

Does the Dose Matter?

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Pharmacokinetic/pharmacodynamic (PK/PD) parameters, such as the ratio of peak to minimum inhibitory concentration (peak/MIC ratio), ratio of 24-hour area under the curve to MIC (24-h AUC/MIC ratio), and the time above MIC, are good indicators of the drug dose–organism interaction. Time above the MIC is the important determinant of the activity of β -lactams, macrolides, clindamycin, and linezolid. Free drug serum levels of these drugs should be above the MIC for at least 40%–50% of the dosing interval to produce adequate clinical and microbiological efficacy. Peak/MIC and 24-h AUC/MIC ratios are major determinants of the activity of aminoglycosides and fluoroquinolones. In general, peak/MIC ratios should exceed 8 and 24-h AUC/MIC values should be >100 to successfully treat gram-negative bacillary infections and to prevent the emergence of resistant organisms during therapy. The successful treatment of pneumococcal infections with fluoroquinolones and azithromycin appear to require 24-h AUC/MIC ratios of only 25–35. Mutation prevention concentrations are being reported for various fluoroquinolones with different pathogens, but their clinical significance has not yet been established. More information is needed on the role of PK/PD parameters and their magnitude for preventing mutations and the emergence of resistant organisms for most classes of antibiotics.

The increasing incidence of bacterial resistance has produced a major challenge for the successful therapy of many bacterial infections. The emergence of resistant bacteria during the course of antimicrobial therapy can also result in clinical failure. A variety of studies done during the past 10–15 years have demonstrated that the success of a specific dose of drug is dependent on both a measure of drug exposure, such as the serum peak level, the area under the serum concentration–versus time curve (AUC), and the duration of time serum levels exceed certain concentrations, and a measure of the potency of the drug against the infecting organisms (e.g., MIC or minimum bactericidal concentration). These so-called pharmacokinetic/ pharmacodynamic (PK/PD) parameters can be major determinants of the in vivo efficacy of an-

timicrobial agents [1]. The specific parameters most commonly correlated with outcome include the ratio of peak to minimum inhibitory concentration (peak/MIC ratio), the ratio of the 24-h area under the curve to MIC (24-h AUC/MIC ratio), and the duration of time serum levels exceed the MIC expressed as the percentage of the dosing interval.

There is an increasing amount of data from in vitro and animal infection models on the relationships between the magnitude of these PK/PD parameters for different antimicrobial agents and their ability to treat less susceptible organisms and to prevent the emergence of resistance. Studies in humans are more limited, but the availability of pharmacologic tools, such as optimal sampling and population pharmacokinetic modeling, have greatly improved the ability of investigators to estimate the extent of drug exposure in individual patients. This brief review will summarize our current knowledge on the relationships between PK/PD parameters and clinical and/or bacteriologic efficacy and the emergence of resistance during therapy.

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Clinical Infectious Diseases 2001;33(Suppl 3):S233–7

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1058-4838/2001/3306S3-0022\$03.00

PATTERNS OF ANTIMICROBIAL ACTIVITY

It is the time course of antimicrobial activity that determines which characteristic of a drug's pharmacokinetics is most important in determining *in vivo* activity. The aminoglycosides and fluoroquinolones are drugs that exhibit concentration-dependent killing and produce prolonged persistent effects. Because higher doses will result in better killing, once-daily dosing of these agents that maximize the peak/MIC ratio could enhance their antimicrobial activity [1, 2]. On the other hand, β -lactams, macrolides, clindamycin, and linezolid have time-dependent killing and produce minimal to modest persistent effects. With these drugs, the frequency of administration and the dose are both important determinants of their antimicrobial activity. Time above the MIC has been the major PK/PD parameter to correlate with efficacy of these drugs [3–5]. Azithromycin, tetracyclines, glycopeptides, and quinupristin-dalfopristin also exhibit time-dependent killing but produce prolonged persistent effects. The dosing frequency is usually not a major factor in the efficacy of these drugs. The 24-h AUC/MIC is the primary parameter to correlate with *in vivo* efficacy [5]. However, in a nonneutropenic model where interactions with neutrophils may also alter efficacy, peak/MIC was an important determinant of the antimicrobial activity of the glycopeptides [6].

