ORIGINAL ARTICLE 10.1111/j.1469-0691.2006.01617.x

The contribution of pharmacokinetic–pharmacodynamic modelling with Monte Carlo simulation to the development of susceptibility breakpoints for *Neisseria meningitidis*

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ABSTRACT

This study used pharmacokinetic–pharmacodynamic (PK–PD) modelling and MICs of 15 antimicrobial agents, derived from testing a large international culture collection, to assist in the development of interpretative criteria, i.e., breakpoints, for *Neisseria meningitidis*. PK parameters, protein binding, percentage penetration into cerebrospinal fluid (CSF), and the variability of these values, were extracted from the published literature for the 15 agents. PK–PD parameters have not been developed specifically for *N. meningitidis* in animal or human studies. Thus, it was necessary to invoke PK–PD targets from other organisms that cause infections at similar sites. The PK–PD targets utilised were: time above the MIC for at least 50% of the dosing interval for all β-lactams, chloramphenicol, sulphafurazole and trimethoprim–sulphamethoxazole; an AUC/MIC ratio of ≥25 for the tetracyclines and macrolides; and an AUC/MIC ratio of ≥125 for the fluoroquinolones. A 10 000-subject Monte Carlo simulation was designed with the usual dosing regimens of each antimicrobial agent at MIC values of 0.03–64 mg/L in both serum and CSF. The PK–PD breakpoint was defined as the MIC at which the calculated target attainment was ≥95%. Using these assumptions, the proposed PK–PD breakpoints were: azithromycin, 0.125 mg/L; doxycycline, 0.25 mg/L; cefotaxime, ciprofloxacin and levofloxacin, 0.5 mg/L; penicillin G, meropenem, rifampicin, tetracycline and minocycline, 1 mg/L; chloramphenicol and sulphafurazole, 2 mg/L; and ampicillin, ceftriaxone and trimethoprim–sulphamethoxazole, 4 mg/L. Proposed PK–PD breakpoints applicable to CSF were: penicillin and cefotaxime, 0.06 mg/L; rifampicin, 0.125 mg/L; ceftriaxone, meropenem and trimethoprim–sulphamethoxazole, 0.25 mg/L; ampicillin, 0.5 mg/L; and chloramphenicol, 1 mg/L.

Keywords Breakpoints, interpretative susceptibility criteria, Monte Carlo simulation, *Neisseria meningitidis*, pharmacokinetics–pharmacodynamics, susceptibility testing

Original Submission: 28 July 2005; **Revised Submission:** 8 June 2006; **Accepted:** 18 August 2006

Clin Microbiol Infect 2007; 13: 33–39

INTRODUCTION

The CLSI (formerly NCCLS) has recently defined antimicrobial susceptibility testing conditions for *Neisseria meningitidis* for the first time [1]. The previous absence of specific interpretative criteria for various antimicrobial agents when tested against *N. meningitidis* has hindered recognition of emerging antimicrobial resistance in an organism of major public health significance. Although relatively uncommon in developed countries, meningococcal infections are associated with a mortality rate of *c.* 10%, and *c.* 13% of survivors will have long-term sequelae, including hearing loss, neurological disability and loss of limbs [2,3]. The disease is highly communicable, but current vaccines have limitations, including an absence of coverage of serogroup B and ineffectiveness in young infants [4,5]. Given the morbidity and mortality associated with meningococcal

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infections, and the absence of vaccines with a broad coverage, it is important that antimicrobial susceptibility criteria, i.e., breakpoints, be developed to assess emerging trends in resistance that would impact on therapy for invasive infections or prophylaxis for case contacts.

