

## Evaluating Ciprofloxacin Dosing for *Pseudomonas aeruginosa* Infection by Using Clinical Outcome-Based Monte Carlo Simulations

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*Pseudomonas aeruginosa* causes serious infections whose outcome is highly dependent on antimicrobial therapy. The goal of this study was to predict the relative efficacies of three ciprofloxacin dosing regimens for *P. aeruginosa* infection using clinical outcome-based Monte Carlo simulations (MCS) with “real patient” demographics, pharmacokinetics, MICs, and pharmacodynamics (PDs). Each cohort consisted of 1,000 simulated study subjects. Three ciprofloxacin dosing regimens were studied, including (i) the recommended standard dose of 400 mg given intravenously (i.v.) every 12 h (q12h), (ii) the recommended high dose of 400 mg i.v. q8h, and (iii) a novel, PD-targeted regimen to attain a fAUC/MIC value of >86. Probability of target attainment (PTA) and probability of cure (POC) were determined for each regimen. POC with the standard dose was at least 0.90 if pathogen MICs were  $\leq 0.25$   $\mu\text{g/ml}$  but only 0.59 or 0.27 if MICs were 0.5 or 1  $\mu\text{g/ml}$ , respectively. Predicted cure rates in these MIC categories were significantly higher at 0.72 and 0.40 with the high dose and 0.91 and 0.72 with the PD-targeted regimen ( $P < 0.0001$ ). Analyses based on the local susceptibility profile produced PTA and POC estimates of 0.44 and 0.74 with the standard ciprofloxacin dose, 0.58 and 0.81 with the high dose, and 0.84 and 0.93 with the PD-targeted regimen, respectively. In conclusion, as demonstrated by clinical outcome-based MCSs, the highest recommended ciprofloxacin dose of 400 mg i.v. q8h should be used in the treatment of *P. aeruginosa* infection to improve PD target attainment and clinical cure. However, even this appears ineffective if pathogen MICs are 1  $\mu\text{g/ml}$ , warranting the consideration of a lower MIC breakpoint,  $\leq 0.5$   $\mu\text{g/ml}$ .

*Pseudomonas aeruginosa* infection is associated with significant patient morbidity and mortality. Clinical outcome is influenced by patient- and infection-related factors and is highly dependent on antimicrobial therapy. Several studies have demonstrated the association between appropriate antimicrobial selection based on sensitive MICs and patient outcome including survival (6–8, 29). More recent work has elucidated the influence of antimicrobial dosing and pharmacodynamics (PDs) on treatment response. In our previous study of *P. aeruginosa* bloodstream infection,  $C_{\text{max}}/\text{MIC}$  and AUC/MIC for ciprofloxacin and gentamicin were significantly associated with clinical cure (30) and demonstrated PD relationships consistent with those observed in the treatment of other serious gram-negative infections (20, 22).

PD targets may be difficult to attain in cases involving antimicrobials with dose-dependent toxicity, variable pharmacokinetics (PKs), or high MICs. For example, standard ciprofloxacin dosing falls within a relatively narrow range, is not adjusted for body weight, and only moderately increased from 400 mg given intravenously (i.v.) every 12 h (q12h) to q8h for severe infections. Furthermore, *P. aeruginosa* is generally less susceptible, with MICs for sensitive isolates more often approaching the Clinical and Laboratory Standards Institute (CLSI) (formerly known as NCCLS) breakpoint of 1  $\mu\text{g/ml}$ . Such factors render ciprofloxacin dosing critical in attaining adequate PD

targets and treatment response. As a result, the goal was to predict the relative efficacies of three ciprofloxacin dosing regimens for *P. aeruginosa* infection using clinical outcome-based Monte Carlo simulations (MCS) with “real patient” demographics, PKs, MICs, and PDs.

