Achieving bacterial eradication using pharmacokinetic/pharmacodynamic principles

Ron Dagan(1)

Evidence from studies in otitis media indicates that antimicrobials and dosing regimens that have equivalent bacteriologic efficacy against susceptible pathogens can have significantly different bacteriologic success rates against resistant strains of the same species. Unlike macrolide and fluoroquinolone resistance, penicillin resistance can be overcome in Streptococcus pneumoniae by increasing the dose, and hence increasing the time for which the serum concentrations are above the MIC. The new clinical formulation of extra-strength amoxicillin–clavulanate provides 90 mg/kg per day amoxicillin plus 6.4 mg/kg per day clavulanate (14:1) divided every 12 h, compared with 45/6.4 mg/kg per day b.i.d. with conventional dosing. The pharmacokinetic/pharmacodynamic (PK/PD) profiles of extra-strength amoxicillin–clavulanate predict that the new formulation will be more effective than the conventional formulation against S. pneumoniae with elevated amoxicillin MICs and against Haemophilus influenzae. In an open-label, non-comparative study in children with acute otitis media, the extra-strength formulation had high bacteriologic success rates against the major respiratory pathogens, including penicillin-resistant S. pneumoniae. The development of new antimicrobial agents and formulations should be aimed at meeting PK/PD parameters predictive of bacterial eradication of both susceptible and resistant strains.

INTRODUCTION

Bacterial eradication is necessary to maximize clinical cure and minimize resistance development and spread (see J. Garau, this issue). It is now widely recognized that the interaction of pharmacokinetic (PK) and pharmacodynamic (PD) parameters determines the in vivo bacteriologic efficacy of antimicrobial agents. For β-lactams, macrolides, clindamycin, and cotrimoxazole, bactericidal activity is dependent on the length of time for which drug concentrations in the serum and/or at the site of infection are above the MIC for an organism (T >MIC). For aminoglycosides, fluoroquinolones, and azithromycin, the ratio of the area under the concentration–time curve (AUC) to the MIC for an organism best predicts bactericidal activity. These predictions can be used to develop breakpoints predictive of bacterial eradication, which are dependent on the PK profile, dosing regimen, and MIC of the antimicrobial. The article by M. R. Jacobs (this issue) provides a detailed outline of the basis of PK/PD antimicrobial assessment and the derivation of PK/PD breakpoints that can be used to predict bacterial eradication. Despite these advances, studies testing the clinical relevance of PK/PD profiles in human respiratory tract infections (RTIs) have been lacking, primarily due to the difficulty in obtaining reliable microbiological samples.1

Acute otitis media is a common infection, particularly in children, with approximately 70% of cases having an identified causative bacterial pathogen.4 As with RTIs, the most common pathogens implicated are Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.5 Samples of middle ear fluid can be obtained by tympanocentesis before, during and after antimicrobial treatment, and cultured to identify the organisms present. Thus, the bacteriologic effect of antimicrobial therapy can be assessed directly, and can then be correlated with both clinical observations and predictions from PK/PD calculations. Acute otitis media therefore represents a good model in which to study the application of PK/PD principles to the antimicrobial therapy of RTIs.1

Another advantage of acute otitis media as a model is the availability of data relating to rates of spontaneous resolution. In a classic study performed 30 years ago, Howie and Ploussard aspirated middle ear fluid from 280 children with acute otitis media before and after starting treatment.6 In 116 children receiving placebo, middle ear culture before treatment was positive for S. pneumoniae in 42% and H. influenzae in 21% of cases. After 2–7 days of placebo therapy, S. pneumonia persisted in 84% and H. influenzae in 52% of cases in which they were identified. In other words, placebo (or no antimicrobial treatment) ‘eradicates’ S. pneumoniae in about 15% of patients and H. influenzae in about 50% of patients within a few days, and this represents the baseline comparator for the efficacy of antimicrobials within 3–5 days.6

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This paper examines the evidence supporting the use of PK/PD breakpoints clinically in otitis media, and how PK/PD principles can be applied to drug development.

