycle repeats itself.

It is often said that more optimal use of antimicrobials is an important part of the effort to contain resistance, though there is usually little discussion on what is meant by optimal use [1, 2]. Historically, the high cost of antimicrobials has been a primary reason for concerns about less-than-optimal use [3]. A number of different efforts to improve antibiotic prescribing have been tried, including education of the prescriber, restrictions on prescribing, and computer-guided antibiotic selection. John and Fishman [4] have recently reviewed these antibiotic management strategies and their impact on antibiotic costs and have concluded that multidisciplinary team efforts to improve antimicrobial use offer the greatest likelihood of success. The focus of these efforts has recently expanded from costs of therapy to evaluating their impact on antibacterial resistance [5].

Criteria appropriate to select an optimal antibiotic for a specific patient include efficacy, risk of adverse events, contraindications, costs of therapy, and details of the clinical condition of the patient. These criteria have been recently reviewed [6, 7]. The purpose of this review is to consider a definition of optimal antibiotic therapy from the perspective of a multidisciplinary antibiotic team and to examine recent trends in the components of optimal use. Investigations that suggest that optimal use is an important part of the solution to antimicrobial resistance will be reviewed.

What Is Optimal Antimicrobial Use?

“It will be necessary to define optimal use of antibiotics to achieve maximum therapeutic effect with minimum selective pressure for resistance” [8].

In 1987, Bryan [9] pointed out that the definition of optimal antimicrobial therapy depends on one’s perspective. He characterized antimicrobial therapy as “effective” when the antibiotic was active in vitro for the pathogen. This definition is of value to epidemiological investigations of antimicrobial therapy. Therapy is considered “appropriate” when the antibiotic not only is active in vitro for the pathogen but also is appropriate to the clinical situation. For example, clinical practice guidelines help guide antibiotic selection for specific infectious diseases [10], and these guidelines narrow antibiotic selection to a relatively few appropriate agents on the basis of available in vitro and in vivo data. This definition is most commonly used by clinicians. Finally, therapy is considered “recommended” when it is the most cost-effective of the appropriate therapies. The drug of choice from the Medical Letter on Drugs and Therapeutics’ “Antimicrobial Drugs of Choice” [11] appears synonymous with “recommended therapy.” This definition is of most interest to policymakers responsible for cost-effective therapy. For this review, optimal antibiotic therapy is equivalent to recommended therapy (above), with the additional qualification that recommended antibiotics are tailored to the local health care setting.

In the hospital, the availability of specific antibiotics is often decided by a committee of interested professionals, often including infectious diseases physicians, clinical microbiologists, clinical pharmacists, and representatives from quality assurance committees [1, 3, 4]. This group will most likely base their decisions on local pathogens and their susceptibilities, an
evaluation of the clinical literature, consultation with clinicians who will use the recommended antibiotics, the patient case mix, and the costs of purchasing, administering, and monitoring antimicrobials. The antibiotic committee is increasingly being asked not only to decide the availability of antibiotics but also to develop quality assurance programs to ensure use of optimal, or recommended, therapy.

What Are the Components of Optimal Antimicrobial Use?

The recent guidelines from a joint committee of the Society for Health Care Epidemiology of America and the Infectious Diseases Society of America (IDSA) for the prevention of antibacterial resistance [1] provide a working definition of the components of optimal use: “Appropriate antimicrobial stewardship that includes optimal selection, dose, and duration of treatment, as well as control of antibiotic use, will prevent or slow the emergence of resistance among microorganisms.” Despite the elegant phrasing of this statement, there is likely to be much disagreement in the interpretation of the various components of antimicrobial stewardship. Each of these components of optimal therapy will be briefly reviewed, using examples from the recent literature in an attempt to identify emerging trends in optimal therapy.

What Is Optimal Selection?

“What constitutes optimal cost-effective antimicrobial therapy becomes increasingly difficult to determine, making ever more urgent the need for effective yet flexible guidelines for antimicrobial use” [9].

On the surface, optimal selection of an antimicrobial for a patient is straightforward—identify the pathogen, and in the absence of contraindications, administer the antibiotic(s) recommended in standard references, such as the Medical Letter on Drugs and Therapeutics [11] or a similar reference. However, since definitive therapy—that is, therapy directed against an organism identified by culture, with known antimicrobial susceptibilities—is relatively uncommon when antimicrobials are used, the selection of the optimal antibiotic is usually more complex.

**Antibiotic selection and community-acquired pneumonia (CAP).** A good example to illustrate optimal antibiotic selection is CAP. Initial therapy for CAP is empirical and usually designed to provide coverage for the common pathogens, including pneumococci, *Haemophilus influenzae*, and atypical organisms [12, 13]. The increasing prevalence of penicillin-resistant pneumococci has added to the complexity of empirical treatment recommendations [13, 14]. Treatment of suspected or confirmed meningitis caused by pneumococci requires a bactericidal drug with reliable activity, such as vancomycin [15]; thus, it is assumed in the following discussion that pneumococcal meningitis is not in the differential diagnosis. For the ambulatory treatment of CAP, many authoritative sources suggest appropriate therapy (versus recommended) with either a macrolide, a newer fluoroquinolone, or doxycycline [9, 12, 13]. The recently published IDSA guidelines for ambulatory treatment of CAP in adults [13], in the absence of an etiologic diagnosis, make the following suggestions for appropriate empirical therapy: “Preferred antimicrobials for most patients (in no special order): macrolide (clarithromycin or azithromycin are preferred if *H. influenzae* infection is suspected), fluoroquinolones (. . . with enhanced activity against *S. pneumoniae*), or doxycycline.”