### MATERIALS AND METHODS

**Simulated study subjects.** MCSs were generated according to the algorithm in Fig. 1 using SYSTAT version 10 (2000; SPSS Inc.). Each cohort consisted of 1,000 simulated study subjects using “real patient” demographics from the prior study of *P. aeruginosa* bloodstream infection (30). In this population, infection was associated with pneumonia in 29%, vascular catheter in 12%, and urinary tract infection in 12% of cases. Inotropes and mechanical ventilation were required for 18% of patients. In the MCSs, demographics were randomly selected from a Gaussian distribution of “real patient” age ( $67 \pm 16$  years, mean  $\pm$  standard deviation) and body weight ( $76 \pm 21$  kg). Age was truncated below 18 and above 90 years, whereas body weight was maintained above 40 kg. Serum creatinine (sCr, mg/dl) was based on the age-based model,  $\text{sCr} = [0.4 + (0.0271 \times \text{age})] (\pm 30\%)$ , with log-normal distribution truncated below 0.5 and above 3 mg/dl. An allowance for natural variability was incorporated as a proportional error randomly selected from a normal distribution. Estimated creatinine clearance ( $\text{CL}_{\text{cr}}$ , ml/min) normalized to 65 kg was determined according to the following equation (10):

$$\text{CL}_{\text{cr}} = \frac{(140 - \text{age}) \times 65}{\text{sCr} \times 72} (\pm 20\%)$$

**Ciprofloxacin dosing regimens and pharmacokinetic model.** Three ciprofloxacin dosing regimens were studied, including (i) the recommended standard dose of 400 mg i.v. q12h or 400 mg i.v. q24h if the  $\text{CL}_{\text{cr}}$  is  $\leq 30$  ml/min, (ii) the recommended high dose of 400 mg i.v. q8h or 400 mg i.v. q24h if the  $\text{CL}_{\text{cr}}$  value is  $\leq 30$  ml/min, and (iii) a novel, PD-targeted regimen to attain a fAUC/MIC value of >86 with maximum doses of 2,400 mg/day or 800 mg/day if the  $\text{CL}_{\text{cr}}$  is  $\leq 30$  ml/min. Doses were assigned based on each simulated study subject’s renal function (i.e., estimated  $\text{CL}_{\text{cr}}$ ).

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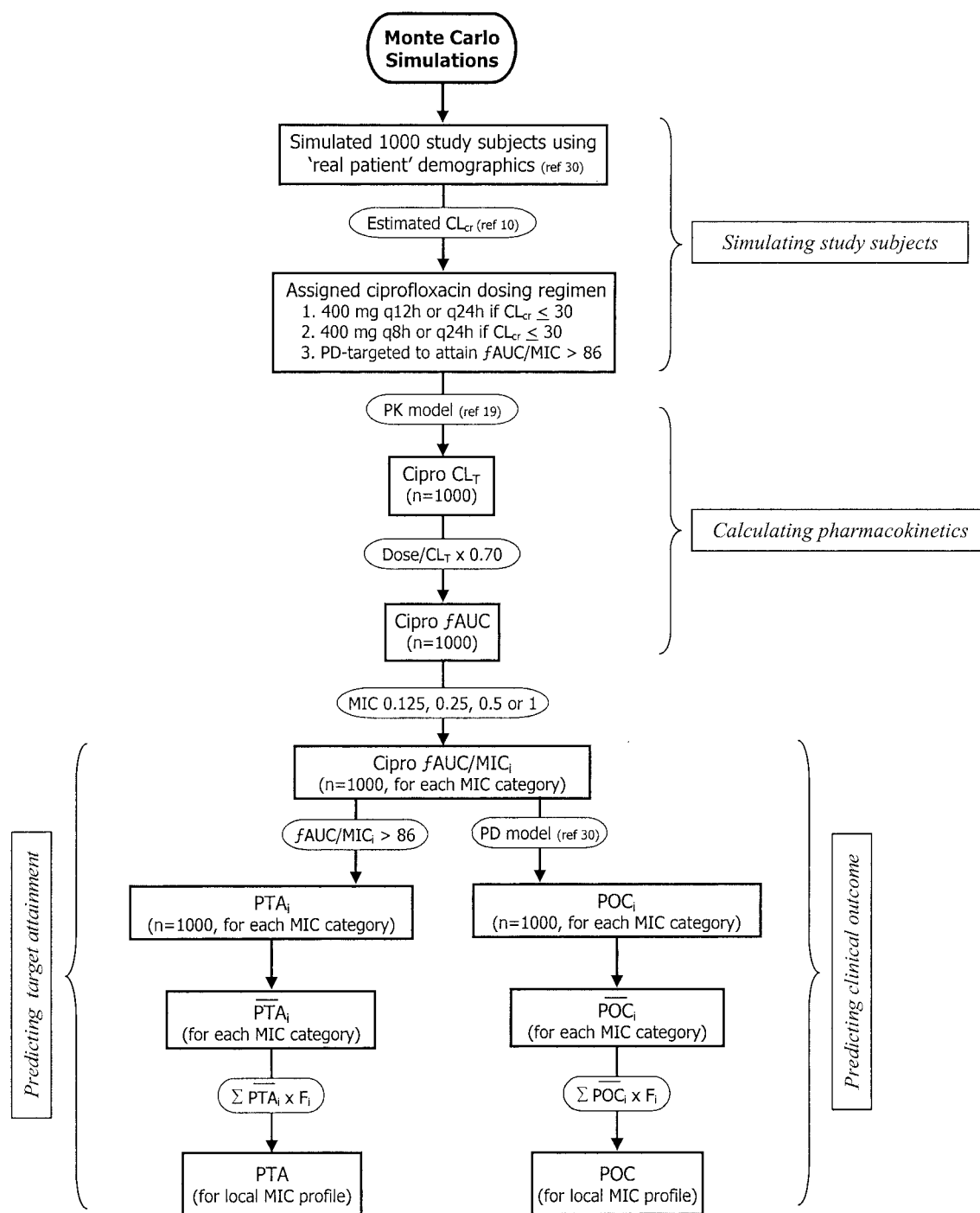


