Overview of Newer Antimicrobial Formulations for Overcoming Pneumococcal Resistance

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The pharmacokinetic (PK) and pharmacodynamic (PD) profile of an antimicrobial agent provides important information that can be used to maximize bacteriologic and clinical efficacy, minimize selective pressure for the development of antimicrobial resistance, and determine an optimal dosing regimen. Judicious selection of an antimicrobial based on local susceptibility data and PK and PD parameters is imperative in this era of increasing resistance among Streptococcus pneumoniae, leading a cause of community-acquired respiratory tract infections. The β-lactam antimicrobials display time-dependent bacterial killing with minimal to no persistent effects. Ketolides and fluoroquinolones display concentration-dependent bacterial killing, and tetracyclines and macrolides display time-dependent killing. All have prolonged persistent effects (e.g., postantibiotic effect) that retard or prevent bacterial regrowth when free drug levels fall below the minimum inhibitory concentration (MIC). New high-dose and/or extended-release formulations of traditional antimicrobials have been added to the current armamentarium for treatment of community-acquired respiratory tract infections. These formulations include amoxicillin-clavulanate potassium powder for oral suspension 90/6.4 mg/kg per day divided every 12 hours (Augmentin ES-600; GlaxoSmithKline, Research Triangle Park, NC), amoxicillin-clavulanate potassium extended-release tablets 2 x 1,000 mg/62.5 mg every 12 hours (Augmentin XR; GlaxoSmithKline), clarithromycin extended-release tablets 2 x 500 mg once daily (Biaxin XL; Abbott Laboratories, North Chicago, IL), and cefaclor extended-release tablets 375 mg or 500 mg every 12 hours (Ceclor CD; Eli Lilly Pharmaceuticals, Indianapolis, IN). Of these agents, only amoxicillin-clavulanate potassium powder for oral suspension and amoxicillin-clavulanate potassium extended-release tablets were designed to treat infections caused by penicillin-resistant pneumococci (penicillin MIC ≤2 µg/mL). Extended-release clarithromycin does not provide higher daily doses than its immediate-release counterpart; rather, it allows for once-daily dosing of this agent because of its slower absorption following oral administration. Extended-release cefaclor is considered clinically equivalent to 250 mg of immediate-release cefaclor pulvules administered 3 times daily; it cannot be used interchangeably with 500 mg 3-times-daily dosages of other cefaclor formulations. Thus, despite providing a similar or higher total daily dose than its immediate-release counterpart, extended-release cefaclor is indicated only for the treatment of patients with mild to moderate infections caused by susceptible strains of certain organisms. Am J Med. 2004;117(6A):16S-22S. © 2004 by Elsevier Inc.

The emergence and subsequent increase in antimicrobial resistance among common community-acquired respiratory pathogens (e.g., penicillin-resistant Streptococcus pneumoniae [PRSP]) have led researchers to develop antimicrobials that can maintain activity against these resistant strains. Data from the Alexander Project, an international surveillance study of antimicrobial susceptibilities of bacterial pathogens from patients with community-acquired respiratory tract infections, suggest that the worldwide prevalence of penicillin resistance (penicillin minimum inhibitory concentration [MIC] ≥2 µg/mL) among 8,882 isolates of S pneumoniae obtained between 1998 and 2000 was 18.2%. Among pneumococcal isolates obtained in the United States (N = 2,432), the prevalence of penicillin resistance was 25.0%. Thus, the need for antimicrobials with activity against penicillin-resistant pneumococci is imperative in this era. Antimicrobial susceptibility breakpoints that integrate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of an antimicrobial with its in vitro activity (i.e., MIC) have been suggested.2-4 These new breakpoints more accurately predict the bacteriologic and clinical efficacy of an antimicrobial than traditional NCCLS (formerly National Committee for Clinical Laboratory Standards) breakpoints. Further, PK and PD parameters also may be used in the selection of an appropriate dosing regimen.5

Recently published guidelines on the treatment of acute bacterial rhinosinusitis use PK and PD breakpoints as the basis upon which recommendations are made.4 Although treatment guidelines for community-acquired pneumonia (CAP) are based on NCCLS breakpoints,6-8 a large segment of infectious disease experts advocate the use of PK and PD breakpoints when treating all respiratory tract infections.1-3 The purpose of this article is to review the PK and PD parameters used in the selection of an appropriate antimicrobial and to describe how these...
parameters were enhanced to develop new antimicrobial formulations.