Since these suggestions are in no special order, an antibiotic committee can apply the usual criteria for antibiotic evaluation—efficacy, toxicity, and cost—to help select optimal, recommended therapy from these appropriate choices. Since all three regimens are equally endorsed, differences in efficacy or risk of adverse reactions are not anticipated for most patients. Since cost is the remaining selection criterion, is not doxycycline the optimal, recommended drug (table 1)? (Although erythromycin is often recommended for empirical treatment of CAP, the gastrointestinal intolerance of erythromycin is a significant clinical problem, and resistance among pneumococci and *H. influenzae* is greater for erythromycin and the other macrolides than for doxycycline [see below].) Consequently, when a committee evaluates newer therapies for CAP, it may recommend that doxycycline is preferred over newer agents. Others have also recently emphasized that doxycycline is an underutilized antimicrobial for ambulatory treatment of mild to moderate CAP [17, 18]. Despite its clear cost advantage and its endorsement by objective reviews and practice guidelines, doxycycline is little used in CAP for at least three reasons: there are few to promote its use (perhaps its main shortcoming), recent susceptibility data for pulmonary pathogens are scant, and there are few recent clinical trials of its use for treatment of CAP.

**In vitro activity of doxycycline for respiratory pathogens causing CAP.** Recent surveys report that doxycycline (or tetracycline) is at least as active for pulmonary pathogens as are

**Table 1. Relative costs of “appropriate” therapy for treatment of community-acquired pneumonia in patients not requiring hospitalization.**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Average wholesale cost (10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline (generic)</td>
<td>100 mg daily</td>
<td>$ 0.85</td>
</tr>
<tr>
<td>Erythromycin (generic, enteric coat)</td>
<td>250 mg every 6 hours</td>
<td>$ 7.17</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>250 mg daily for 5 days</td>
<td>$37.31</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg twice daily</td>
<td>$65.20</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg daily</td>
<td>$62.94</td>
</tr>
<tr>
<td>Trovaflaxacin</td>
<td>200 mg daily</td>
<td>$73.58</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>400–600 mg daily</td>
<td>$41.20–$61.80</td>
</tr>
</tbody>
</table>
most other recommended agents. A survey of in vitro susceptibilities of 6,943 community-acquired lower respiratory tract pathogens from 18 countries found that 100% of isolates of *H. influenzae* and *Moraxella catarrhalis* were susceptible to doxycycline [19]. Doxycycline was active for 78% of *Streptococcus pneumoniae*, the same percentage as were susceptible to azithromycin, clarithromycin, and amoxicillin. In contrast, 96% of *S. pneumoniae* were susceptible to ofloxacin, consistent with previous data showing in vitro superiority of the newer fluoroquinolones [14].

An ongoing survey from 10 adult care hospitals in Franklin Country, Ohio, reported antimicrobial susceptibility of 564 isolates of *S. pneumoniae* from blood collected over 4 years [20]. The following prevalences of resistance were reported for the years 1994, 1995, 1996, and 1997, respectively: high-level penicillin resistance, 1%, 2%, 5%, 5%; macrolide, 4%, 7%, 7%, 9%; ceftriaxone, 1%, 0, 0, 3%; fluoroquinolones, 0, 2%, 2%, 1%; and doxycycline, 1%, 3%, 3%, 3%. A survey of isolates from respiratory tract specimens collected in North America from February to June 1997 included 1,047 isolates of *S. pneumoniae*. Overall, 89% of U.S. isolates and 87% of Canadian isolates were susceptible to tetracycline (MIC of <2.0 μg/mL) [21]. Of the 152 isolates with high-level resistance to penicillin, 63% remained susceptible to tetracycline.

The Centers for Disease Control and Prevention surveillance of isolates of *S. pneumoniae* from 12 hospitals in 11 states reported that tetracycline resistance in 1993–1994 was ~6% and that this had not substantially changed since 1980 [22]. In contrast, resistance rates for penicillin, trimethoprim-sulfamethoxazole, and erythromycin had “increased substantially” over the same period. Since most therapies are not reliably active against all pulmonary pathogens, local data regarding susceptibility of *S. pneumoniae* to recommended therapy, including doxycycline, are probably required to optimally select empirical and “step-down” therapy (switch to a more specific oral therapy) for CAP.

From the preceding review, it appears that doxycycline is at least as active as most other recommended agents in vitro for common respiratory pathogens. Furthermore, if the small differences in in vitro activity between doxycycline and a new quinolone have in vivo significance, the benefit appears to be small. For example, if it is assumed that 65% of all cases of CAP are caused by pneumococci [12], that the prevalence of high-level penicillin resistance is 15% [13], and that all patients infected with these resistant organisms will respond if given a newer quinolone compared with a response rate of 63% if given doxycycline [22] (assuming the rest will have treatment failure because of doxycycline resistance), then 25 patients must be treated with a fluoroquinolone to prevent a single failure of treatment with doxycycline. There has been little discussion in the infectious diseases literature of how to balance the risks of widespread use of potent antimicrobials and the resulting increase in resistance with what may be at best a small gain in clinical response.