FIG. 1. Monte Carlo simulation algorithm, where PTA is probability of target attainment, POC is probability of cure, subscript  $i$  is the MIC category, and  $F_i$  is the fraction of isolates in the population in the MIC category.

PK data were generated from a population model derived from acutely ill patients whose clinical status, age ( $68 \pm 11$  years), body weight ( $70 \pm 17$  kg), and  $CL_{cr}$  ( $63 \pm 30$  ml/min) were consistent with those of the simulated study subjects (19). Total ciprofloxacin clearance ( $CL_T$ , liters/h) was determined by the following:  $CL_T = [(0.0014 CL_{cr} + 0.167) \times \text{weight}] (\pm 20\%)$ .

The steady-state  $fAUC$  (mg · h/liter) was calculated assuming an unbound (free) fraction of 70% (5) according to the following:

$$fAUC = \left[ \frac{\text{Dose (daily)}}{CL_T} \right] \times (0.70 \pm 10\%)$$

**Pharmacodynamic model.**  $fAUC$  data were combined with discrete MICs (i.e., 0.125, 0.25, 0.5, and 1  $\mu\text{g/ml}$ ) to generate  $fAUC/MIC$  values. Probability of target attainment (PTA) was determined using a  $fAUC/MIC$  of  $>86$  (or a total  $AUC/MIC$  of  $>123$ ). This target represented the threshold for 90% probability of cure (POC) in the PD model (below) and matched the established total  $AUC/MIC$  target of 125 for ciprofloxacin (20).  $fAUC/MIC$  data were then incorporated into the PD model to compute POC for each simulated study subject using the logistic function (Fig. 2) (30):  $POC = (1/\{1 + e^{[2.74 - (0.057 \times fAUC/MIC)]}\}) (\pm 5\%)$ .

Briefly, the PD model was developed with a patient population with *P. aerugi-*

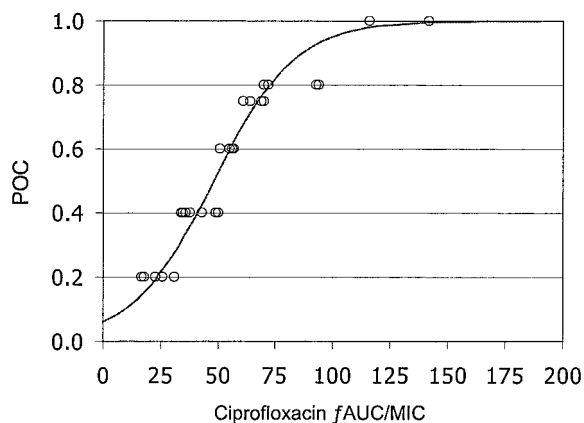


FIG. 2. Pharmacodynamic model for probability of cure (POC) in the treatment of *P. aeruginosa* infection as described by the logistic function  $POC = (1/\{1 + e^{[2.74 - (0.057 \times fAUC/MIC)]}\})$  (30).

