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Use of Pharmacokinetic-Pharmacodynamic and Monte Carlo Simulation as Decision Support for the Re-Evaluation of NCCLS Cephem Susceptibility Breakpoints for Enterobacteriaceae

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AMENDED ABSTRACT

Background: As cephem-resistant Enterobacteriaceae, including ESBL-producing strains, have continued to emerge, the appropriateness of current NCCLS susceptibility breakpoints have been the focus of recent attention. In the face of limited clinical data, Pharmacokinetic-Pharmacodynamics (PK-PD) and Monte Carlo simulation have been increasingly used as decision support for establishing breakpoints. NCCLS susceptibility breakpoints for cephems against Enterobacteriaceae were re-evaluated using this approach.
Methods: Using published mean PK parameter estimates and dispersion measures from volunteer studies and PK-PD targets derived from a murine infection model (% free-drug (*f*) time > MIC ~50), Monte Carlo simulation (10,000 subjects) was used to evaluate the probability of PK-PD target attainment (≥ 90%) for standard cephem dosing regimens.
Results: Simulation results support lowering susceptibility breakpoints 2-16-fold for most agents (see table below). Except for cefoxitin and cefazolin, breakpoints do not bisect contemporary MIC population distributions (SENTRY Program).

Selected Agents from M100-S14 Table 2A	Current Susceptibility Breakpoints	% PK-PD Target Attainment at Current Susceptibility Breakpoints	Representative Dosing Regimen
cefazolin	8 / 16 / 32	1	1 g q 8h
cefamandole	8 / 16 / 32	88	2 g q 6h
cefuroxime IV	8 / 16 / 32	59	0.75 q 8h
cefepime	8 / 16 / 32	91	2 g q 12h
		77	1 g q 8h
cefmetazole/cefoperazone	16 / 32 / 64	0	1 g q 8h
cefotetan	16 / 32 / 64	8	1 g q 12h
cefoxitin	8 / 16 / 32	0	1 g q 6h
cefotaxime	8 / 16-32 / 64	3	1 g q 8h
ceftizoxime	8 / 16 / 32	3	1 g q 8h
ceftriaxone	8 / 16-32 / 64	0	1 g q 24h
ceftazidime	8 / 16 / 32	81	1 g q 8h

Conclusions: Simulation results suggest that susceptibility breakpoints for most cephems against Enterobacteriaceae should be reduced to insure that most patients attain PK-PD exposures associated with efficacy.

INTRODUCTION

As cephem-resistant Enterobacteriaceae, including ESBL-producing strains, have continued to emerge, the appropriateness of current NCCLS susceptibility breakpoints have been the focus of recent attention.

Information from animal infection models, as well as limited clinical data, suggest that ESBL-producing strains with lower MIC values may be effectively treated using appropriate cephem dosing regimens.

Given the paucity of clinical data, pharmacokinetics-pharmacodynamics (PK-PD) and Monte Carlo simulation have been increasingly used as decision support for establishing breakpoints.

In view of the above limitations, susceptibility breakpoints for cephems against Enterobacteriaceae were re-evaluated using this approach.

MATERIALS AND METHODS

Pharmacokinetic Parameter Estimates

- Pharmacokinetic data from healthy volunteers were extracted from the medical literature (Table 1).

Microbiological Susceptibility Data

- Obtained from the SENTRY Antimicrobial Surveillance Program (2001-2003).

Animal PK-PD Models

- Neutropenic murine-thigh infection models were used to study PK-PD indices that correlated best with efficacy for Enterobacteriaceae, including both EBSL- and non-ESBL producing strains.
- Indices of efficacy explored include: Duration of time (T) drug concentration remain above the MIC (T > MIC), ratio of the peak concentration of the agent to the MIC of the pathogen (C_{max}:MIC ratio), ratio of the 24-hour area under the concentration-time curve ($AUC_{0\text{-}24}$) of the agent to the MIC of the pathogen ($AUC_{0\text{-}24}$:MIC ratio).
- Non-linear regression using a Hill-type model was used to describe relationship between the above PK-PD measures and response to therapy.
- Figure 1 shows the relationship between cephem exposure, as measured by %T > MIC, and response in neutropenic murine-thigh infection models involving Gram-negative bacteria.
  - 50% T>MIC was associated with a 0.8 to 2.4 log-unit reduction in bacterial burden.

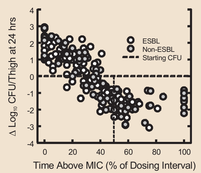
Monte Carlo Simulation

- The following PK-PD structural model was used in the simulations:
  - $T > MIC = (\ln Dose/(V_s/f) - \ln MIC)/(CLT/V8)$ where V_s is the volume estimated from the terminal elimination phase half-life (8) for a two-compartment model, CL_t is total clearance, and *f* is the fraction of unbound drug.
- Pharmacokinetic parameters for each simulated patient were based on mean pharmacokinetic parameter estimates and measures of dispersion.
  - A log-normal distribution was assumed for clearance and volume terms.
- 10,000 patients were simulated for each drug regimen.
  - Simulations were conducted using the computer software Crystal Ball 2000.1 by Decisioneering, Inc. (Denver, CO).