MAGNITUDE OF PK/PD PARAMETERS REQUIRED FOR EFFICACY

Studies in animal infection models and human clinical trials have provided data that suggest that the magnitude of the PK/PD parameter required for clinical and bacteriologic efficacy are relatively similar in different animal species including humans. This is not surprising, because the receptor for the antimicrobial agent is in the pathogen and, therefore, it is the same in both animal models and human infections. There are also data to suggest that the magnitude of the PK/PD parameter required for efficacy is similar for different dosing regimens, for different drugs within the same class (providing free-drug concentrations are used), and at different sites of infection [7–9]. Organisms with decreased susceptibility to penicillins, macrolides, and fluoroquinolones due to decreased affinity at the site of action also appear to require the same magnitude of the PK/PD parameter for efficacy [10–12].

For penicillins and cephalosporins, the time above the MIC required for efficacy is 40%–50% of the dosing interval. Figure 1 shows the relationship between time above MIC and bacteriologic efficacy for amoxicillin and amoxicillin-clavulanate against penicillin-susceptible, penicillin-intermediate, and penicillin-resistant *Streptococci pneumoniae* at 2 different sites of infection in mice. Significant bactericidal activity in both models was observed when serum concentrations exceeded the MIC

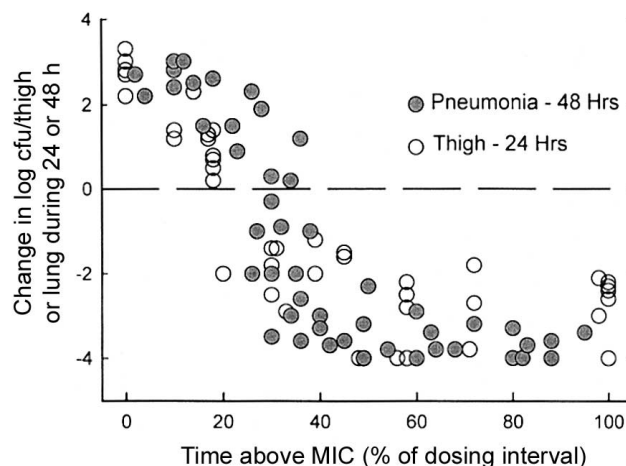


Figure 1. Relationship between time above MIC and change in bacterial numbers for numerous strains of *Streptococcus pneumoniae* at 24 and 48 h in the thighs and lungs, respectively, of mice with neutropenia after they received therapy with amoxicillin or amoxicillin/clavulanate. Data are from [10, 11].

for 40%–50% of the dosing interval. A similar magnitude for time above MIC has been shown to result in 85%–100% bacteriologic efficacy in children with acute otitis media [13]. Retrospective reviews of patients with community-acquired pneumonia have also shown good efficacy with various β -lactams in patients infected with penicillin-intermediate and penicillin-resistant *S. pneumoniae*, as long as the predicted serum concentrations of the drug exceeded the MIC for 40%–50% of the dosing interval [14].

Although animal studies suggest that the magnitude of the time above MIC required for efficacy of macrolides against *S. pneumoniae* is also 40%–50% of the dosing interval, studies on bacteriologic cure have been limited to macrolide-susceptible strains. For these organisms, erythromycin and clarithromycin provide prolonged time above MIC (92%–100% of the dosing interval) and produce high rates of bacteriologic cure [13]. The 24-h AUC/MIC is the PK/PD parameter correlating with the efficacy of azithromycin. In our neutropenic murine thigh infection model, a value of approximately 25–30, which is equivalent to averaging 1 times the MIC during 24 h, is required for efficacy (unpublished data). This value is easily obtained with standard dosing for azithromycin-susceptible strains of *S. pneumoniae*, and high rates of bacteriologic cure have been observed with azithromycin therapy in children with otitis media [15, 16]. However, the 24-h AUC/MIC for azithromycin-resistant *S. pneumoniae* due to the macrolide-lincosaminstreptogramin B mechanism (MICs >16 $\mu\text{g/mL}$) is <0.1, and bacteriologic failure has been observed in most patients. Organisms with the efflux mechanism of resistance have lower MICs, but there are inadequate data on their efficacy in man-

Table 1. Relationship of the ratio of 24-h area under the curve to MIC (24-h AUC/MIC ratio) and monotherapy and combination therapy to the emergence of resistant organisms during therapy with β -lactams and ciprofloxacin.