*nosa* bloodstream infection, where 80% received either ciprofloxacin or an aminoglycoside and 71% were administered combination therapy. Clinical outcome included persistent infection in 21%, death in 21%, and cure in 58% of cases. Numerous risk factors for treatment failure were tested, including patient demographics (i.e., age, gender, and body weight), underlying medical conditions (i.e., chronic lung disease, ischemic heart disease, congestive heart failure, renal or liver disease, diabetes mellitus, malignancy, neutropenia), nosocomial acquisition, infection focus, and surgery or other invasive procedure. Antimicrobials including single versus combination therapy, time to first dose, and relevant PD indices were also tested. Of all potential risk factors, only  $C_{max}/MIC$  and  $AUC/MIC$  values for ciprofloxacin and gentamicin were significantly associated with treatment response ( $P \leq 0.002$ ). Logistic regression analysis was used to mathematically model PD relationships and identify critical thresholds of  $>8$  for  $fC_{max}/MIC$  and  $>86$  for  $fAUC/MIC$ .

**Analysis.** For each dosing regimen, mean PTA and POC in each MIC category were determined by adding probabilities for individual simulated study subjects and dividing by the total number of 1,000 cases. PTA and POC based on the local susceptibility profile were calculated using MIC data from the previous study of *P. aeruginosa* bloodstream infection (30). The MIC profile as shown in Fig. 3 included only sensitive isolates representing clinical scenarios in which ciprofloxacin would be an appropriate selection. Mean PTA and POC for the local MIC profile were determined by multiplying probabilities in each MIC category by the fraction of isolates in that category and adding these values.

Statistical analyses included analysis of variance and Tukey's test for posthoc comparisons ( $\alpha = 0.05$ ) using SPSS, version 11, software (2001; SPSS Inc.). Relative comparisons among ciprofloxacin dosing regimens were presented as numbers needed to treat for one additional cure.

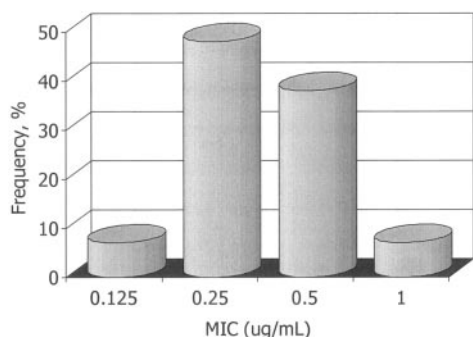


FIG. 3. Local susceptibility profile for *P. aeruginosa* ( $n = 29$  sensitive isolates; MIC at which 50% of isolates are inhibited =  $0.25 \mu\text{g/ml}$ ).

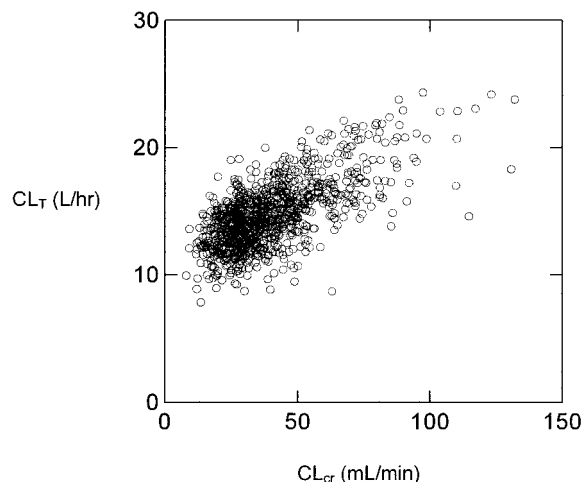


FIG. 4. Estimated  $CL_{cr}$  versus ciprofloxacin  $CL_T$  for 1,000 simulated study subjects.