CONSIDERATIONS IN ANTIMICROBIAL SELECTION

Using animal models and human data, PK and PD effects have been studied both in vitro and in vivo.9-13 Data gathered from animal models demonstrate consistent results across several species that are also similar to results obtained in human studies. Therefore, results from animal studies can be predictive of antimicrobial activity and clinical efficacy in humans and can be used to determine optimal dosage regimens. In addition, animal studies provide important information in situations where collection of sufficient clinical data is difficult, such as those involving emerging resistant pathogens or rare infections.

The PK Parameters
PK involves the absorption, distribution, metabolism, and elimination of a drug. The PK parameters of primary importance in the selection of an appropriate antimicrobial are the area under the serum concentration versus time curve (AUC), the maximum plasma concentration ($C_{\text{max}}$), and the duration of time that effective drug concentrations persist.10 Free drug levels provide a more accurate determination of amount of drug available to elicit a response than total drug levels because protein binding reduces antimicrobial activity. Therefore, free drug levels should be used when comparing the PK profiles of several antimicrobials within the same class. Because several of the most common infectious respiratory pathogens (e.g., S pneumoniae, Haemophilus influenzae, Moraxella catarrhalis) are located primarily in the interstitium, drug concentration in the interstitial fluid may be considered more important than serum drug concentration. Fortunately, interstitial and serum concentrations of free drug are approximately equivalent. As a result, serum drug concentrations are typically used to monitor peak and trough levels and in PD calculations. Drug concentration in tissue homogenates is typically not obtained because it often does not accurately reflect interstitial drug concentrations.

The PD Parameters
With regard to antimicrobials, PD is the relation between drug concentration and antimicrobial activity. One PD parameter of primary importance in the selection of an appropriate antimicrobial is the MIC,10 which is the minimum concentration of antimicrobial needed to inhibit pathogen growth. Although this parameter is a good indicator of the potency of antimicrobial activity, alone it does not provide information about the time course of antimicrobial activity (i.e., whether an agent displays time-dependent or concentration-dependent killing, or whether the antimicrobial effects are persistent). All antimicrobials belong to 1 of 3 categories: concentration-dependent killing with prolonged persistent effects, time-dependent killing with minimal or no persistent effects, or time-dependent killing with moderate to prolonged persistent effects.

Persistent Effects
Several factors may prolong the activity of an antimicrobial beyond the point where drug concentration at the site of infection falls below the MIC.9,10,14 The postantibiotic effect of an antimicrobial is defined as continued suppression of bacterial growth that occurs after brief exposure (e.g., 1-2 hours) to bactericidal or bacteriostatic concentrations of an antimicrobial.10,15,16 The duration of the postantibiotic effect depends on the infecting organism, the antimicrobial, the concentration at the site of infection, and the duration of exposure to the antimicrobial. Growth medium, pH, and inoculum size also may influence the in vivo postantibiotic effect of an antimicrobial. Neutrophils have been shown to enhance in vivo postantibiotic effects in animal models through a phenomenon known as postantibiotic leukocyte enhancement, which enhances the natural host immune defense mechanism. The mechanisms of postantibiotic effect are unknown; however, suggested hypotheses include nonlethal damage to the bacteria by the antimicrobial or persistence of the drug at the bacterial drug-binding site. In theory, antimicrobials with a longer postantibiotic effect require less frequent dosing than antimicrobials with little or no postantibiotic effect, because it is less likely that the bacteria will start to regrow during the period of subinhibitory tissue concentration.9