**PREDICTING BACTERIOLOGIC FAILURE IN OTITIS MEDIA**

Available data for bacteriologic failures in double tympanocentesis studies of otitis media are summarized in Table 1. It is obvious from these data that some commonly used antimicrobials are failing to provide adequate therapy in this indication. But are these failure rates consistent with what would have been predicted using PK/PD parameters?

**Haemophilus influenzae**

The first thing that is obvious from Table 1 is that, of the drugs presented in the table, only ceftriaxone and cefixime achieve complete eradication of *H. influenzae*. Both of these agents are highly active against Gram-negative pathogens. In the two studies cited, however, the MICs of ceftriaxone against *H. influenzae* ranged from 0.006 mg/L to 0.5 mg/L. Gudnason et al found that a single intramuscular dose of 50 mg/kg ceftriaxone gave a peak concentration in middle ear fluid of 35 mg/L at about 24 h, and concentrations were maintained above the MIC for the three major respiratory pathogens, including *H. influenzae*, for approximately 120 h. As ceftriaxone is highly bound to protein, the free concentrations are presumed to be much lower, but still above the MIC of *H. influenzae* for a considerable amount of time. Given that a time above MIC of about 40–50% of the dosing interval is predictive of bacteriologic eradication for cephalosporins, the high efficacy of ceftriaxone against *H. influenzae* in these studies is expected, based on PK/PD predictions. Cefixime is a β-lactamase-stable oral cephalosporin with a PK/PD breakpoint of 1 mg/L (see M. R. Jacobs, this issue, for PK/PD breakpoints). The MICs for cefixime against *H. influenzae* in the study by Johnson et al were not provided for bacterial pathogens isolated post-treatment. It is not, therefore, possible to compare the cefixime MICs with the PK/PD breakpoint for this agent.

Several agents in Table 1 have failure rates of over 25% against *H. influenzae* (azithromycin, amoxicillin (for β-lactamase-producing organisms), and cefaclor). In particular, the failure rates with azithromycin for all *H. influenzae* strains, with amoxicillin for β-lactamase-producing *H. influenzae* strains, and with cotrimoxazole for cotrimoxazole-resistant *H. influenzae* strains, are in the range observed with placebo (Table 1). The PK/PD breakpoint for azithromycin against *H. influenzae* is 0.12 mg/L, and in the two studies of azithromycin, MICs for this antimicrobial against *H. influenzae* were between 0.25 mg/L and 4 mg/L, and 0.5–8 mg/L. The observed high bacteriologic failure rate of azithromycin is, therefore, entirely consistent with PK/PD predictions. These data have important implications for clinical practice when applied to reported azithromycin MIC distributions. For example, data from the Alexander Project, a prospective worldwide surveillance study, show that 99% of azithromycin MICs against 2240 *H. influenzae* strains isolated in 2001 were above the 0.12 mg/L breakpoint. Thus, azithromycin, as well as other macrolide agents, would be predicted to be almost universally bacteriologically ineffective against *H. influenzae*.

Cefaclor also has very poor in vivo bacteriologic efficacy against *H. influenzae* (Table 1). Although cefaclor is a non-β-lactamase-stable cephalosporin,

### Table 1. Bacteriologic failure rates in otitis media for commonly prescribed antimicrobials compared with placebo, after 3–5 days of therapy