The CLSI publishes annual standards for susceptibility testing and interpretation of results. The interpretative susceptibility criteria are the MICs or disk-diffusion zone diameters that provide an indication of likely clinical success when a specific antimicrobial agent is used to treat an infection. The CLSI has traditionally used a combination of MIC distributions of wild-type strains, MICs of strains with known resistance mechanisms, basic pharmacokinetic–pharmacodynamic (PK–PD) data and clinical trial results to establish breakpoints. Recently, the CLSI has added more extensive PK–PD modelling to these criteria as an additional tool for breakpoint determinations. PK–PD models utilise mathematics to simultaneously integrate the activity of antimicrobial agents with bacterial and patient characteristics to enable investigators to predict likely antimicrobial efficacy, based on previously established PK–PD relationships.

The present study used PK–PD modelling to assist in the initial establishment of interpretative susceptibility criteria for *N. meningitidis*. Combined with a previous study that described in-vitro susceptibility testing and the molecular characterisation of relevant resistance mechanisms [6], and some very limited clinical therapy data, the results of the present study contributed to the development of the new CLSI breakpoints for *N. meningitidis* [7].

MATERIALS AND METHODS

Meningococcal isolates

The general characteristics of the isolate collection, susceptibility testing methods and methods for the molecular characterisation of resistance mechanisms have been described previously [6]. In brief, 441 *N. meningitidis* isolates were obtained from the US CDC, numerous US state health departments and international laboratories. All testing was conducted in accordance with CLSI recommendations at the University of Texas Health Science Center at San Antonio, TX, USA.

Antimicrobial agents

Fifteen antimicrobial agents were chosen, based on their recommended use for therapy or prophylaxis of meningococcal infections. PK–PD parameters, protein binding, and the variability of these measurements, were obtained from the published literature for ampicillin, azithromycin, cefotaxime, ceftriaxone, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, meropenem, minocycline, penicillin G, rifampicin, sulphafurazole, tetracycline and trimethoprim–sulphamethoxazole (Table 1) [8–21]. Data concerning penetration into the cerebrospinal fluid (CSF) were also obtained from the literature [22–24]. PK studies were identified using an OVID search engine to query the Medline database. A Medline search was performed individually for each antimicrobial agent by combining the exploded MeSH heading 'pharmacokinetics' with each antimicrobial agent's generic name, and by limiting the results to studies of healthy individuals published in English between 1970 and 2003. In addition, suitable studies were identified that evaluated clinically relevant dosing regimens and provided the means and standard deviations for PK parameters of interest. These values were available, with few exceptions, only for adults.

Table 1. Pharmacokinetic parameters for antimicrobial agents included in the study

Antimicrobial agent	V_d (L/kg)	$t_{1/2}$ (h)	AUC (mg h/L)	f_u (%)	%CSF[a]
Ampicillin 2 g every 6 h [9]	18.9 ± 2.6	1.09 ± 0.16	–	75–85	11–18
Azithromycin 500 mg every 24 h[b]	–	–	8.03 ± 0.86	75–85	–
Cefotaxime 2 g every 8 h [10]	0.23 ± 0.07	1.18 ± 0.34	–	75–85	8–16
Ceftriaxone 2 g every 24 h [11]	0.12 ± 0.02	7.50 ± 0.60	–	3–10	8–16
Chloramphenicol 1 g every 6 h [13]	0.81 ± 0.18	3.20 ± 1.02	–	45–66	45–89
Ciprofloxacin 400 mg every 12 h [19]	–	–	24.4 ± 3.00	65–75	26–37
Doxycycline 100 mg every 12 h [20]	50.5 ± 8.7	16.20 ± 2.60	–	10–20	–
Levofloxacin 500 mg every 24 h [21]	–	–	47.70 ± 7.60	65–75	30–50
Meropenem 1 g every 8 h [12]	18.60 ± 3.00	1.07 ± 0.11	–	90–99	10–30
Minocycline 100 mg every 12 h [15]	9.49 ± 1.20	17.90 ± 4.10	–	30–40	–
Penicillin G 3 MU every 4 h [8]	23.5 ± 11.3	0.53 ± 0.09	–	35–45	5–10
Rifampicin 600 mg every 24 h [18]	0.51 ± 0.10	3.41 ± 0.86	–	50–60	7–56
Sulphafurazole 1 g every 6 h [16]	10.90 ± 2.00	6.80 ± 0.50	–	5–15	–
Tetracycline 500 mg every 6 h [14]	1.54 ± 0.23	10.55 ± 1.49	–	30–40	–
TMP/SMX 360/80 mg every 12 h [17]	1.78 ± 0.43	14.60 ± 2.60	–	50–60	10–30

