Application of pharmacokinetics and pharmacodynamics to antimicrobial therapy of respiratory tract infections

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Antimicrobial dosing regimens historically have been based on the premise that serum concentrations must be higher than the minimum inhibitory concentration (MIC) of the antimicrobial against the pathogen. However, the relationship between serum concentrations and bacterial eradication has only recently been clearly defined, and MICs of some pathogens that are regarded as susceptible to some antimicrobial agents are actually higher than peak serum concentrations of these agents. Although the MIC is an important measure of antimicrobial activity, it does not take into account patient-, drug-, and pathogen-related factors that influence the outcome of antimicrobial therapy. Increasing pathogen resistance and documented treatment failures, particularly in respiratory tract infections, indicate a need to reevaluate dosing strategies with available agents to maximize antimicrobial effectiveness and limit the spread of resistance. It is now understood that to achieve bacteriologic and clinical success, sufficient concentrations of antimicrobial at the site of infection must be maintained for an adequate period of time. These dynamics are determined by combining drug pharmacokinetic and pharmacodynamic (PK/PD) data with MIC data. Different classes of antimicrobials have different patterns of bactericidal action based on pharmacokinetic and pharmacodynamic characteristics, and these patterns influence antimicrobial efficacy. PK/PD characteristics of an antimicrobial

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need to be integrated with MIC data to guide dosing strategies and predict bacteriologic and clinical outcomes. This approach not only improves antimicrobial efficacy but also serves to limit development of further pathogen resistance.

**Principles of pharmacokinetics and pharmacodynamics**

Pharmacokinetics describes the absorption, distribution, metabolism, and elimination characteristics of a drug in the human body (Table 1). Pharmacokinetic parameters that have been shown to correlate with antimicrobial efficacy are area under the serum-concentration-time profile (AUC), peak serum concentration ($C_{\text{max}}$), amount of time that the serum concentration of drug is above the MIC ($T > \text{MIC}$), the serum half-life, and penetration of drug into tissues [1]. For modeling purposes, pharmacokinetic parameters can be calculated either as one- or two-compartment models. In a one-compartment model, it is assumed that the drug is distributed equally and simultaneously to all body tissues. In a two-compartment model, drugs are considered to be distributed in the body in two phases: an initial equilibrating distribution phase into the blood and tissues with high blood flow and a second, slower equilibrating phase.

Pharmacodynamics refers to the actions the drug exerts in the body, including therapeutic effects. Drug pharmacodynamic correlates for antimicrobial therapy are MIC and duration of bactericidal effects, including persistent antibiotic (PAE) effects, rate of killing, and rate of development of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>Proportion of drug absorbed into the systemic circulation after administration. Drugs administered intravenously are usually 100% bioavailable (some are given as prodrugs); other dosage forms may be less bioavailable.</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Peak serum concentration of drug achieved following administration of a single dose.</td>
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<tr>
<td>$T_{\text{max}}$</td>
<td>Time to peak serum concentration.</td>
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<tr>
<td>$V_d$</td>
<td>Volume of distribution. A relative measure of the distribution of the drug throughout the body. $V_d &gt; 3$ L indicates drug is distributed outside the plasma.</td>
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<tr>
<td>AUC</td>
<td>Area under the serum concentration-time curve.</td>
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<tr>
<td>$t_{1/2}$</td>
<td>Elimination half-life. Time required for serum concentration of drug to be reduced by 50%. Also referred to as $\beta t_{1/2}$ to differentiate it from $\alpha t_{1/2}$, which designates the distribution $t_{1/2}$ of a drug.</td>
</tr>
<tr>
<td>$T &gt; \text{MIC}$</td>
<td>Amount of time that the serum concentration is above the minimum inhibitory concentration required for bactericidal/static effects. Applicable to antimicrobials only.</td>
</tr>
</tbody>
</table>
resistant mutants. Some antimicrobials continue to have bactericidal effects even after the antimicrobial has been cleared from the infection site. These post-antibiotic effects (PAEs) are observed in vivo with inhibitors of protein and nucleic acid synthesis with Gram-negative bacilli and Gram-positive cocci and with β-lactams against *Staphylococcus aureus*, but not with β-lactams against Gram-negative bacilli or streptococci [2,3]. Thus, β-lactams that exhibit time-dependent killing usually have minimal or short PAEs, which are therefore of negligible value in contributing to additional antimicrobial efficacy. Antimicrobials that inhibit protein and nucleic acid synthesis can be thought of as having a substantial PAE. A long PAE prevents regrowth after antimicrobial concentrations fall below the MIC. Antimicrobials exhibiting PAEs may be administered less frequently than would be predicted based on elimination half-life (t1/2). Thus, PAEs have a major impact on dosing. An understanding of these concepts has lead to improved dosing regimens for current antibiotics as well as the establishment of appropriate dosing regimens for new antibiotics. This has improved patient care. The interrelationships between these parameters are illustrated in Fig. 1. The PK/PD parameters that best correlate with efficacy for the various classes of antimicrobials are shown in Table 2.

![Fig. 1. Correlation between antimicrobial serum pharmacokinetics and pharmacodynamics of antimicrobials. Antimicrobial agents exhibit either time-dependent killing, in which efficacy correlates with duration of time the concentration exceeds the minimum inhibitory concentration (T > MIC), or concentration-dependent killing, in which efficacy correlates with Cmax/AUC or AUC/MIC. AUC, area under the serum concentration-time curve; Cmax, maximum plasma concentration.](image)
For agents with time-dependent effects, killing occurs once a threshold has been reached, and ceases once the drug concentration falls below this point. However, antimicrobial concentrations need not be above the MIC for the entire dosing interval. The duration of time that the nonprotein-bound drug fraction in serum is above the MIC of the pathogen is the PK/PD parameter that correlates with bactericidal efficacy and is expressed as a percentage of the dosing interval [4]. Time above MIC can be maximized by dosing more frequently, using sustained release delivery systems, using repository dosage forms, or with the concomitant use of a drug that inhibits the elimination of the antimicrobial (eg, probenecid with some β-lactams).

Attaining concentrations significantly higher than the MIC does not provide additional meaningful growth reductions.