Susceptibility Breakpoint Determinations

- 50% T>MIC was utilized as the PK-PD goal of therapy.
- The susceptibility breakpoint was the highest MIC value associated with at least a 90% probability of PK-PD target attainment.
- Contemporary MIC population distributions were considered (*Escherichia. coli* and *Klebsiella pneumoniae*), when available.
  - If a major portion of the MIC distribution was bisected by a PK-PD susceptibility breakpoint, alternative breakpoints were chosen to avoid division but ensure high probabilities of PK-PD target attainment. In these cases, only susceptible and resistant breakpoints chosen.

Figure 1. Relationship between T>MIC and change in bacterial density in thighs of mice at 24 hours. Each data point represents data for one mouse. The dotted line reflects the number of bacteria at the beginning of therapy. The T>MIC required for efficacy is not affected by ESBL-production status.



RESULTS

- Potential susceptibility breakpoints could be stratified into one of five groups based upon probability of PK-PD target attainment and examination of contemporary MIC distributions:
  1. Susceptibility breakpoints did not bisect MIC distribution (Example, Figures 2A and 2B): Ceftazidime, Ceftriaxone, Cefotaxime, Cefepime, Cefamandole, Aztreonam
  2. Susceptibility breakpoints bisecting MIC population distributions could be avoided assuming higher of labeled doses used for serious infections (Figure 3): Cefuroxime
  3. Susceptibility breakpoints bisect MIC distribution (Example, Figure 4): Cefoxitin, Cefazolin
  4. Contemporary MIC populations not available: Ceftizoxime, Cefotetan, Cefoperazone, Cefametazole
  5. Consider removal from NCCLS table 2A due to lack of use and unavailability of contemporary MIC data: Cephalothin, Cefonicid, Moxalactam

Figure 2A. Fractional PK-PD target attainment of ceftriaxone against *Escherichia coli* and *Klebsiella pneumoniae*. The probability of PK-PD target attainment is essentially 1.0 up to MIC values of 1 mg/L when ceftriaxone is dosed 1 g every 24 hours and 2 mg/L when dosed 2 g every 24 hours.

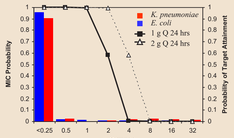
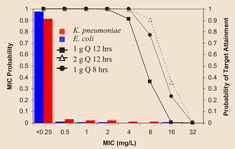


Figure 2B. Fractional PK-PD target attainment of cefepime against *Escherichia coli* and *Klebsiella pneumoniae*. The probability of PK-PD target attainment is greater than 0.9 for MIC values of 4 mg/L irrespective of the three regimens considered. When cefepime is dosed 2 g every 12 hours or 1 g every eight hours, the probability of PK-PD target attainment is 0.9 and 0.77 for a MIC of 8 mg/L, respectively.



- Table 2 shows current cephem NCCLS susceptibility breakpoints, PK-PD based breakpoints, and MIC population-adjusted PK-PD breakpoints.

Figure 3. Fractional PK-PD target attainment of cefuroxime against *Escherichia coli* and *Klebsiella pneumoniae*. The probability of PK-PD target attainment is greater than 0.9 up to MIC values of 4 mg/L when cefuroxime is dosed 0.75 g every 8 hours and 8 mg/L when dosed 1.5 g every 8 hours.

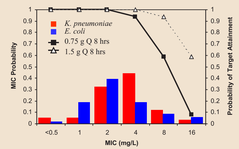


Figure 4. Fractional PK-PD target attainment of cefoxitin against *Escherichia coli* and *Klebsiella pneumoniae*. The probability of PK-PD target attainment is greater than 0.9 at a MIC of 2 mg/L when cefoxitin is dosed 1 g every 6 hours and 4 mg/L when dosed 2 g every 6 hours.

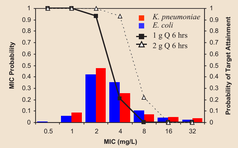


Table 1. Pharmacokinetic parameters utilized for simulations.