V_d, volume of distribution; $t_{1/2}$, half-life; AUC, area under the concentration–time curve; f_u, unbound fraction; %CSF, percentage penetration into the cerebrospinal fluid; TMP/SMX, trimethoprim–sulphamethoxazole.
[a]%CSF was obtained from the literature [22–24].
[b]Information for azithromycin was obtained from the manufacturer's package labelling (Zithromax IV; Pfizer Labs, Division of Pfizer Inc., New York, NY, USA).

PK–PD models

Crystal Ball (Decisioneering, Inc., Denver, CO, USA) was used to perform a 10 000-subject Monte Carlo simulation in both the serum and CSF for each antimicrobial agent at MICs from 0.03 to 64 mg/L. The models permitted variation in protein binding, PK parameters and percentage CSF penetration. Although PK–PD models enable regimen-specific breakpoints to be established, the CLSI has generally advocated only a single set of breakpoints for each antimicrobial agent–organism pair. For this reason, only the most common antimicrobial regimens were modelled. The percentage time above the MIC was calculated according to an established PK–PD equation [25]. The subject weight was fixed at 70 kg for all simulations, and the free percentage time above the MIC was obtained by multiplying the dose by the unbound fraction. Similarly, the free AUC/MIC was calculated by multiplying the AUC/MIC ratio by the unbound fraction. CSF models were created by multiplying each respective equation by the percentage CSF penetration. Basic PK studies have not been performed specifically for *N. meningitidis* in animals or humans. Thus, for the purpose of this study, well-recognised PK–PD concepts that have been developed for other organisms causing serious systemic infections, including meningitis, were used. For β-lactams, chloramphenicol, sulphafurazole, trimethoprim and trimethoprim–sulphamethoxazole, the PK–PD target chosen was a percentage time above the MIC of ≥50% [23,24,26]. In contrast, the PK–PD target chosen was an AUC/MIC ratio of ≥25 for the tetracyclines and macrolides, and of ≥125 for the fluoroquinolones [23,23,26]. The susceptible PK–PD breakpoint was defined as the MIC at which target attainment was ≥95%. The susceptibility of meningococcal isolates was defined on the basis of applying the PK–PD breakpoints. Finally, for azithromycin, the susceptible percentage was based on MICs determined with incubation in ambient air, rather than in a CO_2 atmosphere.

RESULTS

Activities of antimicrobial agents

In-vitro activities of the 15 agents have been described previously [6]. A brief summary of MICs is shown in Table 2. In general, MICs were low ($MIC_{50/90}$, ≤1/≤2 mg/L) and MIC ranges were narrow (MIC_{50}, ≤0.0015–1 and MIC_{90}, ≤0.0015–2 mg/L), except for sulphafurazole ($MIC_{50/90}$, 8/>64 mg/L). Third-generation cephalosporins, fluoroquinolones and carbapenems had the lowest MICs.

PK–PD breakpoints

Detailed data showing the probabilities of target attainment and the MIC distributions of each agent for *N. meningitidis*, based upon the Monte Carlo simulations, are shown in Fig. S1 (see Supplementary material). For drugs known to achieve good CSF penetration, both serum and CSF probabilities are presented. For third-generation cephalosporins, fluoroquinolones and carbapenems, the susceptible PK–PD breakpoint (the MIC at which the probability of target attainment was ≥95%) was well above the observed MIC distribution. However, the susceptible PK–PD breakpoint bisected the MIC distribution for the penicillins, tetracyclines, macrolides, rifampicin, chloramphenicol, sulphafurazole and trimethoprim–sulphamethoxazole.