Therapy	24-h AUC/MIC ratio	Patients with resistance/ total patients (%)		
		All patients	Ciprofloxacin treatment	β -Lactam treatment
Monotherapy	<100	14/17 (82)	12/14 (86)	2/3(67)
Monotherapy	\geq 100	17/84 (20)	4/44 (9)	13/40 (31)
Combination	\geq 100	1/27 (4)	0/16 (0)	1/27 (4)

NOTE. Data obtained from [23].

agement of acute otitis media after treatment with azithromycin or clarithromycin.

The 24-h AUC/MIC and the peak/MIC ratios have been the primary PK/PD parameters determining the efficacy of the fluoroquinolones. Studies in animals and humans with gram-negative bacilli have suggested that the 24-h AUC/MIC ratio needs to exceed 100–125 to obtain high rates of bacteriologic and clinical cure [8, 17]. Values of >250 are associated with a very rapid elimination of gram-negative bacilli from respiratory secretions of patients with nosocomial pneumonia. However, studies that have used in vitro kinetic models, animal survival studies in mice without neutropenia, and clinical trials all suggest that the magnitude of the 24-h AUC/MIC required for the efficacy of fluoroquinolones against *S. pneumoniae* is more in the 25–35 range [18–20]. One-third of the 21 patients who were infected with *S. pneumoniae* in the pharmacodynamic studies of levofloxacin had 24-h AUC/MIC values measured between 30–100 during therapy [20]. A few cases of clinical and bacteriologic failure have been reported with levofloxacin with strains that have MICs of 8 $\mu\text{g/mL}$ [21]. The estimated 24-h AUC/MIC ratios in these patients would be <10 . Failures in patients with pneumococcal pneumonia have also been reported for ciprofloxacin where the 24-h AUC/MIC ratio has been estimated to be around 10–20 with 400 mg given iv every 12 h. Preliminary studies with gemifloxacin against strains of pneumococci with resistance mutations in *GyrA*, *GyrB*, *ParC*, and/or *ParE* suggest that the magnitude of the 24-r AUC/MIC ratio is very similar to values in naïve susceptible strains [12]. However, organisms with efflux appeared to require less drug for efficacy in vivo than predicted by their in vitro MIC.

PK/PD PARAMETERS AND EMERGENCE OF RESISTANCE

In a retrospective review of 173 clinical drug trials from 1970–1992 that included more than 14,000 patients, the emergence of resistance occurred among 4.0% of all organisms and 5.6% of all infections [22]. The development of resistance was

most common in patients with lower respiratory tract infections, varying from 31% in patients with cystic fibrosis to 9% in other patients. The emergence of resistance occurred significantly more frequently with *Pseudomonas aeruginosa* (15.4%), *Serratia* species (7.8%) and *Enterobacter* species (6.8%). It occurred significantly less frequently with gram-positive cocci, such as *Staphylococcus aureus* (2.2%), *Enterococcus* species (1.7%), *S. pneumoniae* (0.5%), and other streptococci (0.3%). In another data set involving 107 acutely ill patients with lower respiratory tract infections associated with 128 pathogens, Thomas et al. [23] observed the emergence of resistance in 32 (25%) of cases. The incidence was highest for *P. aeruginosa* (46%) and other gram-negative bacilli capable of producing type-1 β -lactamase, such as *Enterobacter* and *Serratia* species (27%). No resistance emerged in gram-positive cocci, but the number of strains was quite low. This particular study is important because all 107 patients had PK/PD parameters, primarily the 24-h AUC/MIC ratio, calculated from serial serum concentrations and the MIC. The authors then determined the relationship between the magnitude of the 24-h AUC/MIC and the development of resistance. The results of their pharmacodynamic modeling suggested that a 24-h AUC/MIC ratio of ≥ 100 was associated with a significantly reduced risk for the emergence of resistance during therapy. For example, the emergence of resistance occurred in 82% of cases when the 24-h AUC/MIC ratio was <100 but only in 9% of cases when the ratio was ≥ 100 .