Agent	Pharmacokinetic Parameter Estimates (mean (SD or range)) $T_{1/2}$, hours	L_t, 1/h	Vd, L	*f* (%)
Aztreonam	1.7 (0.2)	---	11.2 (1.4)	0.44 (0.34 to 0.54)
Cefamandole	0.7 (0.04)	---	12.5 (2.3)	0.26 (0.2 to 0.3)
Cefazolin	1.8 (0.38)	0.4 (0.095)	13.01 (4.4)	0.15 (0.1 to 0.2)
Cefepime	2.2 (0.4)	---	18.2 (3.0)	0.84 (0.79 to 0.89)
Cefmetazole	1.31 (0.54)	---	11.6 (1.75)	0.35 (0.15 to 0.35)
Cefonicid	4.4 (0.8)	---	10.4 (1.2)	0.02 (0.02 to 0.05)
Cefoperazone	2.1 (0.3)	---	17.3 (3.3)	0.1 (0.08 to 0.15)
Cefotetan	---	0.23 (0.12)	6.6 (2.5)	0.15 (0.1 to 0.2)
Cefotaxime	1.1 (0.3)	---	16.6 (2.2)	0.64 (0.6 to 0.68)
Cefoxitin	---	0.84 (0.06)	10.05 (0.73)	0.5 (0.25 to 0.55)
Ceftazidime	1.8 (0.2)	---	16.6 (3.5)	0.84 (0.76 to 0.92)
Ceftizoxime	1.9 (0.1)	---	27.9 (0.7)	0.69 (0.59 to 0.79)
Ceftriaxone	6.2 (0.8)	---	9.0 (1.1)	0.07 (0.05 to 0.10)
Cefuroxime	1.3 (0.5)	---	12.0 (3.0)	0.67 (0.57 to 0.77)
Cephalothin	0.56 (0.38)	1.56 (0.66)	22.2 (10.4)	0.35 (0.25 to 0.45)
Moxalactam	2.5 (0.4)	---	0.18 (0.02)	0.35 (0.25 to 0.5)

Table 2. Current, PK-PD-based, PK-PD-based-population distribution adjusted breakpoints for antimicrobial agents in NCCLS M100-S14 Table 2A.

Drugs & Groupings	Current NCCLS in Table 2A	Usual Dose PK-PD Breakpoints	PK-PD Breakpoints Adjusted for MIC Population Distribution	Usual Dose Breakpoints
Cefazolin	8 / 16 / 32	1 / 2 / 4	-----	1 g Q8 hrs
Cephalothin	8 / 16 / 32	0.03 / 0.06 / 0.12	-----	1 g Q4 hrs
Cefamandole or	8 / 16 / 32	2 / 4 / 8	-----	2 g Q6 hrs
Cefonicid or	8 / 16 / 32	0.004 /0.008 /0.015	-----	1 g Q24 hrs
Cefuroxime	8 / 16 / 32	4 / 8 / 16	8 / -- / 16	0.75 g Q8 hrs
Cefepime	8 / 16 / 32	4 / 8 / 16	-----	1 g Q12 hrs
	8 / 16 / 32		-----	1 g Q8 hrs or 2 g Q12 hrs
Cefmetazole	16 / 32 / 64	2 / 4 / 8	-----	1 g Q8 hrs
Cefperozone	16 / 32 / 64	0.25 / 0.5 / 1	-----	1 g Q12 hrs
Cefotetan	16 / 32 / 64	2 / 4 / 8	-----	1 g Q12 hrs
Cefoxitin	8 / 16 / 32	2 / 4 / 8	8 / -- / 16	1 g Q6 hrs
Cefotaxime or	8 /16-32 / 64	1 / 2 / 4	-----	1 g Q8 hrs
Ceftizoxime or	8 /16-32 / 64	2 / 4 / 8	-----	1 g Q8 hrs
Ceftriaxone	8 /16-32 / 64	1 / 2 / 4	-----	1 g Q24 hrs
Ceftazidime	8 / 16 / 32	4 / 8 / 16	-----	1 g Q8 hrs
		8 / 16 / 32	-----	2 g Q8 hrs
Moxalactam	8 /16-32 / 64	2 / 4 / 8	-----	1 g Q8 hrs
Aztreonam	8 / 16 / 32	4 / 8 / 16	-----	1 g Q8 hrs

CONCLUSIONS

- Simulation results suggest that susceptibility breakpoints for most cephems against Enterobacteriaceae should be reduced to insure that most patients attain PK-PD exposures associated with efficacy.
- Adjustment of NCCLS breakpoints to lower values may negate the clinical need for ESBL screening and confirmatory tests.
  - Re-evaluation of susceptibility breakpoints for MIC and corresponding disk zone diameters to better predict presence of ESBLs while potentially eliminating separate screening tests has been completed (see Poster D-303, ICAAC 2004).
  - Current NCCLS Enterobacteriaceae susceptibility breakpoints remain acceptable based on error rate analysis for contemporary isolates. Lower breakpoints could eliminate the routine need for separate ESBL screening tests and disk diffusion zone correlates can be selected to maximize inter-method accuracy pending final approval by the NCCLS.