Table 3 summarises the suggested PK–PD breakpoints, based on both the serum and CSF PK parameters. For serum-based calculations, susceptible PK–PD breakpoints of most antimicrobial agents were 1 or 2 mg/L. However, azithromycin (0.125 mg/L), doxycycline (0.25 mg/L), cefotaxime (0.5 mg/L) and ciprofloxacin (0.5 mg/L) had initial breakpoints <1 mg/L, while

Table 2. MICs (mg/L) of 15 antimicrobial agents for *Neisseria meningitidis*[a]

Agent	No. of isolates	MIC_{50}	MIC_{90}	MIC range
Ampicillin	441	0.06	0.25	0.015–1
Azithromycin (in air)	100	0.06	0.12	≤0.03–0.25
Cefotaxime	441	0.003	0.007	≤0.0015–0.03
Ceftriaxone	441	≤0.0015	≤0.0015	≤0.0015–0.003
Chloramphenicol	441	1	2	0.5–16
Ciprofloxacin	441	0.003	0.003	≤0.0015–0.06
Doxycycline	124	0.5	1	0.12–2
Levofloxacin	124	0.007	0.007	0.007–0.06
Meropenem	441	0.007	0.015	≤0.0015–0.06
Minocycline	441	0.12	0.25	≤0.06–0.5
Penicillin	441	0.06	0.12	≤0.007–1
Rifampicin	441	0.03	0.12	≤0.007 to >256
Sulphafurazole	441	8	>64	≤0.25 to >64
Tetracycline	441	0.5	1	0.12–16
Trimethoprim–sulphamethoxazole	441	0.5	2	≤0.03–8

[a]Isolates were obtained from 20 states in the USA and 14 countries. Isolates represent serogroups A, B, C, W-135, X, Y and Z from 1917–2004.

Table 3. Susceptible pharmacokinetic–pharmacodynamic breakpoints (mg/L) in serum and cerebrospinal fluid (CSF)

Agent	Serum breakpoint	CSF breakpoint
Ampicillin	4	0.5
Azithromycin	0.125	–
Cefotaxime	0.5	0.06
Ceftriaxone	4	0.25
Chloramphenicol	2	1
Ciprofloxacin	0.5	–
Doxycycline	0.25	–
Levofloxacin	0.5	–
Meropenem	1	0.25
Minocycline	1	–
Penicillin G	1	0.06
Rifampicin	1	0.125
Sulphafurazole	2	–
Tetracycline	1	–
Trimethoprim–sulphamethoxazole	4	0.25

ampicillin (4 mg/L), ceftriaxone (4 mg/L) and trimethoprim–sulphamethoxazole (4 mg/L) had the highest tentative breakpoints based on serum concentrations. In general, the suggested CSF PK–PD breakpoints were eight- to 16-fold lower than those for serum.

Antimicrobial susceptibility based on PK–PD breakpoints

Table 4 summarises *N. meningitidis* susceptibility based on the suggested PK–PD breakpoints. Based on serum concentrations, >90% of *N. meningitidis* isolates were susceptible to all agents, except sulphafurazole (42%) and doxycycline (28%). Among antimicrobial agents that penetrated the CSF, >90% of *N. meningitidis* isolates were susceptible to ampicillin, cefotaxime, ceftriaxone, meropenem and rifampicin. The susceptible percentage was lower for penicillin G (83%), chloramphenicol (62%) and trimethoprim–sulphamethoxazole (46%).

DISCUSSION

Clinically relevant susceptibility interpretative criteria are critical for *N. meningitidis* because invasive meningococcal infections are associated with a high degree of morbidity and mortality. While breakpoints can be developed readily from microbiological data alone, the clinical utility of breakpoints for *N. meningitidis* depends on in-vivo factors such as CSF penetration and local activity. Clinical studies in humans provide the best means to account for all of these factors; however, meningococcal clinical studies are few in number and consist primarily of single case reports and small case series [27–33]. In the absence of optimal clinical data, PK–PD studies represent a way to address these clinical questions. While not perfect, PK–PD studies enhance the breakpoint development process by predicting clinical response, based on the integration of microbiological and PK factors.