In animal models such as in the neutropenic mouse thigh infection model, maximal survival 4 days after *S pneumoniae* inoculation was seen when serum concentrations of amoxicillin or amoxicillin-clavulanate exceeded the MIC of the test organism for 40% to 50% of the dosing interval [5]. In four different animal models of *S pneumoniae* infection, bactericidal activity of penicillin occurred when concentrations exceeded the MIC for at least 65% of the dosing interval in murine infections and at least 35% of the dosing interval in rabbit tissue cage infection models [5]. For broad-spectrum cephalosporins, concentrations above the MIC for 35% to 40% of the dosing interval produce

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### Table 2
Antimicrobial agents classified by pattern of bactericidal activity

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Pharmacodynamic class</th>
<th>Therapeutic goal (for <em>S pneumoniae</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>Time-dependent</td>
<td>Time above MIC greater than 40% to 50% of the dosing interval</td>
</tr>
<tr>
<td>penicillins</td>
<td></td>
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<tr>
<td>cephalosporins</td>
<td></td>
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</tr>
<tr>
<td>Macrolides</td>
<td>Time-dependent</td>
<td>AUC to MIC ratio of 25–35 for macrolides; unknown for telithromycin</td>
</tr>
<tr>
<td>erythromycin</td>
<td>(with moderate to prolonged persistent effect)</td>
<td></td>
</tr>
<tr>
<td>clarithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>azithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketolides</td>
<td>Concentration-dependent (with prolonged persistent effect)</td>
<td>AUC to MIC ratio of 25–35</td>
</tr>
<tr>
<td>telithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
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<tr>
<td>gatifloxacin</td>
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<tr>
<td>gemifloxacin</td>
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<td>levofloxacin</td>
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<tr>
<td>moxifloxacin</td>
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</tbody>
</table>

**Abbreviations:** AUC, area under the serum concentration-time curve; MIC, minimum inhibitory concentration.


*Time-dependent agents with no significant post-antiobiotic effects*

For agents with time-dependent effects, killing occurs once a threshold has been reached, and ceases once the drug concentration falls below this point. However, antimicrobial concentrations need not be above the MIC for the entire dosing interval. The duration of time that the nonprotein-bound drug fraction in serum is above the MIC of the pathogen is the PK/PD parameter that correlates with bactericidal efficacy and is expressed as a percentage of the dosing interval [4]. Time above MIC can be maximized by dosing more frequently, using sustained release delivery systems, using repository dosage forms, or with the concomitant use of a drug that inhibits the elimination of the antimicrobial (eg, probenecid with some β-lactams). Attaining concentrations significantly higher than the MIC does not provide additional meaningful growth reductions.

In animal models such as in the neutropenic mouse thigh infection model, maximal survival 4 days after *S pneumoniae* inoculation was seen when serum concentrations of amoxicillin or amoxicillin-clavulanate exceeded the MIC of the test organism for 40% or more of an 8-hour dosing interval [5]. In four different animal models of *S pneumoniae* infection, bactericidal activity of penicillin occurred when concentrations exceeded the MIC for at least 65% of the dosing interval in murine infections and at least 35% of the dosing interval in rabbit tissue cage infection models [5]. For broad-spectrum cephalosporins, concentrations above the MIC for 35% to 40% of the dosing interval produce
bacteriostatic effects against *S. pneumoniae* despite variations in MIC, and maximal efficacy is approached when concentrations are above the MIC for 60% to 70% of the dosing interval [3]. With staphylococci, concentrations above the MIC for 40% or more of the dosing interval are sufficient. For immunocompetent individuals, bacteriostatic effects are deemed acceptable for a positive outcome, because host defenses play a significant role in eradicating infection. Thus, it is generally agreed that for β-lactams, significant bacterial reduction is achieved when concentrations are above the MIC for approximately 40% to 50% of the dosing interval, regardless of infecting pathogen and level of resistance. Evidence suggests that for the carbapenems, a shorter time above the MIC is necessary for efficacy (20% to 30%) than for β-lactams [6].

**Time-dependent agents with significant post-antibiotic effects**

The PK/PD profile seen with macrolides/azalides (such as erythromycin, clarithromycin, and azithromycin), clindamycin, tetracyclines, and oxazolidinones is time-dependent killing with prolonged PAEs [7–9]. The goal of the dosing regimen is to optimize the amount of drug exposure, with AUC:MIC ratio the major parameter correlating with efficacy. Compared with erythromycin, the newer macrolides, azithromycin and clarithromycin, have improved oral bioavailability, longer elimination t1/2, long PAEs, and achieve higher intracellular concentrations [10,11]. The differences in pharmacokinetic profiles among the macrolides influence their varying efficacy profiles against respiratory pathogens. In an early pharmacodynamic study, the antibacterial effects of azithromycin and clarithromycin were compared using strains of *S. pneumoniae*, *S. aureus*, *H. influenzae*, and *M. catarrhalis*, using a pharmacodynamic model simulating the dynamics of serum concentrations of each drug found in human serum after oral administration of recommended doses [12]. In general, killing was dependent on Cmax/MIC ratios, as well as the duration of time levels exceeded the MIC. Killing by azithromycin occurred at a slower rate compared with clarithromycin. Regrowth after reduction of the initial inoculum was observed with azithromycin in all cultures, but not with clarithromycin.

A more recent study evaluated the serum bactericidal activity (SBA) of clarithromycin and azithromycin against *S. pneumoniae* strains [13]. Healthy volunteers received a 500-mg oral dose of clarithromycin, and after a 1-week washout, a 500-mg dose of azithromycin. Blood samples, obtained before dosing and at 2-hour intervals for 12 hours after drug administration, were used to determine serum bacteriostatic and bactericidal titers against a reference strain and various clinical isolates of *S. pneumoniae*. Clarithromycin exhibited SBA for 6 hours (50% of its normal dosing interval) for strains with MICs less than or equal to 2 μg/mL, and, although SBA was not observed at MICs greater than 4 μg/mL, clarithromycin did inhibit clinical isolates with
MICs equal to 4 μg/mL. In contrast, azithromycin exhibited SBA for 6 hours (25% of its dosing interval) for MICs less than or equal to 0.5 μg/mL only, and inhibitory activity was observed only for strains with MICs equal to 1.0 μg/mL. The differences between the two compounds were postulated to be explained by higher peak serum concentrations attained with clarithromycin.

Peak serum levels of azithromycin and clarithromycin do not reach the MICs of these agents against *H. influenzae* [14]. Combined with the fact that the major respiratory pathogens are located extracellularly, while macrolides accumulate intracellularly, it is not surprising that these agents are virtually inactive against this respiratory pathogen in sites where serum concentrations are predictive of local drug concentrations [15,16].