**RESULTS**

The results of PK calculations with 1,000 simulated study subjects are shown in the graph of  $CL_{cr}$  versus ciprofloxacin  $CL_T$  in Fig. 4. Mean PTA and POC results for each dosing regimen are presented in Table 1. Examples of MCS-generated probability density functions showing POC if pathogen MICs were  $0.5 \mu\text{g/ml}$  are seen in Fig. 5. The relative efficacies of dosing regimens across MIC categories are displayed in Fig. 6. There were significant differences among regimens, especially against isolates with higher MICs. POC with the standard dose was 0.59 if MICs were  $0.5 \mu\text{g/ml}$  and 0.27 if MICs were  $1 \mu\text{g/ml}$ . Predicted cure rates were significantly higher at 0.72 if MICs were  $0.5 \mu\text{g/ml}$  and 0.40 if MICs were  $1 \mu\text{g/ml}$  with the high dose ( $P < 0.0001$ ). POC was further increased to 0.91 and 0.72, respectively, with the PD-targeted regimen ( $P < 0.0001$ ). With the latter, mean daily doses of  $381 \pm 103$ ,  $754 \pm 201$ ,  $1,339 \pm 496$ , and  $1,849 \pm 730$  mg were required if pathogen MICs were 0.125, 0.25, 0.5, and  $1 \mu\text{g/ml}$ , respectively. Analyses based on the local MIC profile produced PTA and POC estimates of 0.44 and 0.74 with the standard ciprofloxacin dose, 0.58 and 0.81 with the high dose, and 0.84 and 0.93 with the PD-targeted regimen, respectively. Compared to the standard dose, the number of *P. aeruginosa* bloodstream infections needed to treat for one additional cure was 15 with the high dose and 6 with the PD-targeted regimen.

TABLE 1. Probability of target attainment (PTA) and probability of cure (POC) for each ciprofloxacin dosing regimen<sup>a</sup>

Ciprofloxacin regimen	Mean PTA with MIC of:				Mean POC with MIC of:			
	0.125	0.25	0.5	1.0	0.125	0.25	0.5	1.0
Standard dose	0.99	0.69	0.11	0	0.99	0.90	0.59	0.27
High dose	0.99	0.77	0.38	0	0.99	0.92	0.72	0.40
PD targeted	0.98	0.96	0.76	0.40	0.98	0.97	0.91	0.72

<sup>a</sup> Standard dose is 400 mg i.v. q12h or 400 mg i.v. q24h if  $CL_{cr}$  is  $\leq 30$  ml/min, high dose is 400 mg i.v. q8h or 400 mg i.v. q24h if  $CL_{cr}$  is  $\leq 30$  ml/min, and PD-targeted regimens to attain a  $fAUC/MIC$  value of  $>86$ .