PATTERNS OF ANTIMICROBIAL ACTIVITY

The determination of NCCLS breakpoints for antimicrobial susceptibility is based on population distributions, known mechanisms of bacterial resistance, PK parameters (primarily peak levels), and clinical outcomes. Recently, PD has become a parameter considered for breakpoint determinations. In considering antimicrobials with activity against pneumococci, virtually all antimicrobials are bactericidal. The differentiating criterion is the time course of antimicrobial activity, which is based on 2 factors: the patterns of bactericidal activity (concentration dependent versus time dependent) and the presence of persistent effects after antimicrobial exposure.

Concentration-Dependent Killing with Prolonged Persistent Effects
Ketolides and fluoroquinolones display concentration-dependent killing with prolonged persistent effects.9,10,17 The rate and extent of bacterial eradication depend largely on the amount of drug administered, not on the length of exposure to the antimicrobial. Therefore, these antimicrobials are administered in high doses once or
twice daily to maximize peak serum drug concentration as well as the AUC. The prolonged persistent effects associated with the use of these antimicrobials also support wide dosing intervals because they prevent pathogen regrowth when the concentration at the site of infection falls below the MIC. The AUC/MIC_{90} (the concentration at which 90% of the isolates are inhibited) ratio provides a more accurate estimation of the efficacy of these antimicrobials than the C_{max}/MIC_{90} ratio because AUC takes into consideration serum drug concentration as well as length of exposure to the antimicrobial, an important feature of drugs possessing a long half-life. Results from several animal studies suggest that, for fluoroquinolones, a 24-hour AUC/MIC ratio of <30 is associated with >50% mortality, whereas a ratio of ≥100 is associated with little to no mortality (Figure 1). Similar results were observed in human studies. Lower ratios, in the range of 30 to 35, are required for pneumococci in immunocompetent animals and in non-neutropenic patients.

**Time-Dependent Killing with Minimal or No Persistent Effects**

The β-lactam antimicrobials display time-dependent killing with minimal to no persistent effects. In general, pathogen eradication begins once drug concentration at the site of infection exceeds approximately 4 times the MIC; subsequent increases in concentration do not cause further or faster elimination. Rather, duration of antimicrobial exposure (time above MIC) is the primary determinant of pathogen eradication and clinical cure with these agents. Because regrowth begins once serum levels drop below the MIC, antimicrobials that demonstrate time-dependent killing and have no persistent effects must be dosed frequently throughout the day to maintain the serum drug concentration above the MIC for an extended time. For cephalosporins, concentrations must exceed the MIC for at least 40% to 50% of the dosing interval. Data suggest that lower levels may be acceptable for penicillins.

A compilation of results from several animal studies demonstrates that treatment of pneumococcal infections with penicillins or cephalosporins at doses that produce serum levels above the MIC for 20% or less of the dosing interval are associated with almost 100% mortality. Alternatively, mortality fell to between 0% and 10% with dosing regimens that produced serum levels above the MIC for at least 40% to 50% of the dosing interval. Mortality rates were comparable in infections caused by penicillin-susceptible or penicillin-resistant strains; thus, the need for higher MICs does not increase the length of time required above the MIC.

Clinical studies have produced results similar to those found in animal studies. Studies conducted in patients with acute otitis media (AOM) or acute maxillary sinusitis caused by *S. pneumoniae* demonstrated that bacteriologic cure with β-lactam antimicrobials is dependent on time above the MIC, with longer durations above the MIC conferring greater efficacy (Figure 2). Bacteriologic eradication occurred in >80% of cases when serum levels were above the MIC for at least 40% to 50% of the dosing interval.