Animal models of infection suggest that the AUC/MIC ratio based on free-drug AUC values that correlate with efficacy against *S. pneumoniae* for most macrolides, azalides, and clindamycin is 25 to 50, whereas higher ratios (up to 100) improve survival [9,17].

**Concentration-dependent killing**

For antimicrobials that exhibit concentration-dependent killing, the ratios of unbound serum C\text{max}/MIC and area under the unbound serum concentration-time curve (AUC)/MIC are the parameters that correlate best with bactericidal efficacy. Increasing the dose of a drug with concentration-dependent effects is associated with increased bacterial killing.

Several pharmacokinetic features of the quinolones make them attractive for use in respiratory tract infections. They are extensively distributed into neutrophils, macrophages, and respiratory and lung tissues in concentrations higher than those attained in serum [11,18]. Quinolones exhibit concentration-dependent killing, and their efficacy relates to either the ratio of AUC/MIC or C\text{max}/MIC. In general, optimal bactericidal activity of all quinolones against Gram-positive pathogens occurs at an AUC/MIC ratio of at least 25 to 30 [19–21]. In a recent study using an in vitro pharmacokinetic model, total eradication of four different *S. pneumoniae* strains with gatifloxacin was achieved when AUC/MIC ratios were at least 27 to 36 [19]. With AUC/MIC values of between 17 and 22, viable bacterial counts were unchanged or increased. Against Gram-negative pathogens, AUC/MIC ratios for the quinolones should be at least 100 or 125 for optimal bactericidal efficacy [21].

Compared with other classes of antimicrobials, the PK/PD of the quinolone family have been more extensively studied, including as predictors of efficacy in clinical trials. The pharmacodynamics of levofloxacin and their relationship to efficacy outcomes were studied prospectively in 134 hospitalized patients with culture-proven infections, the majority of which (75%) were of the respiratory tract [22]. Therapeutic dosages of levofloxacin (500 mg twice daily for 5 to 14 days) were associated with a clinical success
rate of 99% when $C_{\text{max}}/\text{MIC}$ ratio was equal to or greater than 12 and $AUC/\text{MIC}$ ratio was equal to or greater than 100, whereas clinical success rate was 88.5% when $C_{\text{max}}/\text{MIC}$ ratio was between 3 and 12 and $AUC/\text{MIC}$ ratio was between 25 and 100 [22,23].

Although the pharmacokinetic properties of many quinolones make them attractive for use in the treatment of respiratory tract infections, safety issues [24–26] and resistance development [27,28] raise concerns about their broad use. For example, several fluoroquinolones have been withdrawn from the market (eg, temafloxacin for hemolysis, grepafloxacin for cardiotoxicity) or have had warnings added to their labeling (eg, hepatotoxicity with trovafloxacin, QTc interval prolongation with gatifloxacin) following discovery of severe adverse events associated with their use [24,29,30]. In addition, all fluoroquinolones have the same mechanisms of action and resistance; by inhibiting bacterial DNA gyrase and topoisomerase IV, they inhibit DNA supercoiling and relaxation, ultimately leading to bacterial cell death [31]. Consequently, when microbial resistance develops against one fluoroquinolone, it is likely to affect all fluoroquinolones, although to varying degrees. If widespread use of fluoroquinolones continues, microbial resistance to these agents also will increase, decreasing the clinical utility of this class of antimicrobials. To prevent this occurrence, fluoroquinolones should be reserved for patients who do not improve after treatment with other classes of antimicrobials or those with severe disease.

Ketolides also have concentration-dependent activity, although the PK/PD relationships of these agents are still under investigation. For one of the ketolides, telithromycin, the $AUC/\text{MIC}$ ratio that correlates with efficacy for *S pneumoniae* may be much higher (between 50 and $\geq 200$) than for other agents in this class [17,32].

**Mutant prevention concentration**

Recently, another PK/PD parameter has been proposed as a means by which the selection of resistant mutant strains can be restricted [33–35]. This concept applies to antimicrobials where the primary mechanism of resistance is simple selection of resistant mutants in a population of a pathogen [36]. Therapeutic concentrations of antimicrobials that are active against the majority of susceptible pathogens are often those at which the resistant mutant population of the bacterial colonies can become selectively enriched [34]. The mutation prevention concentration (MPC) is defined as the lowest concentration of antimicrobial that prevents bacterial colony formation from a culture containing more than $10^{10}$ bacteria. The mutant selection window is defined as the concentration range in which resistant mutants are selectively enriched during antimicrobial therapy. The concept of MPC and mutant selection window for the effects of ciprofloxacin and norfloxacin on *S aureus* in vitro are illustrated in Fig. 2 [35]. The PK/PD parameter that
avoids selection of resistant mutants is to achieve an AUC/MIC ratio of >100, whereas AUC/MIC ratios of 25 to 100 are regarded as being in the mutant selection window, and AUC/MIC ratios of < 25 generally fail to suppress the growth of susceptible populations [36].

Application of pharmacokinetics and pharmacodynamics to antimicrobial agents

Comparative clinical trial data of adequate power to discriminate between the efficacies of antimicrobial agents is the cornerstone of determining drug efficacy. In antimicrobial clinical research, however, obtaining and identifying pathogens involved in respiratory tract infections and monitoring bacteriologic response to antimicrobial therapy in sufficient numbers of patients is difficult because of several factors, including: unwillingness of patients to submit to invasive and uncomfortable procedures to obtain samples for

Fig. 2. The mutant prevention concentration (MPC) and mutant selection window for fluoroquinolones (ciprofloxacin and norfloxacin) against Staphylococcus aureus in vitro (Adapted from Zhao X, Drlica K. Restricting the selection of antibiotic-resistant mutant bacteria: measurement and potential use of the mutant selection window. J Infect Dis 2002;185(4):561-2; with permission.)
culture from the middle ear, lungs, or sinuses; difficulties in separating the contribution of host defense mechanisms from antimicrobial activity to infection eradication; inconclusiveness of culture results when samples of infected tissue/fluids are obtained; and the time and costs necessary to evaluate efficacy over a broad therapeutic dose range. Nevertheless, bacteriologic efficacy studies have frequently been performed in otitis media studies and allowed PK/PD correlations to be made in humans. Given the problems inherent in obtaining dose-response relationships in clinical infection studies, the majority of antimicrobial PK/PD data are obtained from animal models of infection and in vitro models. Such data are compelling even in the absence of clinical data when multiple studies using a variety of experimental methods arrive at the same conclusions, as has been the case in antimicrobial research.