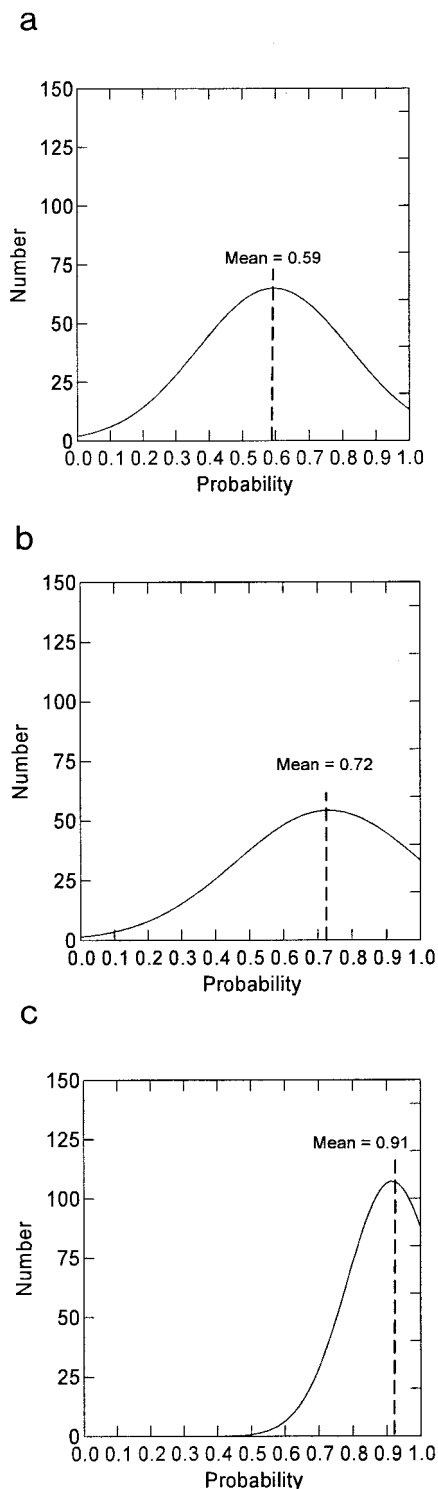


FIG. 5. Monte Carlo simulation-generated probability density functions showing probability of cure if pathogen MICs were 0.5  $\mu\text{g/ml}$  where (a) is the recommended standard dose, (b) is the recommended high dose, and (c) is the PD-targeted regimen.

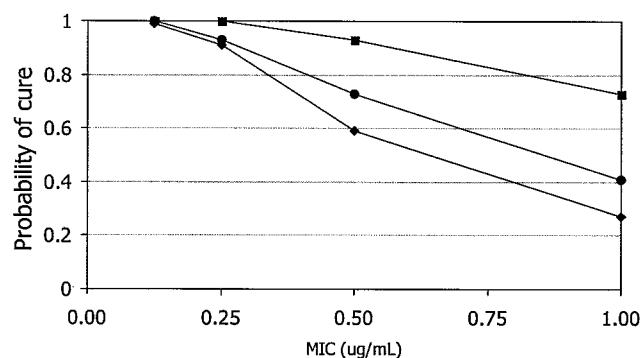


FIG. 6. Relative efficacies of ciprofloxacin dosing regimens across MIC categories using Monte Carlo simulations. ◆, recommended standard dose; ●, recommended high dose; ■, PD-targeted regimen.

## DISCUSSION

PD research incorporates measures of antimicrobial exposure, pathogen susceptibility, and patient outcome to characterize complex interactions involved in the treatment of infectious diseases. The principle relationships between PD indices like AUC/MIC and microbiological or clinical response provide strong support for individualizing antimicrobial dosing to optimize therapy (3, 15, 20, 27, 30). In vitro, animal and human investigations further characterize PD indices, identifying the critical thresholds associated with efficacy. General consensus supports  $C_{\text{max}}/\text{MIC}$  targets of 8 to 10 for concentration-dependent agents like fluoroquinolones and aminoglycosides (22, 27, 30),  $T_{>\text{MIC}}$  (percentage of the dosing interval with concentrations above MIC) values of 40 to 70%, or higher in some populations, for time-dependent agents like  $\beta$ -lactams (4, 11, 12), and AUC/MIC targets of 125 or 30 for fluoroquinolones against gram-negative or gram-positive organisms, respectively (3, 15, 20, 30).

Recent investigations using MCSs have been able to demonstrate the broader impacts of antimicrobial PDs. Simulations are constructed using input variables of patient demographics, antimicrobial PKs, and pathogen MICs. Variables are randomly selected from assigned distributions and incorporated into formulae or models to generate output variables defined by probability density functions. Such methods have led to novel proposals in determining antimicrobial susceptibility breakpoints (17, 25). Drusano et al. detailed dose selection for the investigational agent evernimicin based on achieving PD targets originally derived from animal studies (16). The same author evaluated doses of an investigational protease inhibitor using PD targets from an in vitro hollow-fiber model of viral suppression (13) and selected doses of a nonnucleoside reverse transcriptase inhibitor using time above the viral 90% effective concentration (14). Mouton and colleagues proposed doses and provisional MIC breakpoints for an investigational cephalosporin based on its ability to achieve an acceptable  $T_{>\text{MIC}}$  (26).