Table 4. Susceptibility of meningococcal isolates based on the suggested pharmacokinetic–pharmacodynamic breakpoints

Agent	Serum (%S)	CSF (%S)
Ampicillin	100	97
Azithromycin[a]	97	–
Cefotaxime	100	100
Ceftriaxone	100	100
Chloramphenicol	99	62
Ciprofloxacin	100	–
Doxycycline	28	–
Levofloxacin	100	–
Meropenem	100	100
Minocycline	100	–
Penicillin G	100	83
Rifampicin	98	95
Sulphafurazole	42	–
Tetracycline	93	–
Trimethoprim–sulphamethoxazole	100	46

%S, percentage susceptible.
[a]The percentage susceptible to azithromycin was based on MICs determined in ambient air.

The present study demonstrates the utility of PK–PD modelling for the development of breakpoints for *N. meningitidis*. Since the PK–PD models described in this study are independent of MIC distributions, these models are applicable for all systemic and CSF infections so long as the PK parameters and PK–PD targets remain constant (e.g., AUC/MIC ≥125 for fluoroquinolones). As data from animal models or human infections are not available specifically for meningococci, the present study used PK–PD targets that have been established previously. The absence of background PD data for meningococci represents a potential shortcoming of this study. Despite this, the concepts used in this study represent a rational starting point for the establishment of PK–PD breakpoints for both systemic and CSF infections, regardless of the infecting pathogen.

The need for both systemic and CSF breakpoints depends on the pathogen's propensity to cause meningitis. Among patients infected with *N. meningitidis*, *c.* 50% will develop meningitis [34]. In contrast, <5% of *Streptococcus pneumoniae* infections spread to the central nervous system [35]. While the present study proposes both systemic and CSF PK–PD breakpoints for *N. meningitidis*, the CLSI recognised that *N. meningitidis* frequently causes meningitis, and established only a single set of breakpoints. In contrast, the CLSI endorsed both systemic and CSF breakpoints for *S. pneumoniae* [7].

In addition to the proposal of PK–PD breakpoints for *N. meningitidis*, the present study produced several findings worthy of further discussion. First, the PK–PD breakpoints for ampicillin vs. penicillin G were four-fold higher in serum and eight-fold higher in CSF. While penicillin G was more potent, based on the MIC_{90} (0.12 vs. 0.25 mg/L), ampicillin has more favourable pharmacokinetics, including a longer half-life and a greater unbound serum fraction. The favourable pharmacokinetics were able to

overcome the decreased potency and resulted, ultimately, in higher proposed PK–PD breakpoints for ampicillin than for penicillin G. Second, the proposed PK–PD breakpoint for doxycycline (unlike minocycline) bisected the *N. meningitidis* MIC distribution, resulting in a large portion of isolates that would be reported as resistant. Such a breakpoint would not be clinically useful. Finally, the PK–PD models indicate that the CSF breakpoint for ceftriaxone should be four-fold higher than that for cefotaxime; however, the CLSI selected a susceptible breakpoint of 0.12 mg/L for both these agents, similar to existing breakpoints for *S. pneumoniae* [7].