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose</th>
<th>S. pneumoniae</th>
<th>H. influenzae</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8 mg/kg/day b.i.d.</td>
<td>84 (48/57)</td>
<td>52 (13/25)</td>
<td>6</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>10 mg/kg/day b.i.d.</td>
<td>21 (7/33)</td>
<td>61 (28/46)</td>
<td>7</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>80 mg/kg/day t.i.d.</td>
<td>11 (2/18)</td>
<td>25 (6/24)</td>
<td>9</td>
</tr>
<tr>
<td>Amoxicillin–clavulanate</td>
<td>40 mg/kg/day o.d.</td>
<td>7 (1/15)</td>
<td>38 (5/13)</td>
<td>11</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>40 mg/kg/day t.i.d.</td>
<td>48 (16/33)</td>
<td>62 (18/29)</td>
<td>8</td>
</tr>
<tr>
<td>Cefixime</td>
<td>50 mg/kg/day o.d.</td>
<td>43 (13/30)</td>
<td>0 (0/27)</td>
<td>14</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>8/40 mg/kg/day b.i.d.</td>
<td>46 (11/24)</td>
<td>18 (7/40)</td>
<td>16</td>
</tr>
</tbody>
</table>

*Day 2–7.*

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2 Cefixime is a β-lactamase-stable oral cephalosporin with a PK/PD breakpoint of 1 mg/L (see M. R. Jacobs, this issue, for PK/PD breakpoints). The MICs for cefixime against *H. influenzae* in the study by Johnson et al were not provided for bacterial pathogens isolated post-treatment. It is not, therefore, possible to compare the cefixime MICs with the PK/PD breakpoint for this agent.

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Cefaclor also has very poor in vivo bacteriologic efficacy against *H. influenzae* (Table 1). Although cefaclor is a non-β-lactamase-stable cephalosporin,
it also has low inherent efficacy against β-lactamase-negative strains. Based on a PK/PD target of a $T > \text{MIC}$ of 40%, the PK/PD breakpoint for cefaclor is 0.5 mg/L. Information on cefaclor MICs for the infecting pathogens are available from two studies. Combined data from these studies show that bacteriologic failure was similar against strains with cefaclor MICs $> 1$ mg/L (41% (25/61)) to that seen against strains with MICs $\leq 1$ mg/L (50% (12/22)), suggesting that the breakpoint should be $< 1$ mg/L. In the 2001 Alexander Project, 98% of cefaclor MICs against 1893 β-lactamase-negative H. influenzae isolates were $> 0.5$ mg/L, and 98% exceeded this concentration against 347 β-lactamase-positive strains. As very few strains have cefaclor MICs $\leq 0.5$ mg/L, it is difficult to confirm the PK/PD breakpoint exactly using H. influenzae. What is certain, however, is that cefaclor provides suboptimal bacterial efficacy against both β-lactamase-positive and -negative H. influenzae strains, with results similar to those obtained with placebo.

Amoxicillin is not stable to β-lactamase, and so its bacteriologic efficacy against H. influenzae will be determined by the presence of β-lactamase-producing strains. In a study in which the amoxicillin failure rate overall against H. influenzae was 27%, the failure rate against β-lactamase-positive strains was 60% (3/5), compared with 21% (6/28) against β-lactamase-negative strains. In contrast, for amoxicillin combined with the β-lactamase inhibitor clavulanate, β-lactamase-positive H. influenzae was successfully eradicated from 8/9 patients. Cefuroxime axetil, a β-lactamase-stable cephalosporin, has a relatively low rate of bacteriologic failure against H. influenzae (13%). The PK/PD breakpoint of cefuroxime axetil is 1 mg/L, and the bacteriologic failure rate corresponds well with this, with 100% (1/1) failures against H. influenzae strains with cefuroxime MICs $> 2$ mg/L, 20% (1/5) failures for MICs 1.5–2 mg/L, and 11% (4/38) failures for MICs $\leq 1$ mg/L.

The impact of cotrimoxazole resistance in H. influenzae was indicated in one study in which 100% (28/28) of H. influenzae strains with cotrimoxazole MICs $< 0.5$ mg/L were eradicated, compared with 50% (6/12) for MICs $\geq 0.5$ mg/L. No PK/PD breakpoint has been determined for cotrimoxazole, but the effect of resistance on bacteriologic efficacy can be clearly seen.