(Figure 1. Relation between the 24-hour area under the concentration versus time curve and the minimum inhibitory concentration (AUC/MIC ratio) and survival among animal models infected with a variety of gram-positive and gram-negative pathogens and treated with a fluoroquinolone. The 24-hour AUC/MIC ratio is the sum of the AUCs for all doses administered every 24 hours divided by the MIC. Solid circles = data obtained in the thigh-infection model; open circles = data obtained in other animal models. (Reprinted with permission from Clin Infect Dis.))

(Figure 2. Relation between time above the minimum inhibitory concentration (MIC) and bacterial eradication with various β-lactams against *Streptococcus pneumoniae* in patients with acute otitis media (circles) or acute maxillary sinusitis (squares). PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*. (Adapted with permission from J Antimicrob Chemother.))
dosing interval. Drug levels above the MIC for 60% to 70% of the dosing interval were associated with nearly 100% bacterial eradication. A comparison of time above MIC\textsubscript{90} values achieved with standard dosing regimens of several orally administered \(\beta\)-lactam antimicrobials reveals that, although these agents achieve serum levels above the MIC for >40% of the dosing interval against penicillin-susceptible \textit{S. pneumoniae} (Table 1), only amoxicillin with or without clavulanate achieves serum levels above the MIC for ≥40% of the dosing interval against penicillin-intermediate and many, but not all, penicillin-resistant \textit{S. pneumoniae}.\textsuperscript{28}

**Table 1.** Time Above the MIC\textsubscript{90} (Minimum Concentration Necessary to Inhibit 90% of Isolates) for Orally Administered \(\beta\)-Lactam Antimicrobials Against Penicillin-Susceptible, Penicillin-Intermediate, and Penicillin-Resistant \textit{S. pneumoniae}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
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<tr>
<td></td>
<td>MIC\textsubscript{90}</td>
<td>T&gt;MIC\textsuperscript{a}</td>
<td>MIC\textsubscript{90}</td>
<td>T&gt;MIC\textsuperscript{a}</td>
</tr>
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<tr>
<td>Cefaclor</td>
<td>400 mg qd\textsuperscript{b}</td>
<td>0.5</td>
<td>59</td>
<td>16</td>
</tr>
</tbody>
</table>

MIC = minimum inhibitory concentration; T>MIC = duration of time (%) that serum levels exceed the minimum inhibitory concentration during the dosing interval.

\textsuperscript{a}Dose expressed in terms of amoxicillin component.

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**NEWER ANTIMICROBIALS USED TO TREAT RESPIRATORY INFECTIONS**

Several new high-dose and/or extended-release formulations of traditional antimicrobials have been introduced in recent years to treat respiratory tract infections. These include amoxicillin-clavulanate potassium powder for oral suspension 90/6.4 mg/kg per day divided every 12 hours (Augmentin ES-600; GlaxoSmithKline, Research Triangle Park, NC), amoxicillin-clavulanate potassium extended-release tablets 2 × 1,000 mg/62.5 mg every 12 hours (Augmentin XR; GlaxoSmithKline), clarithromycin extended-release tablets 2 × 500 mg tablets once daily (Biaxin XL; Abbott Laboratories, North Chicago, IL), and cefaclor extended-release tablets 375 mg or 500 mg every 12 hours (Cefradyn; Eli Lilly Pharmaceuticals, Indianapolis, IN). The extended-release formulations of amoxicillin-clavulanate potassium, clarithromycin, and cefaclor provide extended absorption after oral administration. Extended-release clarithromycin provides lower and later steady-state peak plasma concentrations, but the same total daily dose and AUC as immediate-release clarithromycin tablets.\textsuperscript{29} Extended-release cefaclor differs pharmacokinetically from the suspension formulation, and the 2 formulations cannot be used interchangeably.\textsuperscript{30} It is, however, considered clinically equivalent to 250 mg of immediate-release cefaclor pulvules administered 3 times daily. Much like extended-release clarithromycin, extended-release cefaclor provides lower and later steady-state peak plasma concentrations than equivalent doses of immediate-release cefaclor pulvules; however, it also provides a lower AUC. Extended-release formulations are an appealing option for treatment of respiratory infections because they can help increase patient adherence by offering once- or twice-daily administration of these agents. However, the PK and PD profiles of extended-release clarithromycin and extended-release cefaclor do not provide any enhanced activity against resistant pneumococci. Thus, these agents are indicated only for the treatment of patients with mild to moderate infections caused by susceptible strains of certain organisms, including \textit{S. pneumoniae}.\textsuperscript{29,30} In contrast, 2 new high-dose formulations of amoxicillin-clavulanate, extended-release tablets (adult formulation) and powder for oral suspension (pediatric formulation), have been developed to overcome pneumococcal resistance on the basis of PK and PD parameters.
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Amoxicillin-Clavulanate Potassium Extended-Release Tablets