While PK–PD models are helpful in establishing breakpoints, it is important to remember that these models are based on a number of assumptions. First, the basic justification for PK–PD modelling is that previous studies have identified correlations between PK–PD indices (i.e., AUC/MIC) and treatment outcomes. For *N. meningitidis*, there is no confirmation of the specific, relevant, PK–PD targets; therefore, the PK–PD assumptions used in this study were extrapolated from PK–PD studies with other organisms. For example, with the fluoroquinolones, it has been shown that AUC/MIC is the most appropriate parameter for meningococci [23,24], while other investigations have shown that the magnitude of the PK–PD index for fluoroquinolones vs. Gram-negative bacteria should be 100–125 [36,37]. Since *N. meningitidis* is a Gram-negative bacterial species, it was considered rational to use an AUC/MIC of 125 as the PK–PD target. For tetracycline, trimethoprim–sulphamethoxazole and chloramphenicol, the appropriate PK–PD indexes have not been firmly established; thus, PK–PD breakpoints based on both AUC/MIC and %*T*>MIC were evaluated, but no major differences were found (data not shown).

A second potential limitation is that these PK–PD simulations were derived using MICs as the microbiological data instead of minimum bactericidal concentrations. However, since these PK–PD models predict the likelihood of clinical success in CSF, it may be worthwhile utilising minimum bactericidal concentrations in a future study. This alternative approach is unlikely to change the results for bactericidal antimicrobial agents, e.g., β-lactams, but may impact on the probabilities of target attainment for bacteriostatic antimicrobial agents [24]. With regard to the PK data, the parameters used were from healthy adults and pertained to values measured in serum rather than CSF. This was necessary because of the extremely limited PK data for children, for infected patients, and for CSF. For ethical reasons, PK studies are not conducted in healthy children. In contrast to volunteers, patients may have compromised renal function, but since many antimicrobial agents are eliminated by renal excretion, compromised renal function may result in increased serum concentrations and a greater likelihood of achieving PK–PD targets. Consequently, since CLSI breakpoints are used for patients with both normal and compromised renal function, the most conservative approach is to utilise PK parameters from healthy volunteers. In support of this practice, it has been demonstrated that the probability of target attainment is similar whether PK parameters are obtained from healthy volunteers or from patients [38].

Third, differences in CSF compared to serum may impact on antibiotic activity. Thus, while the CSF penetration data used in this study were obtained primarily from studies among meningitis patients rather than healthy adults, it is known that CSF penetration varies substantially among different studies [23,24]. This variation has been attributed to study methodology, the presence of inflamed meninges, and the administration of concomitant medications (e.g., corticosteroids) [23,24]. To account for these issues, the PK–PD models used in the present study were designed to permit variation in CSF penetration by modelling the penetration as a probability distribution rather than a single value.

Finally, much debate exists as to the appropriate value for target attainment (e.g., 90%, 95% or 100%). The most commonly used value has been 90%, but the present study utilised a more conservative value (i.e., 95%), mainly because of the serious nature of meningococcal disease. However, the data shown in Fig. S1 (see Supplementary material) allow possible PK–PD breakpoints to be determined for any target attainment value desired. Review of these targets suggests that the breakpoints would be largely unchanged whether targets of 90%, 95% or 100% were chosen.

Clinicians should recognise that this study modelled only one dosing regimen for each antimicrobial agent. The rationale behind the dosing regimen selected was that the CLSI establishes breakpoints for the global community and

that there is wide variation in the regimens used in different countries. Higher doses can be used to improve the PK–PD parameters and enhance the probability of clinical success. For some agents, the CLSI intermediate category represents a situation in which higher doses might prove efficacious, assuming that they can be administered safely. In addition, paediatric dosing regimens can be quite different for many antimicrobial agents. It should be recognised that the microbiological data (MIC distributions) and PK–PD modelling results do not always suggest the same breakpoints for an agent. It is therefore necessary to consider all relevant data to establish the most realistic and safest interpretative breakpoints for each agent.

Findings from the present study, together with previously described microbiological data, known resistance mechanisms and limited clinical data, were considered by the CLSI Antimicrobial Susceptibility Testing Sub-Committee during the establishment of the final breakpoints that were published in January 2005 [7]. The CLSI did not approve the breakpoints for tetracycline or doxycycline, as these agents are not used for treatment of meningitis, and the doxycycline PK–PD model did not suggest a clinically useful breakpoint.