**Streptococcus pneumoniae**

Resistance in S. pneumoniae exists for all the commonly used classes of antimicrobial, and will have a major influence on bacteriologic efficacy. Agents with more favorable PK/PD profiles will be able to retain activity against pathogens with elevated MICs, whereas the efficacy of those with marginal PK/PD profiles will be undermined. Cotrimoxazole provides a unequivocal example of the negative impact of bacterial resistance in S. pneumoniae on bacteriologic efficacy. Among 67 organisms isolated from 54 children with otitis media, all S. pneumoniae strains with a cotrimoxazole MIC of $< 0.5$ mg/L were eradicated. In contrast, bacteriologic failure was 73% (11/15) for S. pneumoniae strains with cotrimoxazole MICs $\geq 0.5$ mg/L, i.e. similar to that of placebo (84% bacteriologic failure).

The Gram-positive activity of the cephalosporins varies greatly between the different agents, and increasing bacterial resistance will impact upon the weaker members of the class first. For example, in the 2001 Alexander Project, the MIC$_{50}$ of cefaclor were 1 mg/L against penicillin-susceptible S. pneumoniae (n=1654), 4 mg/L against intermediate strains (n=378), and >64 mg/L against resistant strains (n=451). In comparison, the MIC$_{50}$ for cefuroxime in the same study were 0.03 mg/L, 0.5 mg/L, and 8 mg/L, respectively. Given that the PK/PD breakpoint of cefaclor is 0.5 mg/L, it would be expected to be active against some penicillin-susceptible strains, a minority of the penicillin-intermediate strains, and none of the penicillin-resistant strains. With a PK/PD breakpoint of 1 mg/L, cefuroxime would be expected to be effective against the majority of penicillin-susceptible strains, many penicillin-intermediate strains, and none of the penicillin-resistant strains. A comparative clinical study of cefaclor and cefuroxime axetil illustrates this. At day 4–5, bacteriologic persistence of penicillin-susceptible S. pneumoniae strains was observed in similar percentages of children treated with cefaclor (4% (1/25)) and with cefuroxime axetil (9% (2/22)) (Figure 1). However, against penicillin-intermediate strains, while bacteriologic failure occurred in 58% (7/12) of children after cefaclor treatment, failure occurred in only 21% (4/19) of children treated with cefuroxime axetil. As predicted from the PK/PD breakpoints for these two cephalosporins, therefore, cefaclor and cefuroxime axetil would be expected to be effective against the majority of penicillin-susceptible strains, many penicillin-intermediate strains, and none of the penicillin-resistant strains. A comparative clinical study of cefaclor and cefuroxime axetil illustrates this. At day 4–5, bacteriologic persistence of penicillin-susceptible S. pneumoniae strains was observed in similar percentages of children treated with cefaclor (4% (1/25)) and with cefuroxime axetil (9% (2/22)) (Figure 1). However, against penicillin-intermediate strains, while bacteriologic failure occurred in 58% (7/12) of children after cefaclor treatment, failure occurred in only 21% (4/19) of children treated with cefuroxime axetil. As predicted from the PK/PD breakpoints for these two cephalosporins, therefore, cefaclor and cefuroxime axetil...
have similar bacteriologic efficacy against penicillin-susceptible *S. pneumoniae* strains, whereas against penicillin-intermediate strains, cefuroxime retains good activity and cefaclor is little better than placebo.6,19

Although no PK/PD breakpoint has been calculated for intramuscular ceftriaxone, a study comparing the effect of a 1-day versus a 3-day dosing regimen indicates the importance of changes in PK/PD characteristics for bacteriologic response.14 Children with nonresponsive acute otitis media were given a 50 mg/kg per day dose of intramuscular ceftriaxone for either 1 or 3 days.14 Bacterial eradication of penicillin-susceptible *S. pneumoniae* strains was achieved by day 4–5 with both regimens. However, bacteriologic failure with the 1-day regimen was 48% (13/27) for penicillin-non-susceptible strains, compared with 3% (1/34) for the 3-day regimen.14