Amoxicillin-clavulanate potassium extended-release tablets (2 × 1,000 mg/62.5 mg every 12 hours) provide both immediate and sustained release of amoxicillin and immediate release of clavulanate through a bilayer tablet formulation and have excellent in vitro activity against major respiratory pathogens, including *S. pneumoniae* with penicillin MICs of 2 µg/mL and 4 µg/mL.31 A single dose of extended-release amoxicillin-clavulanate (2,000 mg/125 mg) exceeds an amoxicillin concentration of 4 µg/mL for 49.4% of a 12-hour dosing interval, a value not achievable with a comparable dose of immediate-release amoxicillin-clavulanate (Figure 3).32 Thus, based on PK and PD considerations alone, the results of this study suggest that extended-release amoxicillin-clavulanate would be an effective treatment for bacterial infections caused by strains with an amoxicillin MIC of ≤4 µg/mL. These results are supported by the results of a study in rats that simulated the PK of humans33,34 in which extended-release amoxicillin-clavulanate was found to be highly effective against all strains of *S. pneumoniae* (amoxicillin MICs of 4 or 8 µg/mL) and was comparable to or more effective than 3 other amoxicillin-clavulanate formulations, azithromycin, and levofloxacin.

A total of 9 clinical studies including >4,100 patients evaluated extended-release amoxicillin-clavulanate in patients with respiratory infections caused by *S. pneumoniae*, including strains with penicillin MICs of 2 to 16 µg/mL.35 The studies showed that patients treated with extended-release amoxicillin-clavulanate had successful bacteriologic and clinical outcomes after 7 to 10 days of antimicrobial therapy. Of the 56 patients infected with PRSP (penicillin MIC ≥2 µg/mL), 55 (98%) had successful bacteriologic eradication.

Extended-release amoxicillin-clavulanate is indicated for the treatment of patients with CAP or acute bacterial sinusitis caused by *S. pneumoniae* with a penicillin MIC of 2 µg/mL and β-lactamase–producing pathogens (i.e., *H. influenzae*, *M. catarrhalis*, *H. parainfluenzae*, *K. pneumoniae*, or methicillin-susceptible *S. aureus*).31 This pharmacokinetically enhanced formulation provides high enough levels of amoxicillin during a 12-hour dosing interval that it may help eradicate *S. pneumoniae* with an amoxicillin MIC of ≤4 µg/mL.32

Amoxicillin-Clavulanate Potassium Powder for Oral Suspension

Amoxicillin-clavulanate (90/6.4 mg/kg per day) contains twice the amount of amoxicillin as the previous formulation, but the 2 are not interchangeable (i.e., the 45/6.4 mg/kg per day dose of the previous formulation cannot be doubled to equal the 90/6.4 mg/kg per day formulation) because of the clavulanate concentration provided in each.30 This formulation was designed to provide high concentrations of amoxicillin to eradicate *S. pneumoniae* with penicillin MIC values of ≤2 µg/mL. As with the adult formulation (amoxicillin-clavulanate extended-release tablets), this pediatric formulation has been shown
to eradicate *S. pneumoniae* with elevated amoxicillin MICs (2 or 4 µg/mL) in a rat study simulating human PKs. The reduction with the 90/6.4 mg/kg per day formulation was found to be statistically significantly greater than the 45/6.4 mg/kg per day comparator (P < 0.01). Furthermore, this study demonstrated that dosing regimens that achieved amoxicillin concentrations in excess of the MIC for a minimum of 34% of the 12-hour dosing interval significantly reduced bacterial load.