ACKNOWLEDGEMENTS

This study was presented, in part, at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2004. The Fastidious Organisms Working Group of the CLSI had considerable input regarding a consensus of breakpoints ultimately approved for *N. meningitidis*. This study was supported by grant RS1/CCR622402 from the CDC. The authors would like to thank M. Carden, S. Crawford and M. Tomasini for their excellent technical assistance.

SUPPLEMENTARY MATERIAL

The following supplementary material is available for this article online at http://www.blackwell-synergy.com:

Fig. S1. Probability of target attainment and MIC distributions of 15 antimicrobial agents with Neisseria meningitidis.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically*. Approved standard M7-A6. Wayne, PA: NCCLS, 2003.
2. Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J* 1996; **15**: 967–979.
3. Edwards MS, Baker CJ. Complications and sequelae of meningococcal infections in children. *J Pediatr* 1981; **99**: 540–545.
4. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. *N Engl J Med* 2001; **344**: 1378–1388.
5. Musher DM. How contagious are common respiratory tract infections? *N Engl J Med* 2003; **348**: 1256–1266.
6. Jorgensen JH, Crawford SA, Fiebelkorn KR. Susceptibility of *Neisseria meningitidis* to 16 antimicrobial agents and characterization of resistance mechanisms affecting some agents. *J Clin Microbiol* 2005; **43**: 3162–3171.
7. Clinical Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing*. Supplement M100-S15. Wayne, PA: CLSI, 2005.
8. Ebert SC, Leggett J, Vogelman B, Craig WA. Evidence for a slow elimination phase for penicillin G. *J Infect Dis* 1988; **158**: 200–202.
9. Ripa S, Ferrante L, Prenna M. Pharmacokinetics of sulbactam/ampicillin in humans after intravenous and intramuscular injection. *Chemotherapy* 1990; **36**: 185–192.
10. Kemmerich B, Lode H, Belmega G, Jendroschek T, Borner K, Koeppe P. Comparative pharmacokinetics of cefoperazone, cefotaxime, and moxalactam. *Antimicrob Agents Chemother* 1983; **23**: 429–434.
11. Chiu LM, Menhinick AM, Johnson PW, Amsden GW. Pharmacokinetics of intravenous azithromycin and ceftriaxone when administered alone and concurrently to healthy volunteers. *J Antimicrob Chemother* 2002; **50**: 1075–1079.
12. Dreetz M, Hamacher J, Eller J *et al*. Serum bactericidal activities and comparative pharmacokinetics of meropenem and imipenem–cilastatin. *Antimicrob Agents Chemother* 1996; **40**: 105–109.
13. Burke JT, Wargin WA, Sherertz RJ, Sanders KL, Blum MR, Sarubbi FA. Pharmacokinetics of intravenous chloramphenicol sodium succinate in adult patients with normal renal and hepatic function. *J Pharmacokinet Biopharm* 1982; **10**: 601–614.
14. Raghuram TC, Krishnaswamy K. Pharmacokinetics of tetracycline in nutritional edema. *Chemotherapy* 1982; **28**: 428–433.
15. Welling PG, Shaw WR, Uman SJ, Tse FL, Craig WA. Pharmacokinetics of minocycline in renal failure. *Antimicrob Agents Chemother* 1975; **8**: 532–537.
16. Oie S, Gambertoglio JG, Fleckenstein L. Comparison of the disposition of total and unbound sulfisoxazole after single and multiple dosing. *J Pharmacokinet Biopharm* 1982; **10**: 157–172.
17. Stevens RC, Laizure SC, Sanders PL, Stein DS. Multiple-dose pharmacokinetics of 12 milligrams of trimethoprim and 60 milligrams of sulfamethoxazole per kilogram of body weight per day in healthy volunteers. *Antimicrob Agents Chemother* 1993; **37**: 448–452.
18. Peloquin CA, Jaresko GS, Yong CL, Keung AC, Bulpitt AE, Jelliffe RW. Population pharmacokinetic modeling of