A critical reexamination of this study is necessary for 2 reasons. The authors eliminated cases due to *Enterobacteriaceae* that can produce type-1 β -lactamase and were treated with β -lactam monotherapy. However, they included cases with β -lactam monotherapy for *P. aeruginosa*, which can also develop resistance by producing enhanced amounts of type-1 β -lactamase. The data set also included 27 cases in which patients received combination therapy with ceftazidime and tobramycin or piperacillin and ciprofloxacin. The 24-h AUC/MIC ratios for combination therapy were calculated by adding the magnitude of the ratios for each individual drug. The validity of this methodology has not been proven. In fact, a recent animal infection model designed to determine the pharmacodynamics of antibiotic combinations against *P. aeruginosa* demonstrated that summing the 24-h AUC/MIC values for β -lactams in combination with an aminoglycosides or fluoroquinolone is a poor predictor of in vivo antimicrobial activity [24]. Furthermore, the reduced emergence of resistant organisms with drug combinations may be similar to tuberculosis where the risk of resistance to 2 drugs is the product of their individual mutation frequencies.

Table 1 shows the impact of the PK/PD parameter with monotherapy and combination therapy for all patients and for those who were treated with ciprofloxacin or a β -lactam. For

Table 2. Relationship of the 24-h area under the curve to MIC (24-h AUC/MIC ratio) to the emergence of resistant *Pseudomonas* and other gram-negative bacilli (GNB) during monotherapy with ciprofloxacin and β -lactams.

24-h AUC/MIC ratio	Patients with resistance/total patients (%)			
	Ciprofloxacin therapy		β -Lactam therapy	
	<i>Pseudomonas</i>	Other GNB	<i>Pseudomonas</i>	Other GNB
<100	10/10 (100)	2/4 (50)	2/3 (67)	
≥ 100	2/8 (25)	2/28 (7)	2/3 (67)	10/28 (36)
P	.002	.07	2/3 (67)	

NOTE. Data obtained from reference [23]. $P < .001$; Fisher exact test.

patients who received monotherapy, a 24-h AUC/MIC <100 was associated with a significantly greater risk for emergence of resistance ($P < .001$; χ^2), primarily in patients treated with ciprofloxacin. However, for patients who received both ciprofloxacin and β -lactams, combination therapy was associated with a further reduction in the emergence of resistance pathogens during therapy, but the differences were not statistically significant. As shown in table 2, the reduced risk for the emergence of resistance with ciprofloxacin therapy that produced a 24-h AUC/MIC ratio of >100 was observed primarily in strains of *P. aeruginosa*, but it was also observed in other gram-negative bacilli. This was not the case for either group of patients who received β -lactam therapy. As mentioned in the study by Thomas et al. [23], resistance emerged in 50% of strains of *Enterobacter* and *Serratia* species even when the 24-h AUC/MIC ratio was >100 . A recent study in the murine thigh-infection model with a strain of *Enterobacter cloacae* managed with ceftriaxone suggested that it was the duration of time that serum levels exceeded 32 times the MIC that was important in preventing the emergence of resistance [25]. Therefore, drug combinations may be the more effective method for preventing the emergence of resistance to β -lactams in these organisms.

Several animal and in vitro studies have suggested that a peak/MIC ratio of at least 8–10 can significantly reduce the emergence of resistant subpopulations with fluoroquinolones and aminoglycosides [26, 27]. Peak/MIC ratios were not specifically analyzed in the paper by Thomas et al. [23]. As shown in table 3, data published on a subset of the patients treated with ciprofloxacin demonstrates that a peak/MIC ratio of 8 or higher was just as predictive as a 24-h AUC/MIC value of >100 in significantly reducing the emergence of resistance during therapy [28].

It is not clear if the same magnitudes for the peak/MIC and 24-h AUC/MIC ratios apply to gram-positive cocci, especially *S. pneumoniae*. As mentioned earlier, the emergence of resistance has been a relatively uncommon phenomenon in *S. pneumoniae*. Preston et al. [20] did not observe any emergence of resistance to levofloxacin in the patients with 24-h AUC/MIC

values of 30–100. It has also been difficult in in vitro models that simulate human pharmacokinetics of fluoroquinolones to observe the emergence of resistance in pneumococci when the 24-h AUC/MIC ratio has exceeded 30 [18, 19].