**Animal models of infection**

Animal models are an integral part of the evaluation of antimicrobials. Studies in rats, mice, and rabbits have been used to define PK/PD parameters for antimicrobials, including the time course of antimicrobial activity, degree of drug penetration to the site of infection, magnitude of the parameters that correlate with antimicrobial efficacy, dose-response relationships, and comparative efficacy between agents. The neutropenic mouse model is one of the most common animal infection models used in this regard. A neutropenic state, achieved by injecting intraperitoneal cyclophosphamide several days before injection of inoculum, eliminates the contribution of host defense mechanisms to the eradication of infection or allows use of pathogens with low virulence in mice such as some serotypes of pneumococci. A thigh injection model is advantageous for study because the thigh muscle can be easily inoculated, removed, and homogenized for assessment of study parameters. A limitation to the application of this model to humans is that thigh infections do not simulate common human sites of infections by these pathogens.

The thigh infection model in neutropenic mice was used to describe the in vivo post-antibiotic effects of various antimicrobials (discussed earlier) [2]. In these experiments, infection was created by injecting the thighs of the mice with clinical isolates of $10^5$ to $10^6$ colony-forming units (CFU) of *S. aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, or *Escherichia coli*. Beginning 2 hours after inoculation, mice received subcutaneous injections of one of the antimicrobial agents being studied, the doses of which were based on producing serum concentrations exceeding the MICs of the study organisms for 1 to 4 hours. Pharmacokinetic parameters were described for single doses; post-antibiotic effects were determined from pharmacokinetic observations, MIC, and log changes in bacterial load in the thighs over time obtained after multiple inoculations and antimicrobial injections.
Neutropenic mice also were used to demonstrate the importance of the dosing interval to β-lactam efficacy and the AUC/MIC ratio to aminoglycoside efficacy in thigh infection and pneumonia models [4]. Neutropenia and *K. pneumoniae* thigh infections were induced as described earlier [2]. Pneumonia was induced by exposing mice to aerosolized cultures of 4 to 5 × 10^{12} CFU/min of *K. pneumoniae* in a closed chamber. Various dosing regimens, achieving serum concentrations above and below those achieved in humans, were used for treating infected mice. Changes in bacterial load, serum pharmacokinetics, and tissue concentrations of drug were assessed. E_{max} (maximum drug effect) modeling, effective in determining the slope of the dose-response curve, determined that the dosing interval had significant impact on antimicrobial efficacy. The duration of time that serum levels exceeded the MIC during a 24-hour period was the only pharmacokinetic parameter that had significant correlation to β-lactam efficacy in both infection models. For aminoglycosides, the important pharmacokinetic parameter predicting efficacy was AUC/MIC ratio.

Although antimicrobial agents generally are eliminated much more rapidly in animals than in humans, the magnitude of the pharmacokinetic parameters is similar. To more closely simulate human pharmacokinetics, renal impairment can be produced in mice with peritoneal uranyl nitrate injections at least 3 days before study. This method was used in neutropenic mice to correlate in vivo efficacy of amoxicillin and amoxicillin-clavulanate with time above MIC in thigh infections caused by *S. pneumoniae* [37].

Other animal models of infection include pneumococcal murine peritonitis, bacteremia, otitis media, and rabbit tissue cage infection [5,38]. PK/PD data obtained from murine peritonitis and rabbit tissue cage infection models correlated well with data obtained from pneumococcal murine thigh and pneumonia infections.

**In vitro pharmacokinetic models of infection**

In vitro pharmacokinetic models are becoming increasingly popular in antimicrobial research [19,39–44]. Results from studies using these models complement animal data. Although various models have been described, in general, they use a series of reservoirs, pumps, filters, and tubing to simulate a two-compartment pharmacokinetic model, in which the first (central) compartment mimics distribution of drug through the systemic circulation, and the second (peripheral) compartment represents distribution of drug to the site of infection. Bacteria are introduced into the model at concentrations similar to those that would be expected in infection, with incubation and constant stirring to ensure continued growth and homogenous mixing of the culture. Antimicrobial agents are added to the model at varying concentrations and intervals, exposing bacteria to changing antimicrobial concentrations. Drug pharmacokinetics are simulated by changing concentrations through the addition of broth diluent and elimination of
drug-containing broth through an elimination reservoir. Other, more sophisticated systems use computer-controlled flow meters and pumps for more accurate simulation of the human serum-concentration time profile [39].

In vitro pharmacokinetic models are easily reproducible and amenable to manipulation of antimicrobial concentration, antimicrobial elimination half-life, bacterial load, and pH, and thus accommodate a wide variety of pharmacodynamic applications. They are far less costly and time-consuming than clinical trials. In addition, the problem of host defense mechanisms contributing to bacterial reduction is eliminated. These characteristics make in vitro models valuable adjuncts to animal models and clinical data for antimicrobial pharmacodynamic evaluations.

In an in vitro pharmacokinetic model, the effects of different doses of amoxicillin were compared for treatment of simulated pneumococcal otitis media [42]. Nine different clinical isolates of logarithmic phase cultures of *S* pneumoniae were exposed to amoxicillin peak concentrations of 3, 6, and 9 μg/mL every 12 hours to reflect middle-ear concentrations following oral doses of 15, 35, and 45 mg/kg every 12 hours, respectively. Adjusting pump flow rate simulated a t1/2 of 6 hours. Amoxicillin doses and elimination t1/2 from the middle-ear fluid were estimated based on the few published data available in chinchillas and humans. All three doses rapidly decreased bacterial counts for penicillin-susceptible strains, with equal rates of killing. For penicillin-intermediate and -resistant strains, results were more variable. The 3-μg/mL peak was unable to maintain reductions in viable bacterial counts for two of three penicillin-intermediate strains and all penicillin-resistant strains tested. For penicillin-resistant strains, this effect was evident during the first 12-hour dosing interval. Viable counts of both penicillin-intermediate and -resistant strains were reduced by the higher dosages. The 6- and 12-μg/mL peaks were active against most of the penicillin nonsusceptible strains; the minimum effect being able to reduce growth by at least 1.5 logs. When inoculum regrowth was observed, it coincided closely to the time when the amoxicillin concentration fell below the MIC, supporting the time-dependent pattern of activity of β-lactams. These data, together with limited human data, were among the first to influence changes in standard amoxicillin dosing in acute otitis media (AOM).