**Efficacy of doxycycline for CAP.** A MEDLINE search (National Library of Medicine: http://www.nlm.nih.gov/) for “doxycycline,” “pneumonia,” “lower respiratory tract infection,” and “clinical trial” from 1966 to 1998 yielded eight studies [23–30]. Five of these were published between 1975 and 1980, before widespread prevalence of multiresistant *S. pneumoniae*, and are uncontrolled observations of patients with mild upper and lower respiratory tract infections [23–27]. Clinical response was assessed as uniformly good to excellent. Another is a recent large prospective clinical trial that compared levofloxacin with ceftriaxone/cefuroxime axetil for CAP; doxycycline was not used [28]. There are two controlled trials in which doxycycline was used in comparison with a fluoroquinolone. In the first, doxycycline (100 mg b.i.d.) was compared with ofloxacin (200–400 mg b.i.d.) for treatment of lower respiratory tract infection [29]. Of 219 evaluated patients, 131 were reported to have pneumonia. Of the 62 patients who received ofloxacin, 34 were cured, 26 showed improvement (97% cure or improvement), and there were 2 treatment failures. Of the 69 patients with pneumonia who received doxycycline, 39 were cured, 23 showed improvement (90% cure or improvement), and there were 7 treatment failures. The difference in response is not significant (P = .224 by χ²), although the relatively small sample might be obscuring a true difference.

The second randomized trial of 411 patients from Scandinavia compared doxycycline with fleroxacin for treatment of presumed atypical pneumonia [30]. An intention-to-treat analysis found a short-term clinical response rate of 86% (157 of 182) in the fleroxacin arm and 93% (177 of 191) in the doxycycline arm (P = .064, χ²). The few isolates of pneumococci appeared to respond better to doxycycline than to fleroxacin, the latter having poor activity in vitro (and apparently in vivo) for *S. pneumoniae*.

Finally, a recent prospective, randomized clinical trial of intravenous doxycycline compared with “routine antibiotics” in the treatment of 87 hospitalized patients with mild to moderately severe CAP found that doxycycline was at least as efficacious as control antibiotics and was significantly less expensive [31]. These three controlled trials support the IDSA guidelines that doxycycline is appropriate therapy for CAP in certain patients. Furthermore, these data support policy makers who may decide that doxycycline is recommended therapy at their institution.

In addition to the traditional selection criteria for an antibiotic (above), the potential for the recommended antibiotic to exacerbate bacterial resistance should be considered [32]. One of the attractions of using doxycycline for step-down therapy following empirical parenteral therapy, such as ceftriaxone with or without erythromycin, is the potential to relieve some of the selective pressure of cephalosporin therapy on emer-
gence of superinfections with enterococci [33]. In addition, the routine use of a fluoroquinolone for treatment of CAP further increases the selective pressure for quinolone resistance. The observation that the prevalence of quinolone-resistant *Pseudomonas aeruginosa* is greater in the community than in the hospital [34], presumably reflecting extensive quinolone use in the community, further suggests that doxycycline deserves consideration as recommended therapy. Consideration of doxycycline as first-line therapy, in conjunction with examination of sputum and other noninvasive tests [35], may help limit use of fluoroquinolones in the community, thereby preserving their usefulness for more serious infections.

**Newer antibiotics and CAP.** Fluoroquinolone antibiotics are generally well-tolerated and highly effective and are considered to be appropriate therapy for CAP [13]. To a large extent, use of fluoroquinolones for community-acquired respiratory tract infections is being driven by concern for the reported high prevalence of penicillin-resistant pneumococci [36]. However, if these penicillin-resistant pneumococci are clinically prevalent, and clinically resistant to older therapies, some of the recent large multicenter clinical trials should have demonstrated an advantage of the quinolone compared with standard therapeutic modalities that have relatively poor in vitro activity, including macrolides, oral cephalosporins, and amoxicillin. A review of the most recent large clinical trials of CAP suggests that a wholesale switch to newer therapies for this infection is premature.

A trial from France compared oral amoxicillin (1 g t.i.d.) with trovafloxacin (200 mg q.d.) for treatment of CAP in 312 evaluated patients. The clinical response (cure plus improvement) at 10 days of treatment was statistically equivalent (89% vs. 93%) [37]. At 35 days after treatment, all four penicillin-resistant *S. pneumoniae* isolates were eradicated in the trovafloxacin arm compared with eradication of three of five isolates in the amoxicillin arm. In a similar randomized, blinded trial, 516 patients with “nonsevere” CAP received oral levofloxacin at one of two dosages (500 mg either q.d. or b.i.d.) or oral amoxicillin/clavulanate (500 mg/125 mg t.i.d.) [38]. The intent-to-treat analysis found no significant difference in response rate between the three groups (84%, 80%, and 86%, respectively). The prevalence of penicillin-resistant *S. pneumoniae* and their response to amoxicillin was not stated. Recent pharmacodynamic investigations in animals provide a rationale for use of amoxicillin for treatment of moderately resistant *S. pneumoniae*. When doses of amoxicillin that approximate serum concentrations in humans were given, Andes and Craig [39] concluded that isolates of *S. pneumoniae* requiring MICs of up to 2 µg/mL should be regarded as susceptible to oral amoxicillin. Currently, many of these isolates are categorized as either nonsusceptible or intermediate in susceptibility.