MUTATION PREVENTION CONCENTRATION

The mutation prevention concentration (MPC) is defined as the lowest drug concentration in agar that prevents the growth of any colonies of resistant mutants from very large inocula. Initial data suggest that the MPC can vary for different organisms and for different drugs [29, 30]. For *S. pneumoniae*, the MPC values have varied from 4–7 times the MIC. However, these long-term exposures to constant concentrations of drug do not let us know whether shorter exposures to similar or higher concentration will be just as effective in preventing resistance. Much more data are needed on the significance of the MPC and the relationship of PK/PD parameters to the emergence of resistance.

CONCLUSIONS

The dose, as reflected by the magnitude of the PK/PD parameter required for efficacy, does appear to be an important determinant of clinical and bacteriological efficacy, even for organisms with reduced susceptibility. For β -lactams, macrolides, clindamycin, and linezolid, free drug levels in serum need to exceed the MIC for at least 40%–50% of the dosing interval. The 24-h AUC/MIC should be at least 25–35 for azithromycin and fluoroquinolones when treating patients with *S. pneumoniae* infections. Higher ratios (≥ 100) for the 24-h AUC/MIC are required for fluoroquinolones to have efficacy against gram-negative bacilli. Ratios of this magnitude, along with peak/MIC values of >8 , can also significantly reduce the risk for the emergence of resistance during fluoroquinolone therapy of *Pseudomonas* and other gram-negative bacillary infections. High peak concentrations also appear to be capable of reducing the emergence of resistant gram-negative bacilli with exposure to aminoglycosides. Much

Table 3. Relationship of peak/MIC or the 24-h area under the curve to MIC (24-h AUC/MIC ratio) to the emergence of resistance during monotherapy with ciprofloxacin.

PK/PD parameter	Patients with or without resistance/total patients (%)	
	Emergence of resistance	No resistance
Peak/MIC ≥ 8 or 24-h AUC ≥ 100	3/31 (10)	28/31 (90)
Peak/MIC < 8 or 24-h AUC/MIC < 100	8/10 (80)	2/10 (20)

NOTE. Data obtained from reference [28]. AUC, area under the curve; PK/PD, pharmacokinetic/pharmacodynamic. $P < .001$ by Fisher exact test.

more information is required to determine the PK/PD parameter and the magnitude necessary to prevent the emergence of organisms that are resistant to β -lactams, macrolides, and other frequently used antimicrobial agents.