*Correlation between plasma and tissue concentrations*

Because many common bacterial infections are extracellular, it is the concentration of antimicrobial in the interstitial fluid that is pharmacodynamically active against these infections. Determining antimicrobial pharmacokinetics, including the extent of penetration, in an infected interstitial area has not been achieved easily. The volume of distribution (Vd), calculated from serum pharmacokinetics, gives an idea of the compartment size occupied by the drug in the body but does not reveal the actual sites of distribution. For example, a Vd greater than 3 L merely indicates that drug is distributed outside the plasma, because this compartment comprises a volume of 3 L [45]. The
ability of a drug to penetrate tissues also depends on its lipid solubility and plasma protein binding. Drugs that are hydrophilic, such as β-lactams and aminoglycosides, diffuse freely into the interstitial fluid without penetrating cells. Only the free, unbound portion of drug is able to be distributed outside the plasma and be pharmacodynamically active. Thus, free serum concentrations are a more accurate measure of available drug than total serum concentrations. Protein binding can affect drug clearance, thereby increasing serum concentrations. Observations that increased protein binding of antimicrobials eliminated by glomerular filtration increases the t_{1/2} of the drug and prolongs the time above MIC have been important in the development of some cephalosporins [46,47]. Human serum drug concentrations often are considered an acceptable surrogate marker when determining antimicrobial PK/PD in nonmeningeal infections, because they are more accurate than tissue concentrations obtained in animal models of infection using tissue homogenates. Tissue homogenates mix interstitial, intracellular, and vascular compartments within the tissue and thus may underestimate or overestimate the concentration of drug in the interstitial space, depending on the intracellular penetration of the agent being investigated.

The newer macrolide and quinolone antimicrobials are distributed extensively to body tissues, including respiratory tissues, at concentrations higher than those attained in serum [18,48,49]. However, not all agents penetrate to the same degree, and free antibacterial concentrations in serum may not be proportional to those in other body fluids with all macrolides or quinolones. Indeed, serum levels of ciprofloxacin are below the MIC of drug necessary to inhibit 90% of isolates (MIC_{90}) of \( S \) pneumoniae, and borderline against \( S \) aureus, although there is some evidence that levels attained at the site of infection are bactericidal [18]. A recent experiment used human tonsillar pharmacokinetic data for azithromycin and roxithromycin in the central compartment of an in vitro pharmacokinetic model to compare their antibacterial effects [40]. The areas between the control growth and time-kill curves were 22% and 36% greater with azithromycin than with roxithromycin for \( S \) pyogenes and \( S \) pneumoniae, respectively. In addition, bacterial regrowth was observed with roxithromycin but not with azithromycin. These differences might not have been apparent had plasma concentrations been used, because the plasma concentration of roxithromycin is higher than that of azithromycin. However, in tonsillar tissues, the concentration of azithromycin is 55 times greater than that of roxithromycin, and in sinus mucosa, the azithromycin concentration is six times higher than that of roxithromycin.

Thus, for some antimicrobials, their efficacy in respiratory tract infections might best be elucidated using tissue instead of plasma concentrations. In a human otitis media study, plotted amoxicillin middle-ear fluid concentrations after a 25-mg/kg dose were generally less than those attained in serum, and time to peak concentration (T_{max}) was delayed slightly [50]. Nonetheless, in 60% of children studied, middle-ear fluid concentrations were above the amoxicillin breakpoint for resistant pneumococci (>2.0 μg/mL).
A blister technique is sometimes used for assessing interstitial antimicrobial concentrations. After multiple doses of the antimicrobial under study are administered to achieve steady state, blister formation is induced on the forearm with an irritant/vesicant preparation. Blister fluid samples and plasma samples can then be compared pharmacokinetically to determine the relative penetration of the antimicrobial. For example, using this method, the $C_{\text{max}}$, $T_{\text{max}}$, $t_{1/2}$, and AUC were determined for linezolid, a member of the oxazolidinones, a new class of antimicrobials, in both plasma and blister fluid [51]. The mean penetration of linezolid into inflammatory fluid relative to plasma was 104%.

Whenever possible, known human tissue pharmacokinetic data at the site of infection should be used in antimicrobial pharmacokinetic analyses. When these are not available, free serum concentrations are a reasonable alternative.

**Effects of obesity on pharmacokinetics/pharmacodynamics**

Obesity is associated with increased $V_d$ and enhanced total body clearance of antimicrobials [52]. Depending on the patient and drug, the magnitude of these changes can affect antimicrobial efficacy. With hydrophilic antimicrobials such as $\beta$-lactams and aminoglycosides, using total body weight for dosing overestimates $V_d$ and may result in overdosage. Conversely, using ideal body weight for hydrophilic antimicrobials underestimates $V_d$. For this reason, the use of a correction factor is advocated to normalize $V_d$ when dosing hydrophilic antimicrobials in obese patients [52,53]. Increased renal elimination and hepatic metabolism also have been documented in obese patients; thus, drugs eliminated by these mechanisms may not achieve adequate concentrations at the site of infections for sufficient periods of time at standard doses [52,53]. Unfortunately, the net effect of these changes on antimicrobial dosing in respiratory tract infections in obese patients is largely unknown because of the paucity of data on this subject.

**Correlation of pharmacokinetic/pharmacodynamics parameters to antimicrobial efficacy for combinations of antimicrobials**

Pharmacodynamic relationships have not been adequately defined for combinations of antimicrobials. One study suggests that the same PK/PD parameters determining efficacy of agents used alone apply to agents used in combination [54]. Additive or synergistic effects between agents that exhibit different patterns of killing may alter the magnitude of the PK/PD relationship, and additional work is needed in this area.

**Pharmacokinetic/pharmacodynamic relationships and bacterial resistance**

The increasing prevalence of antimicrobial resistance, including multiple drug resistance, among the three key respiratory pathogens *S. pneumoniae*,
H influenzae, and M catarrhalis has been well documented through ongoing surveillance programs [55–59]. It has been suggested that reports of treatment failures now being seen in clinical practice and documented in the literature represent the “tip of the iceberg” with respect to the impact that resistance has on successful clinical treatment of infection [60–62]. Thus, in addition to successfully treating the infection at hand, a primary goal of antimicrobial therapy is to limit the spread of resistance. Recently, several reports of clinical failure after empiric treatment of pneumococcal infections with azithromycin (500 mg orally on day 1, followed by 250 mg orally on days 2 to 4), clarithromycin (500 mg orally twice daily), or levofloxacin (500 mg orally once daily) have been published [63–65]. Of particular note is a case report involving a 28-year-old patient who died of complications relating to treatment failure with intravenous azithromycin (500 mg once daily) [66]. Evaluation of sputum cultures revealed that the initial isolate was susceptible to penicillin, clindamycin, erythromycin, azithromycin, and quinupristin-dalfopristin. However, a mutation near the macrolide-binding site on the 23s RNA occurred during the course of treatment, resulting in development of resistance to erythromycin, azithromycin, and quinupristin-dalfopristin. Consequently, the patient relapsed and died.