A large clinical trial (n = 590) compared levofloxacin and ceftriaxone/cefuroxime axetil with or without a macrolide for treatment of mild to severe CAP and found that the efficacy of levofloxacin was at least equivalent to that of the β-lactam regimen [28]. However, only 6 of the 28 isolates of *S. pneumoniae* available for susceptibility studies were not fully susceptible to penicillin, and all 6 were of intermediate susceptibility. The clinical and microbiological responses in patients with pneumococcal infection were similar in both groups, including those with the less susceptible isolates. A similar double-blind, randomized, multicenter clinical trial compared trovafloxacin and ceftriaxone/cefepodoxime with or without erythromycin in 443 patients with CAP sufficiently severe to require hospitalization [40]. Only 11 isolates of penicillin-resistant *S. pneumoniae* were isolated at baseline (10 in the trovafloxacin arm, 1 in the β-lactam arm), and all responded to treatment.

The difficulty of finding sufficient numbers of penicillin-resistant *S. pneumoniae* to document a clinical advantage of a fluoroquinolone is illustrated by a report at the 1997 International Conference on Antimicrobial Agents and Chemotherapy [41]. Six multicenter, randomized, blinded clinical trials of the efficacy of trovafloxacin for CAP were combined, for a total of 1,998 patients. Of these, 127 *S. pneumoniae* were isolated at baseline from the trovafloxacin groups and 130 from the control groups. The clinical responses to trovafloxacin and control agents at end of treatment were 93% and 94%, respectively. Of the patients with penicillin-resistant *S. pneumoniae*, 25 (96%) of 26 treated with trovafloxacin showed clinical response, compared with 8 (73%) of 11 patients treated with control agents. Since statistical comparison of these pooled data is inappropriate, and the numbers are small, the question of the clinical relevance of penicillin-resistant *S. pneumoniae* in CAP from this database of nearly 2,000 patients remains unsettled.

These preceding large-scale clinical trials were initiated when the prevalence of penicillin-resistant pneumococci was low [42], and it is possible that future studies may confirm that patients with CAP will not be effectively treated by older therapies, including selected β-lactams (e.g., amoxicillin) and doxycycline. Yet current promotional strategies for modern antimicrobial agents such as fluoroquinolones suggest that these penicillin-resistant pneumococci require empirical treatment in all patients, despite failure of the largest clinical trials to find these organisms in sufficient numbers to document a clinical advantage for the newer antimicrobials.

Another important observation in investigations in which β-lactams were used alone as the active control [28, 37, 38] was that patients infected with atypical pathogens, such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, were as likely to respond to β-lactam monotherapy as they were to the combination of β-lactam plus macrolide. Since these organisms are not susceptible in vitro to β-lactams, the apparent clinical response to β-lactam monotherapy presumably reflects the adequacy of host defenses in the patients enrolled in these trials and the low virulence of these organisms [43].
observations raise further questions regarding the need to use new broad-spectrum drugs for routine treatment of organisms that usually cause self-limiting disease.

The point of the preceding review is not to argue that newer antimicrobials have no place in treatment of CAP but to illustrate the complexity of deciding what is meant by “optimal selection” of an antibiotic. However, the optimal use of modern antimicrobials should be, in many instances, less use.

What Is the Optimal Dose?

“We know everything about antibiotics except how much to give”—attributed to Maxwell Finland.

Far more is known about the basic chemistry of antibiotics, their pharmacokinetics, and their mechanisms of action and of resistance than is known about the practical problem of what dose to give. Whereas some dose-ranging studies in humans are possible, ethical concerns and the understandable desire on the part of the sponsor to avoid clinical failures due to underdosage make it likely that excessive doses have been used for most infections during phase II and phase III investigations. On a superficial level, the optimal dose of an antimicrobial can be considered straightforward—that dose found to be effective for a specific condition in well-controlled clinical trials or the dose appearing in the package insert. However, this apparent simplicity masks a far more complex issue, since the effective dose is a function of MIC for the pathogen, adequacy of host defenses, and location of the infection. Furthermore, the pharmacodynamic profile of an antibiotic (its time-effect characteristics) is more recently recognized as an important determinant of the appropriate dosage [44–48].

There are three pharmacodynamic relationships that quantify the exposure of the pathogen to an antimicrobial: the ratio of the area under the plasma concentration-vs.-time curve (AUC) to MIC, ratio of maximum serum concentration (C$_{\text{max}}$) to MIC, and time over a dosing interval that plasma concentrations exceeded the MIC. These are illustrated in figure 1. These three relationships tend to be correlated, especially the ratios of C$_{\text{max}}$ to MIC and AUC to MIC, and it can be difficult in a clinical trial to isolate the most important pharmacodynamic determinant of response. The pharmacodynamic profile of an antibiotic class is characterized as either concentration-dependent (fluoroquinolones, aminoglycosides), such that an increase in antibiotic concentration leads to a more rapid rate of bacterial death, or time-dependent (β-lactams, vancomycin), such that a reduction in bacterial density is a function of the time that concentrations exceed the MIC. For concentration-dependent antibiotics, the ratios of C$_{\text{max}}$ to MIC or AUC to MIC correlate best with the reduction in microbial density in vitro and animal investigations [48]. Dosing strategies attempt to maximize these ratios by administering a “large” dose relative to the MIC for anticipated pathogens, often at “long” intervals relative to the serum half-life. In contrast, dosage strategies for time-dependent antibiotics will emphasize the administration of a dose sufficient to maintain serum concentration above the MIC, typically for ≥ 40%–50% of the dosing interval. With respect to antibiotic doses, “one size does not fit all” [50], and recent pharmacodynamic investigations provide evidence that more rational and individualized doses that integrate the variables known to influence response can be developed.