Studies in otitis media have also demonstrated the impact of macrolide resistance on bacteriologic outcomes with macrolide therapy.7,8 For azithromycin, the PK/PD breakpoint is 0.12 mg/L. Two studies are relevant in terms of determining whether or not these predictions are supported by bacterial eradication rates with azithromycin treatment in children with acute otitis media,7,8 and the results are summarized in Figure 2.6–8 Combined data from these two studies indicate that bacteriologic failure against strains with azithromycin MICs ≤0.25 mg/L was 5% (2/37), compared with 79% (11/14) for MICs >2 mg/L, i.e. no better than placebo. In the 2001 Alexander Project, the MIC<sub>50</sub> and MIC<sub>90</sub> of azithromycin were both 0.12 mg/L against 1732 erythromycin-susceptible *S. pneumoniae* strains, and so most of these strains would be eradicated with erythromycin therapy.17 However, against 749 erythromycin-resistant strains, the azithromycin MIC<sub>50</sub> and MIC<sub>90</sub> were both >32 mg/L, and only one strain had an azithromycin MIC of <1 mg/L.17 Thus, based on PK/PD parameters, azithromycin would be predicted to be ineffective against all erythromycin-resistant strains.

**PK/PD-DIRECTED THERAPY**

Using PK/PD predictions, a 3-day course of intramuscular ceftriaxone is the most effective therapy currently available for the treatment of otitis media, and this is supported by clinical data (Table 1). However, administration of the doses requires clinic visits on three consecutive days, which can be inconvenient for many parents. As far as oral therapy is concerned, amoxicillin-clavulanate currently provides the greatest coverage of the major pathogens, followed by cefuroxime axetil. Cefuroxime axetil 30 mg/kg per day will provide coverage of penicillin-susceptible and -intermediate pneumococci, and is effective against β-lactamase producing *H. influenzae* and *M. catarrhalis*. Amoxicillin-clavulanate is also effective against β-lactamase-producing strains. In addition, with a PK/PD breakpoint of 2 mg/L for a 40–50 mg/kg per day dose, amoxicillin ± clavulanate has high predicted activity against *S. pneumoniae*—amoxicillin MIC<sub>50</sub> in the 2001 Alexander Project were 0.03 mg/L for penicillin-susceptible, 0.25 mg/L for penicillin-intermediate and 2 mg/L for penicillin-resistant *S. pneumoniae*.17 For the penicillin-susceptible and -intermediate strains, none of the amoxicillin MICs were >2 mg/L, so all of these strains and about 80% of penicillin-resistant strains will be covered by amoxicillin-clavulanate.17 However, particularly in areas of high resistance prevalences, there remains a need for an oral agent with bacteriologic efficacy comparable with, or better than, that of intramuscular ceftriaxone.

With the penicillins, it is possible to increase the time above MIC (*T* > MIC) by increasing the dose. If higher concentrations can be maintained for a longer period, it will be possible to provide coverage for higher MICs. The standard regimen of amoxicillin–clavulanate of 45/6.4 mg/kg per day b.i.d. provides amoxicillin concentrations in excess of 2 mg/L for more than 40% of the dosing interval, i.e. the *T* > MIC predictive of bacterial eradication.20,21 Doubling the dose of amoxicillin to 90 mg/kg per day b.i.d. improves the PK of the formulation to provide amoxicillin concentrations that exceed an MIC of 4 mg/L for 41% of the dosing interval.21 Thus, the PK/PD breakpoint is doubled, and a greater proportion of strains can be covered. Based on 2001 Alexander Project MIC distributions, the bacteriologic efficacy of oral amoxicillin–clavulanate 90 mg/kg per day b.i.d. should be comparable to that of intramuscular ceftriaxone (Table 2).17