isoniazid, rifampin, and pyrazinamide. *Antimicrob Agents Chemother* 1997; **41**: 2670–2679.
19. Lettieri JT, Rogge MC, Kaiser L, Echols RM, Heller AH. Pharmacokinetic profiles of ciprofloxacin after single intravenous and oral doses. *Antimicrob Agents Chemother* 1992; **36**: 993–996.
20. Nguyen VX, Nix DE, Gillikin S, Schentag JJ. Effect of oral antacid administration on the pharmacokinetics of intravenous doxycycline. *Antimicrob Agents Chemother* 1989; **33**: 434–436.
21. Chien S, Rogge M, Gisclon L *et al*. Pharmacokinetic profile of levofloxacin following once-daily 500-milligram oral or intravenous doses. *Antimicrob Agents Chemother* 1997; **41**: 2256–2260.
22. Gilbert DN, Moellering RC, Sande MA. *The Sanford guide to antimicrobial therapy*. Hyde Park, VT: Antimicrobial Therapy Inc., 2002.
23. Lutsar I, McCracken GH, Friedland IR. Antibiotic pharmacodynamics in cerebrospinal fluid. *Clin Infect Dis* 1998; **27**: 1117–1127.
24. Andes DR, Craig WA. Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. *Infect Dis Clin North Am* 1999; **13**: 595–618.
25. Turnidge JD. The pharmacodynamics of beta-lactams. *Clin Infect Dis* 1998; **27**: 10–22.
26. Drusano GL. Prevention of resistance: a goal for dose selection for antimicrobial agents. *Clin Infect Dis* 2003; **36**: S42–S50.
27. Shultz TR, Tapsall JW, White PA *et al*. Chloramphenicol-resistant *Neisseria meningitidis* containing *catP* isolated in Australia. *J Antimicrob Chemother* 2003; **52**: 856–859.
28. Casado-Flores J, Osona B, Domingo P, Barquet N. Meningococcal meningitis during penicillin therapy for meningococcemia. *Clin Infect Dis* 1997; **25**: 1479.
29. Woods CR, Smith AL, Wasilauskas BL, Campos J, Givner LB. Invasive disease caused by *Neisseria meningitidis* relatively resistant to penicillin in North Carolina. *J Infect Dis* 1994; **170**: 453–456.
30. Turner PC, Southern KW, Spencer NJ, Pullen H. Treatment failure in meningococcal meningitis. *Lancet* 1990; **335**: 732–733.
31. Saez-Nieto JA, Fontanals D, Garcia de Jalon J *et al*. Isolation of *Neisseria meningitidis* strains with increase of penicillin minimal inhibitory concentrations. *Epidemiol Infect* 1987; **99**: 463–469.
32. Galimand M, Gerbaud G, Guibourdenche M, Riou JY, Courvalin P. High-level chloramphenicol resistance in *Neisseria meningitidis*. *N Engl J Med* 1998; **339**: 868–874.
33. Van Esso D, Fontanals D, Uriz S *et al*. *Neisseria meningitidis* strains with decreased susceptibility to penicillin. *Pediatr Infect Dis J* 1987; **6**: 438–439.
34. Rosenstein NE, Perkins BA, Stephens DS *et al*. The changing epidemiology of meningococcal disease in the United States, 1992–1996. *J Infect Dis* 1999; **180**: 1894–1901.
35. Centers for Disease Control and Prevention. Effect of new susceptibility breakpoints on reporting of resistance in *Streptococcus pneumoniae*—United States, 2003. *MMWR* 2004; **53**: 152–154.
36. 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**: 1073–1081.
37. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; **26**: 1–10.
38. Kuti JL, Horowitz S, Nightingale CH, Nicolau DP. Comparison of pharmacodynamic target attainment between healthy subjects and patients for ceftazidime and meropenem. *Pharmacotherapy* 2005; **25**: 935–941.