Preston et al. [51] analyzed the responses of 134 evaluated patients from a study of 313 patients treated prospectively with iv levofloxacin for 3 days, followed by oral therapy in most patients, for respiratory, skin, and urinary tract infections. The dosage of levofloxacin was 250–500 mg every 24 hours for 5–14 days, depending on severity and site of infection. Both the ratios of AUC to MIC and C$_{\text{max}}$ to MIC were closely correlated to clinical response, consistent with previous in vitro and animal investigations. A ratio of C$_{\text{max}}$ to MIC of 12.2 was predictive of an 80%–100% clinical and microbiological response, depending on the site of infection (figure 2).

If these data are confirmed for other fluoroquinolones and extended to other antimicrobials and infections caused by additional organisms, the implications are great. First, a solid rationale for the in vitro break point can be established. For example, since the C$_{\text{max}}$ for levofloxacin following recommended oral doses of 500 mg every 24 hours is ~ 6 μg/mL, the break point concentration to yield a ratio of C$_{\text{max}}$ to MIC of 12.2 is 0.5 μg/mL. (The National Committee for Clinical Laboratory Standards [NCCLS]-approved break point for levofloxacin is four times higher, or 2 μg/mL. The fact that
Theoretically optimal to achieve a ratio of various new fluoroquinolones and common bacteria that can be dismissed [49]. Table 2 illustrates the range of doses for variability in pharmacokinetic profile following a fixed dose variability in MIC for susceptible organisms, and intersubject the variability in serum concentrations is much less than the have the same serum concentration-vs.-time profile. However, there was no relationship between any of the three calculated pharmacodynamic measures—the ratio of AUC to MIC, the ratio of $C_{\text{max}}$ to MIC, or the time over the dosing interval that plasma concentrations exceeded the MIC—and eradication. These data serve as a reminder that determination of a rational dose for an antibiotic in humans, despite application of the most current understanding of the determinants of response from in vitro and animal studies, remains a difficult undertaking.

Pharmacodynamic models may also eventually reveal the relationship between dose and antimicrobial resistance. A retrospective investigation assessed the relationship between the ratio of AUC to MIC for different antimicrobial regimens and the development of resistance of the treated isolate during therapy [56]. Of 107 eligible patients with a diagnosis of nosocomial pneumonia, resistance (defined as an increase in MIC for a pretreatment respiratory isolate to a value exceeding the NCCLS break points in a subsequent isolate of the same genus and species) developed in 32 (25%) of 128 organisms isolated from bronchial aspirates. Emergence of resistance was significantly more common when the ratio of the area under the concentration for levofloxacin to MIC and probability of clinical response to treatment for infection at different sites. A ratio of 12.2 was found to produce an optimal response. The vertical dotted line represents a ratio of peak serum concentration to MIC of 12.2. The curved dotted line represent the estimated response of respiratory tract infections, the solid curve represents response of skin and skin structure infection, and the horizontal line of alternating dots and dashes represents the response of patients with urinary tract infection. Adapted from [51].

Levofloxacin has proven effective for organisms requiring MICs up to 1 $\mu$g/mL, such as $S.\text{pneumoniae}$ [28], suggests that a ratio of 12.2 may be too conservative.) Second, assuming that the optimal ratio of 12.2 is a class effect applicable to all quinolones, investigations with experimental fluoroquinolones might optimize the dose in phase II and III clinical trials to provide a peak serum concentration of ~12 times the MIC for the expected pathogen, or 12 times the expected MIC for the most resistant organism in the case of multiple potential pathogens. This would lead to doses tailored to infection site and susceptibility for the infecting organism and raises the possibility of using lower doses than usual for highly susceptible organisms or larger doses and possibly combination therapy for less susceptible organisms.

Not every patient given the same dose of an antibiotic will have the same serum concentration-vs.-time profile. However, the variability in serum concentrations is much less than the variability in MIC for susceptible organisms, and intersubject variability in pharmacokinetic profile following a fixed dose can be dismissed [49]. Table 2 illustrates the range of doses for various new fluoroquinolones and common bacteria that are theoretically optimal to achieve a ratio of $C_{\text{max}}$ to MIC of 12.2.