A recent international study has examined the bacteriologic efficacy of extra-strength amoxicillin-clavulanate in otitis media in children. The study included patients with risk factors for penicillin-resistant
Table 2. Percentages of penicillin-susceptible (Pen-S), penicillin-intermediate (Pen-I) and penicillin-resistant (Pen-R) *S. pneumoniae* and β-lactamase-positive and -negative *H. influenzae* strains isolated in the 2001 Alexander Project susceptible to conventional (45/6.4 mg/kg/day) and extra-strength (90/6.4 mg/kg/day) formulations of amoxicillin–clavulanate (AMX/CA), compared with ceftriaxone and amoxicillin.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>PK/PD breakpoint (mg/L)</th>
<th>Pen-S (n=1654)</th>
<th>Pen-I (n=378)</th>
<th>Pen-R (n=451)</th>
<th>β-Lactamase* (n=347)</th>
<th>β-Lactamase* (n=1893)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>2</td>
<td>100</td>
<td>100</td>
<td>78.3</td>
<td>0.6</td>
<td>97.7</td>
</tr>
<tr>
<td>AMX/CA</td>
<td>2</td>
<td>100</td>
<td>99.7</td>
<td>78.9</td>
<td>96.3</td>
<td>97.8</td>
</tr>
<tr>
<td>Extra-strength AMX/CA</td>
<td>4</td>
<td>100</td>
<td>100</td>
<td>89.6</td>
<td>100</td>
<td>99.4</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>100</td>
<td>99.7</td>
<td>80.7</td>
<td>100</td>
<td>99.9</td>
</tr>
</tbody>
</table>

*S. pneumoniae* infection and recurrent acute otitis media. Tympanocentesis was conducted before and after 4–6 days of treatment. Bacteriologic failure was observed in 4% (8/180) of children overall, with failure rates of 2% (3/125) for *S. pneumoniae* and 6% (5/83) for *H. influenzae*. When these results are compared with bacterial eradication rates obtained with the standard amoxicillin–clavulanate dose, it can be seen that persistence of *H. influenzae* is significantly reduced with the extra-strength formulation (*p* = 0.01, Figure 3). This brings the eradication rate for extra-strength amoxicillin–clavulanate more into line with that of ceftriaxone (94% versus 100%, respectively). The persistence of *S. pneumoniae* was also reduced with the extra-strength formulation, though not significantly. The bacteriologic failure rate was 0% (88/88) with amoxicillin–clavulanate 90/6.4 mg/kg per day b.i.d. against penicillin-susceptible and -intermediate *S. pneumoniae* and 9% (31/34) against penicillin-resistant strains (penicillin MICs ≥2 mg/L). In comparison, studies of a 3-day course of intramuscular ceftriaxone report bacteriologic failure rates of 12% (4/34) and 3% (1/34) against penicillin-intermediate strains—no data are available for penicillin-resistant strains. The successful development of the extra-strength amoxicillin–clavulanate 90/6.4 mg/kg per day b.i.d. formulation indicates that, by using PK/PD principles to guide changes in antimicrobial dosing, it is possible to achieve greater eradication rates of the main pathogens of acute otitis media, and hence improve clinical success.

**CONCLUSIONS**

Double-tympanocentesis studies in otitis media provide strong evidence supporting the clinical relevance of PK/PD predictions of bacteriologic efficacy. Consideration of the data outlined in this paper indicate that only limited choices now exist for the treatment of children with acute otitis media. Some agents have suboptimal PK/PD characteristics even in the absence of resistance, such as macrolides and cefaclor against *H. influenzae*. Increased prevalences of resistance will initially undermine the bacteriologic efficacy of antimicrobials with marginal PK/PD profiles, e.g. macrolide resistance in *S. pneumoniae*. However, all currently available therapy will be compromised if bacteriologic susceptibility decreases sufficiently. It is, therefore, important that we are not complacent and continue to develop new antimicrobials and formulations with improved PK/PD profiles. The development of the extra-strength formulation of amoxicillin–clavulanate (90/6.4 mg/kg per day b.i.d.) has shown that PK/PD principles can be directly applied to the optimization of antimicrobial therapy. The choice of current antimicrobial therapy and the development of new antimicrobial agents and formulations should aim to meet PK/PD parameters predictive of bacterial eradication of both susceptible and resistant strains.

**REFERENCES**

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