Numerous pathways exist by which resistant bacteria are selected. These include acquisition of resistance through genetic mutations, horizontal transfer of genetic material from a resistant genus or species to a susceptible one, emergence of inducible resistance, and selection of a small, resistant subpopulation of organisms [67]. A change in as little as a single amino acid can result in the genetic promulgation of resistance.

The magnitude of PK/PD parameters required to produce clinically meaningful antimicrobial efficacy in susceptible organisms is not different in resistant organisms [1,5,20]. In four different animal S pneumoniae infection models, the bactericidal activity of penicillin correlated with time above MIC and was significant when time above MIC was at least 65% of the experimental time for both penicillin-susceptible and -nonsusceptible strains [5]. Similarly, a number of experiments have shown that the AUC/MIC ratios required for various quinolones to produce a 2 log10 kill of ciprofloxacin-resistant S pneumoniae strains were similar to those for ciprofloxacin-susceptible strains [20].

Resistant mutants represent the minority of a given susceptible bacterial population. Once resistant mutants are generated, they can be selected for and flourish under certain environmental conditions, such as during prolonged exposure to subinhibitory antimicrobial concentrations or when bacteria are exposed to very high antimicrobial concentrations for a very short period followed by prolonged subtherapeutic levels. These conditions can be created via inadequate dosing and poor compliance with antimicrobial therapy. Susceptible bacteria will be killed but those with mutations that lead to resistance will proliferate. This phenomenon has been demonstrated in clinical settings, where suboptimal antimicrobial PK/PD in lower respiratory tract
infections were found to be a risk factor for the emergence of resistant strains [68]. Data from 107 patients (128 organisms) participating in four clinical trials of nosocomial lower respiratory tract infections at one study site demonstrated that the probability of developing resistance increased significantly when the AUC/MIC ratio was less than 100, with the exception of β-lactam monotherapy against Bush type 1 β-lactamase–producing Gram-negative organisms. Thus, by maximizing PK/PD parameters with adequate dosing, the selection of resistance can be minimized. If infection with an antimicrobial-resistant pathogen is suspected or likely because of patient risk factors, higher doses of certain antimicrobials may be used. Guidelines for the management of acute otitis media and acute bacterial sinusitis recommend higher doses of amoxicillin or amoxicillin/clavulanate in patients at risk of infection with resistant pathogens (eg, previous antimicrobial therapy) [69,70].

The concept of the MPC and mutant selection window is based on the idea that an antimicrobial concentration exists at which resistant mutants can be selectively amplified, with the upper boundary being the antimicrobial concentration that blocks growth of resistant mutants, and the lower boundary being the drug concentration at which growth of the susceptible cells begins [34,71]. In vitro studies using various isolates of Mycobacterium tuberculosis have estimated the MPCs of fluoroquinolones and other antituberculosis agents by plating more than 10^10 cells on drug-containing agar and determining the concentration that allowed no growth of colonies [72]. Of the agents tested, only two fluoroquinolones had MPCs that were below their serum C_{max} values; thus, only these agents would be expected to restrict the selection of resistant mutants when used at recommended doses (Table 3). Other in vitro studies have shown that structural changes in the quinolone molecule substantially impact the magnitude of the MPC [33].

The MPC and mutant selection window have been determined with numerous antimicrobials and bacteria (although not with common respiratory pathogens), and findings suggest they are probably applicable to most pathogen-antimicrobial relationships. Confirmation of these observations is necessary in animal and clinical infection models to more completely support the MPC concept. If relevant concentrations of an antimicrobial in the infected tissue can be maintained above the MPC, then selection of mutants should be severely restricted. Additional work with MPC and mutant selection window may prove to have important implications for limiting the spread of resistance by changing dosing patterns.

Use of pharmacokinetics and pharmacodynamics to optimize treatment and minimize resistance

Drug PK/PD can be combined with MIC values to determine the adequacy of antimicrobial dosing regimens. For example, plasma and middle-ear fluid data were used to determine the pharmacodynamics of
amoxicillin in the treatment of AOM [50]. Thirty-four children with AOM received amoxicillin doses of 40 mg/kg/day divided in three doses for 2 to 3 days, followed by a single 25-mg/kg dose of amoxicillin. Serum and middle-ear fluid amoxicillin concentrations from the infected ear(s) were measured 0.5 to 4 hours after the 25-mg/kg dose. The most frequently occurring bacterial pathogens were *S pneumoniae* and *H influenzae*. Total middle-ear fluid amoxicillin concentrations were maintained above 1\(\mu\)g/mL for 4 hours (50% of the dosing interval) and above 2.0\(\mu\)g/mL for 2.5 hours (31% of the dosing interval). This corresponded to plasma concentrations being above 2.0\(\mu\)g/mL for 62% of the dosing interval, predicting approximately 100% killing even of most penicillin-resistant pneumococci. Plasma concentrations following a 13.3-mg/kg dose, estimated assuming linear absorption kinetics, only exceeded an MIC of 1.0\(\mu\)g/mL for 30% of the dosing interval. Thus, at standard dosing of 25 mg/kg/day, amoxicillin is ineffective against penicillin-resistant pneumococci. Based on these observations, the investigators recommended an amoxicillin dosing increase from 40 mg/kg/day to 75 to 90 mg/kg/day.

Drug PK/PD also guide new antimicrobial drug development. Two new formulations of amoxicillin/clavulanate have been developed to increase the effectiveness of the combination against pathogens with increasing resistance to amoxicillin. The pediatric formulation, previously mentioned, has a recommended dosing schedule of 90 mg/kg/day divided every 12 hours. The second, adult formulation provides both immediate- and sustained-release amoxicillin in a 16:1 ratio with clavulanate (2 g amoxicillin/125 mg clavulanate per dose; recommended dosing every 12 hours) [73]. In healthy adults, this new formulation was as well tolerated as the current formulation. In addition, the duration of time that serum levels exceeded 4\(\mu\)g/mL was 49.4% of a 12-hour dosing interval. Compared with conventional amoxicillin-clavulanate formulations, the pharmacokinetically enhanced formulation has a slower decline in plasma concentrations, contributing to a longer time above MIC (Fig. 3).