The theory and methods of clinical pharmacodynamic inves-
tigations in humans are sufficiently sound to allow for incorporation into investigational trials. Linezolid, an oxazolidinone with activity against gram-positive cocci, was found in an animal model to exhibit a time-dependent pharmacodynamic profile for $Staphylococcus\text{aureus}$ and $S.\text{pneumoniae}$ [54]. Furthermore, a dose of 500 mg b.i.d. was estimated to produce serum concentrations in humans of $>4$ $\mu$g/mL, a typical MIC for $S.\text{aureus}$. A dose-ranging study in humans evaluated eradication of nasal colonization by $S.\text{aureus}$ in 48 subjects following 200-mg, 400-mg, or 600-mg doses of linezolid, each dose given b.i.d. for 3 or 5 days [55]. $S.\text{aureus}$ was eliminated in 45 (94%) of 48 treated subjects and in 0 of 8 given placebo. However, there was no relationship between any of the three calculated pharmacodynamic measures—the ratio of AUC to MIC, the ratio of $C_{\text{max}}$ to MIC, or the time over the dosing interval that plasma concentrations exceeded the MIC—and eradication. These data serve as a reminder that determination of a rational dose for an antibiotic in humans, despite application of the most current understanding of the determinants of response from in vitro and animal studies, remains a difficult undertaking.

Table 2. Theoretical doses for different fluoroquinolone antibiotics and pathogens, and their respective MICs required to produce a ratio of peak serum concentration to MIC of 12.2.

<table>
<thead>
<tr>
<th>Drug, pathogen</th>
<th>MIC for pathogen</th>
<th>Dose to produce ratio of $C_{\text{max}}$ to MIC of 12.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>$E.\text{coli}$</td>
<td>0.03 $\mu$g/mL 30 mg</td>
</tr>
<tr>
<td></td>
<td>$S.\text{pneumoniae}$</td>
<td>1.0 $\mu$g/mL 1,000 mg</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>$Klebsiella\text{pneumoniae}$</td>
<td>0.03 $\mu$g/mL 25 mg</td>
</tr>
<tr>
<td></td>
<td>$S.\text{pneumoniae}$</td>
<td>0.12 $\mu$g/mL 100 mg</td>
</tr>
<tr>
<td></td>
<td>$Pseudomonas\text{aeruginosa}$</td>
<td>1.0 $\mu$g/mL 800 mg</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>$E.\text{coli}$</td>
<td>0.03 $\mu$g/mL 100 mg</td>
</tr>
<tr>
<td></td>
<td>$S.\text{pneumoniae}$</td>
<td>0.5 $\mu$g/mL 1.7 g</td>
</tr>
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</table>

NOTE. The calculated doses are greater than those found to be clinically effective for the more resistant pathogens, such as $S.\text{pneumoniae}$ [28, 52] and $P.\text{aeruginosa}$ [53]. This suggests that the ratio of 12.2 found necessary for levofloxacin in a prospective clinical trial [51] may be overly conservative and that a lower ratio (and lower doses for these fluoroquinolones) is appropriate for many infections.
Table 3. Recent investigations, reviews, and position papers addressing shorter duration of antimicrobial therapy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Infection Type</th>
<th>Type of publication</th>
<th>Recommendation or conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>[60]</td>
<td>Acute otitis media</td>
<td>Position paper</td>
<td>5–7 days of antibiotic therapy for uncomplicated cases</td>
</tr>
<tr>
<td>[61]</td>
<td>Community-acquired pneumonia</td>
<td>Prospective clinical trial</td>
<td>2 days of iv therapy followed by 8 days of oral therapy is as effective as 10 days of iv therapy</td>
</tr>
<tr>
<td>[62]</td>
<td>Community-acquired pneumonia</td>
<td>Review paper</td>
<td>Recommend individualized switch to oral therapy</td>
</tr>
<tr>
<td>[63]</td>
<td>Dentoalveolar infection (after drainage)</td>
<td>Uncontrolled clinical trial</td>
<td>2–3 days of antibiotic therapy found sufficient</td>
</tr>
<tr>
<td>[64]</td>
<td>Intraabdominal infections</td>
<td>Pharmacokinetic modeling</td>
<td>An individualized approach suggests that a shorter course is possible for many patients</td>
</tr>
<tr>
<td>[65]</td>
<td>Neonatal infections</td>
<td>Prospective clinical trial</td>
<td>C-reactive protein reported to be a useful guide to shorten total duration of antibiotic therapy</td>
</tr>
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serum concentration-vs.-time curve over 24 hours (AUC₀–₂₄) to MIC was <100. Not surprisingly, 17 of 32 isolates that became resistant during therapy were P. aeruginosa treated with monotherapy regimens no longer believed to be appropriate, such as 200–300 mg of ciprofloxacin every 12 hours or cefmenoxime. In contrast, the baseline ratio of the AUC₀–₂₄ to MIC for Enterobacter species was not predictive of emergence of resistance during monotherapy with cefmenoxime and ceftazidime. The authors believed that this occurred because these initially “susceptible” organisms harbor a subpopulation of derepressed mutants that constitutively produce large amounts of type 1 β-lactamase and that exhibit high-level resistance to cefmenoxime and ceftazidime. The ratio of AUC₀–₂₄ to MIC for these organisms is low, and as a result they are not expected to respond.