References

- Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* **1998**; 26: 1–12.
- Craig WA, Redington J, Ebert SC. Pharmacodynamics of amikacin in vitro and in mouse thigh and lung infections. *J Antimicrob Chemother* **1991**; 27(Suppl C):29–40.
- Vogelman B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA. Correlation antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. *J Infect Dis* **1988**; 158:831–47.
- Leggett JE, Fantin B, Ebert S, et al. Comparative antibiotic dose-effect relationships at several dosing intervals in murine pneumonitis and thigh-infection models. *J Infect Dis* **1989**; 159:281–92.
- Craig WA. Postantibiotic effects and the dosing of macrolides, azalides, and streptogramins. In: Zinner SH, Young LS, Acar JF, Neu HC, eds. Expanding indications for the new macrolides, azalides and streptogramins. New York: Marcel Dekker, **1997**:27–38.
- Knudsen JD, Fuursted K, Raber S, Espersen F, Frimodt-Moller N. Pharmacodynamics of glycopeptides in the mouse peritonitis model of *Streptococcus pneumoniae* or *Staphylococcus aureus* infection. *Antimicrob Agents Chemother* **2000**; 44:1247–54.
- Craig WA. Interrelationships between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Drug Microbiol Infect Dis* **1995**; 22:89–93.
- Craig WA, Dalhoff A. Pharmacodynamics of fluoroquinolones in experimental animals. In: Kulman J, Dalhoff A, Zeiler HJ, eds. Quinolone antibacterials. Heidelberg, Germany: Springer-Verlag Berlin, **1998**: 207–32.
- Leggett JE, Ebert S, Fantin B, Craig WA. Comparative dose-effect relations at several dosing intervals for beta-lactam, aminoglycoside and quinolone antibiotics against gram-negative bacilli in murine thigh-infection and pneumonitis models. *Scand J Infect Dis* **1991**; (Suppl 74): 179–84.
- Andes D, Craig WA. In vivo activities of amoxicillin and amoxicillin-clavulanate against *Streptococcus pneumoniae*: application to breakpoint determination. *Antimicrob Agents Chemother* **1998**; 42:2375–9.
- Woodnut G, Berry V. Two pharmacodynamic models for assessing the efficacy of amoxicillin-clavulanate against experimental respiratory tract infections caused by strains of *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* **1999**; 43:29–34.
- Andes DR, Craig WA. Pharmacodynamics of gemifloxacin (GEM) against quinolone-resistant strains of *S. pneumoniae* (SP) with known resistance mechanisms [abstract 27]. In: Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington DC: American Society for Microbiology, **1999**:8.
- Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatr Infect Dis J* **1996**; 15:255–9.
- Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the drug-resistant *Streptococcus pneumoniae* therapeutic working group. *Arch Intern Med* **2000**; 160:1399–1408.
- Dagan R, Leibovitz E, Fliss DM, et al. Bacteriologic efficacies of oral azithromycin and oral cefaclor in treatment of acute otitis media in infants and young children. *Antimicrob Agents Chemother* **2000**; 44: 43–50.
- Dagan R, Johnson CE, McLinn S, et al. Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media. *Pediatr Infect Dis J* **2000**; 19:95–104.
- Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* **1993**; 37:1073–81.
- Lacy MK, Lu W, Xu X, et al. Pharmacodynamic comparisons of levofloxacin, ciprofloxacin, and ampicillin against *Streptococcus pneumoniae* in an in vitro model of infection. *Antimicrob Agents Chemother* **1999**; 43:672–7.
- Lister PD, Sanders CC. Pharmacodynamics of levofloxacin and ciprofloxacin against *Streptococcus pneumoniae*. *J Antimicrob Chemother* **1999**; 43:79–86.
- Preston SL, Drusano GL, Berman AL, et al. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. *JAMA* **1998**; 279: 125–9.
- Fishman NO, Suh B, Weigel WM, et al. Three levofloxacin treatment failures of pneumococcal respiratory tract infections. In: Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington DC: American Society for Microbiology, **1999**.
- Fish DN, Piscitelli SC, Danziger LH. Development of resistance during antimicrobial therapy: a review of antibiotic class and patient characteristics in 173 studies. *Pharmacotherapy* **1995**; 15:279–91.
- Thomas JK, Forrest A, Bhavnani SM, et al. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob Agents Chemother* **1998**; 42:521–7.
- Mouton JW, van Ogtrop ML, Andes D, Craig WA. Use of pharmacodynamic indices to predict efficacy of combination therapy in vivo. *Antimicrob Agents Chemother* **1999**; 43:2473–8.
- Berkhout J, van Ogtrop ML, van den Broek PJ, et al. Pharmacodynamics of ceftriaxone against cephalosporin-sensitive and -resistant *Enterobacter cloacae* in vivo. In: Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington DC: American Society for Microbiology, **1999**.
- Blaser J, Stone BB, Groner MC, Zinner SH. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. *Antimicrob Agents Chemother* **1987**; 31:1054–60.
- Drusano GL, Johnson DE, Rosen M, Standiford HC. Pharmacodynamics of a fluoroquinolone antimicrobial agent in a neutropenic rat model of *Pseudomonas* sepsis. *Antimicrob Agents Chemother* **1993**; 37:483–90.
- Peloquin CA, Cumbo TJ, Nix DE, Sands MF, Schentag JJ. Evaluation of intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections. *Arch Intern Med* **1989**; 149:2269–73.
- Dong Y, Zhao X, Domagala J, Drlica K. Effect of fluoroquinolone concentration on selection of resistant mutants of *Mycobacterium bovis* BCG and *Staphylococcus aureus*. *Antimicrob Agents Chemother* **1999**; 43:1756–8.
- Blondeau JM, Borsos S, Drlica K. Mutation prevention concentration of moxifloxacin and levofloxacin against clinical isolates of *S. pneumoniae* and *S. aureus*. In: Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington DC: American Society for Microbiology, **1999**.