### Table 3

The activity (expressed as minimum inhibitory concentration for 99% of organisms [MIC\(_{99}\)] and mutation prevention concentration [MPC]) and maximum serum concentrations (C\(_{\text{max}}\)) of antituberculosis agents against *Mycobacterium tuberculosis*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (mg)</th>
<th>MIC(_{99}) ((\mu)g/mL)</th>
<th>MPC ((\mu)g/mL)</th>
<th>C(_{\text{max}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>600</td>
<td>0.02</td>
<td>&gt;80</td>
<td>9.5</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1000</td>
<td>0.2</td>
<td>&gt;320</td>
<td>34</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>250</td>
<td>0.06</td>
<td>20</td>
<td>7.6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>750</td>
<td>0.15</td>
<td>8</td>
<td>4.4</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400</td>
<td>0.037</td>
<td>2.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>200</td>
<td>0.075</td>
<td>2.5</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Once the PK/PD breakpoint has been established, the question remains as to how frequently it is achieved in patients. The closer MIC values of pathogens are to breakpoints, the more variation between individuals. Monte Carlo simulation affords a means by which probability outcomes, such as achieving the PK/PD target, can be attained without the rigor, time, and expense of a clinical trial. It has been recently introduced in the area of pharmacodynamics [74–77]. Pharmacokinetic values for levofloxacin obtained from a sample of patients and published levofloxacin MIC surveillance data for clinical isolates were used to generate thousands of random, single-point AUC/MIC estimates, and their probability of occurrence were plotted. Using this methodology and sample data from patients, the probability of attaining an AUC/MIC ratio greater than or equal to 30 with levofloxacin was 99% [76]. Another Monte Carlo simulation assessed the probability of achieving target AUC/MIC ratios for *S. pneumoniae* with intravenous, once-daily gatifloxacin 400 mg or levofloxacin 500 mg with AUC data obtained from acutely ill patients with community-acquired infections [77]. The median AUC/MIC ratios were 144 for gatifloxacin and 50 for levofloxacin. The probability of attaining AUC:MIC ratios of 30 and 100 for gatifloxacin were
99% and 68%, and for levofloxacin were 82% and 17%, respectively (Fig. 4). Gatifloxacin in this study therefore had a higher probability of achieving these target AUC:MIC ratios than levofloxacin at a 500-mg dose, and use of the new 750-mg dose of levofloxacin is recommended. Monte Carlo simulation, using patient-based AUC and MIC distributions, may have implications for selection of optimal antibiotics for the empiric treatment of infections. Using PK/PD values from sick patients rather than healthy individuals provides a more accurate portrayal of antimicrobial PK/PD. For example, the mean levofloxacin AUC in healthy volunteers is 47.5 mg·L/hour. In the Monte Carlo analysis described previously in which patients received once-daily doses of levofloxacin 500 mg, 92% of patients had AUC values greater than or equal to 51, and 12% had AUC values greater than or equal to 121.75 The differences between these values reflect the effects of age (many patients were older than 70 years of age), renal function (the mean creatinine clearance of patients was half that of younger, healthy volunteers), and possibly other aspects relating to infection that might alter drug pharmacokinetics. Had published AUC values for young, healthy volunteers been used, the accuracy of the derived probabilities would be in question.

Another model, the Poole Therapeutic Outcome Model, can be used to predict bacteriologic and clinical efficacy of various antimicrobials based on frequency distributions of pathogens, spontaneous resolution rates of the pathogens, PK/PD parameters, and antimicrobial resistance patterns [70,78]. This model is a tool to help predict the likelihood of bacteriologic success in diseases such as AOM and acute sinusitis with particular antimicrobial agents by accounting for various factors including: (1) the proportion of patients with a clinical diagnosis of acute bacterial infection and a positive culture from the site of infection; (2) the clinical resolution of disease in the culture-negative patient group; (3) the distribution of pathogens frequently encountered in the disease; (4) the spontaneous resolution rate associated with each pathogen; and (5) the in vitro susceptibility of the predominant pathogens to antimicrobial agents at PK/PD breakpoints. The model can predict overall clinical outcomes for the total patient group (ie, those with either bacterial or nonbacterial disease) and for the bacterial infection group.

A probability model has also been developed to estimate the impact of antimicrobial resistance on clinical outcomes for adult outpatients with community-acquired pneumonia [79]. This model assumed patients would be evaluated at 48 to 72 hours, with those failing to improve being either hospitalized or switched to a different antibiotic. Two strategies were considered: amoxicillin followed by erythromycin (amoxicillin/erythromycin) and erythromycin followed by levofloxacin (erythromycin/levofloxacin). Analyses were conducted based on susceptibility of the major pathogens in France, a country with high rates of resistance in respiratory pathogens, and the United Kingdom, where resistance rates are low. Primary outcome measures were the proportion of patients successfully treated with first-line therapy and the proportion of patients subsequently hospitalized. The model
Fig. 4. (A, B) Distribution of gatifloxacin and levofloxacin minimum inhibitory concentrations (MICs) against *Streptococcus pneumoniae* from the 1999–2000 Sentry Respiratory Surveillance Program study. (C) Distribution of gatifloxacin free-drug area under the concentration-time curve (AUC)₀⁻²₄ (µg·hr/mL) ratio in the patient population. (D) Distribution of levofloxacin free-drug area under the concentration-time curve (AUC)₀⁻²₄ (µg·hr/mL) ratio in the patient population. (E) Results of a 5000-patient Monte Carlo simulation for gatifloxacin based on MIC and AUC distributions presented in (A, C). The dark bars represent the number of simulated patients with AUC:MIC ratios < 30, whereas the light bars represent patients with AUC:MIC ratios ≥ 30. The probability of gatifloxacin attaining an AUC:MIC ratio of at least 30 is 98.80%. (F) Results of a 5000-patient Monte Carlo simulation for levofloxacin based on MIC and AUC distributions presented in (B, D). The dark bars represent the number of simulated patients with AUC:MIC ratios < 30, whereas the light bars represent patients with AUC:MIC ratios ≥ 30. The probability of levofloxacin attaining an AUC:MIC ratio of at least 30 is 81.7%. (Adapted from Nicolau DP, Ambrose PG. Pharmacodynamic profiling of levofloxacin and gatifloxacin using Monte Carlo simulation for community-acquired isolates of *Streptococcus pneumoniae*. Am J Med 2001;111(Suppl 9A):13S–18S [discussion 36S–38S]; with permission.)
estimated that in France, the amoxicillin/erythromycin strategy would lead to 67.8% improving within 48 to 72 hours and 12.7% subsequently being hospitalized, compared with 48.6% and 13.7% for erythromycin/levofloxacin. For the United Kingdom, first-line success and hospitalization rates were, respectively, 71.7% and 8.1% for amoxicillin/erythromycin, and 65.3% and 9.3% for erythromycin/levofloxacin. The model estimated that antimicrobial resistance was responsible for >40% of hospitalizations in France and 15% in the United Kingdom. These data suggest that antimicrobial resistance may be a significant contributor to subsequent hospitalization in adults initially treated as outpatients for community-acquired pneumonia and that choice of outpatient treatment strategy should consider local resistance rates to minimize treatment failures and hospitalizations.