A final example of the uncertainty as to the appropriate dose for an antibiotic is illustrated by grepafloxacin, a new fluoroquinolone administered at a dosage of either 400 mg or 600 mg per day. Grepafloxacin is metabolized by the hepatic P450 enzyme, CYP1A2 [52]. Cigarette smoking induces this enzyme, and smokers metabolize grepafloxacin more rapidly than do nonsmokers, resulting in an AUC that is 40% lower. This effect was reported to “not have an effect on clinical efficacy” in smokers [51]. A reasonable conclusion is that nonsmokers with similar infections can be effectively treated with doses of grepafloxacin that are 40% less than the standard dose, or between 240 mg and 360 mg per day. Although this is not a serious recommendation, it illustrates the problem of knowing the correct dose for a new antimicrobial.

Ciprofloxacin is currently available in four dosage strengths for oral administration: 100 mg, 250 mg, 500 mg, and 750 mg, allowing for the greatest dosing flexibility among available quinolones. In contrast, levofloxacin is available in 250-mg and 500-mg tablets, and trovafloxacin is provided as a 100-mg or 200-mg tablet. If many different dosage forms and approved regimens become available for other newer antibiotics, each to be used for infections at different sites and organisms with differing susceptibilities, what are the implications? Will the use of smaller yet effective doses of an antibiotic for highly susceptible bacteria result in greater or lesser resistance? Since the use of any dose of an antibiotic will select for resistant strains, the magnitude of dose most likely determines which organisms are selected [57, 58]. Widespread use of lower yet effective doses and a shorter duration of therapy than currently recommended (below) is probably desirable from the point of view of resistance, because the selective pressure exerted by the antibiotic, presumably reflecting the overall tonnage of drug in the environment, will be reduced.

If subsequent investigations confirm that pharmacodynamic relationships can be used to individualize antibiotic doses, there remain a number of practical difficulties. Application of these concepts to patient care will be limited in a hospital that does not test and report quantitative susceptibility results [59]. Furthermore, antimicrobial therapy is already confusing infection, especially in the community setting, will further add to the confusion. A marketing strategy by the competition, by promoting a “one size fits all” antibiotic, will have appeal. However, if clinical data become available to support doses derived on pharmacodynamic principles, the resulting lower doses for treatment of highly susceptible pathogens may become an important method for delaying emergence of resistant organisms. Similarly, higher doses for treatment of patients infected with organisms requiring higher MICs, or combination chemotherapy, may be shown to reduce emergence of resistant strains.

What Is Optimal Duration?

“Most would agree that reducing the length of therapy minimizes exposure of bacteria to antibiotics and therefore reduces selective pressure for the emergence of resistance. However there is often little information regarding the optimal duration of treatment” [57].

The optimal duration of therapy is unknown for most infections. There are ethical concerns to conducting a randomized study to evaluate different durations of therapy, with the possibility that subjects will have treatment failure or relapse when the duration is too short, much like the difficulty of performing dose-response investigations. Consequently, there is a natural
bias to treat for an excessively long duration to minimize failure or relapse. Nevertheless, useful duration-response studies have been recently performed for many infections. Table 3 summarizes some recent clinical trials and position papers that have investigated or advocated a shorter duration of therapy for various infections.

One of the more contentious issues has been the recommended duration of antimicrobial therapy for acute otitis media [60]. It is beyond the scope of this paper to review all arguments, but a 1998 position paper from the Centers for Disease Control and Prevention and the American Academy of Pediatrics [60] recommended a 5- to 7-day duration instead of the more common 10 days. A 1999 position paper from the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group [66] recommended a larger dose of amoxicillin than historically used, 80–90 mg/(kg · d), but did not recommend a duration of therapy. Meta-analyses of trials of treatment for acute otitis media conclude that 5 days of therapy is similar in efficacy to a longer course [67, 68]. Although a longer course of treatment appears to be slightly more effective than treatment of 5 days’ duration, it was estimated that 44 children would have to receive a longer course of therapy (≥7 days) to prevent a single treatment failure (measured at 20–30 days after treatment) resulting from a 5-day course of treatment [67]. Even this 5-day duration of therapy has been challenged as being unnecessarily long, since most cases of acute otitis media are self-limiting [69]. A meta-analysis of six placebo-controlled trials of treatment for acute otitis media found that 60% of patients responded to both placebo and active drug at 24 hours, and the main benefit of antibiotic treatment is limited to reducing the probability of pain at 2–7 days [70]. The authors calculated that 17 children must be treated at initial presentation for each child that can be expected to benefit. Since the benefit of antimicrobial treatment appears small, dose- and duration-response studies in this disease will most likely show that all regimens are equally effective [69].

A shorter yet effective duration of therapy has many practical advantages, perhaps the most obvious being to decrease the overall selective pressure for resistant bacteria. It would be desirable during phase III trials of new antimicrobials to define the shortest effective duration of therapy. For example, it is commonly stated that patients are usually not compliant with the recommended duration of antimicrobial therapy and often terminate treatment when they feel better. Phase III investigations of a new oral antimicrobial could be conducted to determine the relationship between compliance and response, perhaps with use of computer chips implanted in the prescription vial cap, as has been done for antiretroviral therapy with HIV-1 protease inhibitors [71]. In addition, subjects participating in phase III trials could be randomized to a treatment arm with a fixed duration for the experimental and control agents and to a third arm of variable duration, such as for 2–3 days, after resolution of fever.