To date, 2 clinical trials have been conducted with the high-dose pediatric formulation. Dagan and colleagues conducted an open-label, multicenter study to evaluate the bacteriologic and clinical efficacy of high-dose amoxicillin-clavulanate in 521 children with AOM. High-dose amoxicillin-clavulanate eradicated 98% (122 of 125) of the *S. pneumoniae* isolates, including 91% (31 of 34) with penicillin MICs of 2 or 4 µg/mL. Clinical success at the end of therapy was documented in 91% of patients (96 of 105) with pneumococcal AOM. Thus, high-dose amoxicillin-clavulanate was found to be highly effective in the treatment of pneumococcal AOM, including in patients most likely to fail antimicrobial therapy (e.g., those infected with PRSP, or children <24 months old, who attend daycare, or who have recently been treated with an antimicrobial).

Hoberman and colleagues conducted a multicenter, randomized, investigator-blind study comparing clinical and bacteriologic efficacy and tolerability of high-dose amoxicillin-clavulanate with that of azithromycin in children with AOM. In this study, 730 children were randomized to receive amoxicillin-clavulanate (90/6.4 mg/kg per day for 10 days) or azithromycin (10 mg/kg per day for 1 day, followed by 5 mg/kg per day for days 2 to 5). Clinical cure or improvement of symptoms at all 3 visits was significantly greater with high-dose amoxicillin-clavulanate than with azithromycin (P < 0.05). In addition, high-dose amoxicillin-clavulanate eradicated 96% of *S. pneumoniae* (72 of 75), including 92% (23 of 25) of PRSP, compared with 80% (74 of 92) and 55% (12 of 22) in the azithromycin group, respectively (P < 0.01).

Amoxicillin-clavulanate powder for oral suspension (90/6.4 mg/kg per day) is indicated for the treatment of pediatric patients with recurrent or persistent AOM caused by *S. pneumoniae* with penicillin MICs of ≤2 µg/mL, *H. influenzae*, or *M. catarrhalis* (including β-lactamase-producing strains of the latter 2 pathogens), characterized by antimicrobial exposure within the previous 3 months and either age of ≤2 years or daycare attendance. Much like with the adult formulation, data suggest that this high-dose pediatric formulation provides high enough levels of amoxicillin during a 12-hour dosing interval that it may help eradicate *S. pneumoniae* with an amoxicillin MIC of ≤4 µg/mL.

### CONCLUSION

The application of PK and PD parameters to the selection of an appropriate antimicrobial agent and dosing regimen can maximize clinical efficacy and minimize selective pressure for the development of resistance. The goal of therapy with β-lactams is to maximize the length of time that free drug levels exceed the MIC of a particular pathogen. Ideally, free drug levels should exceed the MIC for 40% to 50% of the dosing interval to prevent pathogen regrowth. For fluoroquinolones, tetracyclines, macrolides, and azithromycin, on the other hand, the goal is to maximize serum concentration. With the prevalence of pneumococcal resistance on the rise, newer high-dose formulations of traditional antimicrobials are being used to treat respiratory tract infections caused by PRSP. Amoxicillin-clavulanate potassium extended-release tablets (2,000 mg/125 mg every 12 hours) and amoxicillin-clavulanate potassium powder for oral suspension (90/6.4 mg/kg per day divided every 12 hours) have favorable PK and PD profiles, which make them appealing to use in treating respiratory infections as well as in overcoming pneumococcal resistance. Despite the wealth of available data on the impact of PKs and PDs on bacteriologic and clinical efficacy of antimicrobials, additional research and education are necessary to transform this concept into a reality of daily prescribing.

### REFERENCES

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