Nasopharyngeal carriage of pathogens represents an important component in the development and spread of respiratory tract infections, including those caused by resistant strains. In certain types of infection in which nasopharyngeal carriage rates are high, such as pediatric otitis media, a goal of antimicrobial therapy should be to prevent nasopharyngeal colonization by resistant organisms to reduce the development of infection, outbreaks, and resistance. Higher dosages of antimicrobials may be needed in these cases. It has been suggested that a concentration above the MIC for 80% to 100% of the dosing interval is necessary to achieve high rates of eradication in the nasopharynx [14]. This may not be possible with many standard antimicrobial regimens used for respiratory tract infections, and additional work in this area is needed.

Finally, drug pharmacokinetics and pharmacodynamics are now being used in surveillance testing to determine susceptibility breakpoints in a more clinically meaningful way [56,59,80,81]. Susceptibility breakpoints are defined in this manner as either: (1) for time-dependent antimicrobials with minimal PAE, the unbound concentration in serum that is maintained for at least 40% to 50% of a dosing interval, based on published serum pharmacokinetics and standard dosing regimens or (2) for time-dependent antimicrobials with prolonged PAE and for concentration-dependent agents, unbound serum AUC divided by 25. The differences in susceptibility of *S. pneumoniae* and *H. influenzae* isolates to various antimicrobials using PK/PD breakpoints versus MIC breakpoints have been demonstrated [23,56]. Significant differences exist in both the breakpoint and the percentage of isolates susceptible based on how the breakpoint is determined (Table 4). Using the PK/PD breakpoints of the antimicrobials tested, only amoxicillin-clavulanate and newer quinolones would be effective against more than 90% of *S. pneumoniae* and *H. influenzae* strains. This type of information has important implications in the empiric treatment of respiratory infections, as well as consideration of the need to cover “atypical” pathogens, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* in community-acquired pneumonia. Antimicrobial breakpoints based on PK/PD breakpoints have been adopted by the National Committee for Clinical Laboratory Standards...
### Table 4
Percent of world-wide isolates of *S pneumoniae* and *H influenzae* susceptible to various antimicrobials based on NCCLS and pharmacokinetic/pharmacodynamic (PK/PD) breakpoints

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Streptococcus pneumoniae</th>
<th>Haemophilus influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCCLS</td>
<td>PK/PD</td>
</tr>
<tr>
<td></td>
<td>Breakpoint (µg/mL)</td>
<td>Susceptible (%)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>≤2</td>
<td>95.1</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>≤2</td>
<td>95.5</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate, new formulations</td>
<td>NA</td>
<td>≤4</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>≤1</td>
<td>60.2</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>≤1</td>
<td>78.6</td>
</tr>
<tr>
<td>Cefixime</td>
<td>NA</td>
<td>≤1</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>≤2</td>
<td>79.7</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>≤0.5</td>
<td>76.5</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤0.25</td>
<td>75.5</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>≤0.5</td>
<td>75.4</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>≤0.25</td>
<td>86.0</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>≤0.5</td>
<td>63.3</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≤2</td>
<td>98.9</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>≤1</td>
<td>98.5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤1</td>
<td>98.9</td>
</tr>
</tbody>
</table>

**Abbreviations:** NCCLS, National Committee for Clinical Laboratory Standards; NA, not reported.

(NCCLS) for *S. pneumoniae*, but many breakpoints are still in need of revision, particularly for *H. influenzae* [82].

**Summary**

Our knowledge of the impact of drug pharmacokinetics and pharmacodynamics on antimicrobial efficacy has been elucidated during the past 20 years using animal, in vitro, and limited clinical observations. We now know that classes of antimicrobials fall into one of three patterns of killing: time-dependent, concentration-dependent, or time-dependent plus PAEs, with each class exhibiting a similar magnitude of activity against a pathogen, including resistant strains. The efficacy of an antimicrobial agent can be predicted based on its pattern of activity relative to the MIC against a pathogen. These observations have led to a change in the paradigm of treating respiratory infections, developing new antimicrobials and dosing regimens, and establishing clinically relevant susceptibility breakpoints.

Currently, unbound serum concentrations are used to define antimicrobial pharmacodynamics because they are easy to obtain and reflect, to some measure, the extracellular concentration of drug at many sites of infection. However, the penetration of antimicrobials into sites of infection is variable, and not all penetrate to the same degree relative to serum concentrations. A more accurate prediction of antimicrobial efficacy would be to use pharmacokinetic data for drugs at the site of infection obtained during an active infection. Unfortunately, such information is rarely available and is confounded by the need to distinguish between intracellular and extracellular compartments.

For some newer antimicrobials, respiratory tissue concentrations in healthy volunteers have been determined, and it may be more appropriate to use these data rather than serum concentrations. However, evidence for currently available agents supports use of serum, and not tissue, pharmacokinetic parameters for extracellular pathogens [62]. For the seriously ill patient, individual pharmacokinetic data and organism MIC data should be obtained to optimize dosing.

The prevalence of resistance and patterns of infection are varied depending on patterns in a given geographic area. The clinician should consult local antimicrobial surveillance data when selecting treatment for respiratory tract infections. Applying PK/PD parameters to dosing not only increases the likelihood of successful treatment of that infection but also serves to limit resistance. Agents should have adequate potency to minimize the selection and spread of resistant strains, while the most potent antimicrobials should be kept in reserve when treating respiratory tract infections in outpatients. In the future, the MPC and mutant selection window may, like susceptibility breakpoints, guide researchers and clinicians in selecting optimal antimicrobial therapy.
References