The dynamics of bacterial response to antibiotic exposure reflect both dose and duration [48]. A recent observational study of children 3–6 years of age found that both a lower-than-recommended dose of penicillin and a long duration of therapy (>5 days) were associated with selection of and colonization by penicillin-resistant pneumococci in the oropharynx [72]. Although there were a number of shortcomings of the study [57], the authors concluded that ensuring that the recommended dose is taken for a limited time sufficient to eradicate the infection may be less likely to encourage the selection of penicillin-resistant isolates. Perhaps analogous to this investigation, a low-dose formulation of doxycycline (Periostat; Collagenex Pharmaceuticals, Newtown, PA), 20 mg b.i.d., to be taken for 9–12 months, has recently been approved for dental use. Whether organisms with reduced susceptibility to doxycycline, such as H. influenzae and S. pneumoniae, will emerge and compromise the clinical utility of doxycycline for CAP remains to be determined.

**Will Optimal Use, Including Control of Antibiotic Use, Prevent or Slow the Emergence of Resistance?**

“It is unlikely that the resistance problem will rapidly wane, simply by being more prudent in our use of antimicrobial agents; on the other hand, it is certain that if we do not cut back on the use of these agents, the resistance problem will worsen” [73].

In 1994, McGowan [5] reviewed whether antibiotic control programs result in a reduction in the prevalence of resistance. He concluded that the existing data suffered from bias and confounding, such as simultaneous implementation of antibiotic restriction and infection-control procedures, and that a causal relationship between antibiotic restriction and resistance rates could not be established. There are additional methodological difficulties. These include the presence of a lag time between the change in antibiotic use and emergence of resistance, movement of patients from one unit to another, and antibiotic use in the community [2, 5]. In addition, population biologists have used mathematical models to argue that once a resistant gene has made its way into a bacterial population, even severe reductions in use of the antibiotic may reduce only the phenotypic expression of resistance [6]. Once antibiotic use resumes, resistance will rapidly emerge. Burke [74] has also argued that antimicrobial management programs are too intrusive to the physician and that the answer to improved antibiotic use lies in computer-assisted decision support that provides timely information and guidance and that encourages diversity of antibiotic selection.

A final problem of establishing the efficacy of antimicrobial control in reducing resistance has been called “squeezing the balloon” [74]. Many studies have shown that a reduction in use of an antibiotic in response to emerging resistance is often associated with a reduction in infection rates of a specific resistant organism [75, 76]. What is often not measured is the
resistance that can develop to the antibiotic used to replace the original offending agent. Despite these obstacles, recent investigations suggest that antibiotic control efforts may decrease resistance and nosocomial infections.

Finnish investigators reported that macrolide resistance among group A streptococci decreased significantly after educational efforts resulted in a substantial reduction in country-wide macrolide consumption [75]. Unfortunately, the educational efforts that were apparently so successful in curtailing antibiotic use in Finland have not been found to be particularly effective in North America [1]. Furthermore, if physicians simply switched from macrolides to a different antibiotic, a follow-up evaluation is required to determine whether resistance has emerged to the second antibiotic.

Frank et al. [77] reported the results of an antimicrobial restriction program at Indiana University Medical Center, a 365-bed teaching hospital. Prior approval for certain broad-spectrum, expensive antimicrobials resulted in a significant reduction in overall antibiotic use and expenditures. Infection-control procedures did not change over the 3-year study period. Comparisons, before and after implementation of the program, of rates of infections with certain marker organisms (including enterococcal bacteremia, selected gram-negative bacteremias, and methicillin-resistant S. aureus colonization) showed significant decreases. Other infections, including Clostridium difficile toxin–positive diarrhea and candidemia, did not change. Rates of resistance were not reported.

Finally, White et al. [78] prospectively investigated the effect of implementation of an antibiotic management program on antibiotic use and resistance rates. The program required prior approval for a variety of broad-spectrum antimicrobials at Ben Taub General Hospital, a 575-bed teaching hospital in Houston, over a 1.5-year period. Use of the restricted antimicrobials declined as expected, and the program saved sufficient antimicrobial expenses to pay for the cost of the program. More important, hospitalwide susceptibilities of a large number of organisms improved significantly, most importantly in the intensive care units. A follow-up of these reductions in resistance rates and antibiotic use will be required to document a long-term benefit.

Perhaps encouraged by these investigations, the Centers for Disease Control and Prevention announced in May 1998 the availability of funds to study the effects of novel antimicrobial management programs on antimicrobial resistance in community and institutional networks [79]. The notice states, “It is anticipated that these programs will be effective and that they could subsequently be replicated widely in order to reduce antimicrobial resistance throughout the U.S.” If these programs do result in more optimal antimicrobial use, and if a reduction of resistance is demonstrated, they may become national standards of care.

In 1999 the optimal use of modern antimicrobials can no longer follow the policies of the past—widespread use of the

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<th>Table 4. Comparison of the historical components of optimal antimicrobial use with an evolving strategy.</th>
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most broad-spectrum agents to cover all potential pathogens. The infectious diseases community has been challenged to adopt a sense of stewardship for ensuring optimal antimicrobial use [1]. Evidence is accumulating that the application of policies that optimize antibiotic selection, dose, and duration of therapy (table 4) can reduce or reverse the emergence of resistant pathogens without compromise of patient care.

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References