MCSs have also been used to evaluate current antimicrobials. Gatifloxacin and levofloxacin have been compared using PK data from healthy volunteers and MIC patterns from worldwide susceptibility studies of *Streptococcus pneumoniae* (2, 21). AUC/MIC targets of at least 30 were attained more

often by gatifloxacin than by levofloxacin. Ambrose et al. found that cefepime was better than piperacillin-tazobactam in achieving  $T_{>MIC}$  values of 30 to 70% against gram-negative bacteria producing extended-spectrum  $\beta$ -lactamases (1). Finally, Tam et al. assessed the ability of standard cefepime doses to achieve PD targets in patients with various degrees of renal function (28). Trough concentrations exceeded the MIC in 80% of cases when values were  $\leq 2$   $\mu\text{g/ml}$  but were suboptimal when MICs were  $\geq 4$   $\mu\text{g/ml}$  as seen for less susceptible *P. aeruginosa*.

Where MCS studies to date have focused on the probability of attaining target PD indices, ours was extended to the probability of achieving clinical cure. We simulated "real patients" using demographics, PKs, and MICs relevant to *P. aeruginosa* bloodstream infection and incorporated a PD model of the relationship between ciprofloxacin  $fAUC/MIC$  values and POC (30). As such, MCSs were used to extrapolate the implications of antimicrobial dosing from individuals to the patient population.

As seen in Table 1, PTA and POC both approached 1 if pathogen MICs were 0.125  $\mu\text{g/ml}$ . PTA was significantly lower than POC across the remaining MIC categories. Such differences are likely explained by PD thresholds which do not indicate a dichotomous response. For example, the original study by Forrest and colleagues reported cures in 42% of those with total  $AUC/MIC$  below 125 (20), and our PD study of *P. aeruginosa* bloodstream infection had responses in 48% of patients with  $fAUC/MIC$  values less than 86 (30). An important consideration in the latter study was the frequent use of combination therapy, which may have contributed to cures in those with suboptimal  $fAUC/MIC$ s for ciprofloxacin or gentamicin. The original PD model and hence POC results from the current study apply to cases in which ciprofloxacin is used in combination. Predicted cure rates may be significantly lower if these data were extrapolated to ciprofloxacin monotherapy.

In the MCSs, high-dose ciprofloxacin had reasonable efficacy if pathogen MICs were 0.5  $\mu\text{g/ml}$  (POC = 0.72) but poor activity if MICs were 1  $\mu\text{g/ml}$  (POC = 0.40). The PD-targeted regimen using mean daily doses of less than 800 mg was very effective against the more susceptible isolates. However, daily doses exceeding 1,300 mg and 1,800 mg were required to produce the more desirable cure rates of 0.91 and 0.72 if the MICs were 0.5 or 1  $\mu\text{g/ml}$ , respectively. The PD-targeted regimen was arbitrarily limited at twice the highest recommended daily doses to predict requirements, within reason, for good clinical outcome across MIC categories. Given a susceptibility breakpoint of  $\leq 1$   $\mu\text{g/ml}$ , it showed the risks of underdosing and requirements for effective doses exceeding those with acceptable or proven safety.

Uncertainty related to the appropriate susceptibility breakpoint for ciprofloxacin is evident in different recommendations from the CLSI (i.e.,  $\leq 1$   $\mu\text{g/ml}$ ) and European Committee on Antimicrobial Susceptibility Testing (i.e.,  $\leq 0.5$   $\mu\text{g/ml}$ ) (9, 18). The current study adds to the debate by evaluating dosing regimens in relation to discrete MICs and MIC profiles based on the local susceptibility data. In support of the European Committee on Antimicrobial Susceptibility Testing breakpoint, ciprofloxacin at recommended doses was not effective if pathogen MICs were 1  $\mu\text{g/ml}$  as demonstrated by a PTA of 0 and a POC of 0.40. The local MIC profile including 38% of

isolates with MICs of 0.5  $\mu\text{g/ml}$  and 7% with MICs of 1  $\mu\text{g/ml}$  produced PTA results of 0.44 and 0.58 for the standard and high ciprofloxacin doses, respectively. The findings were similar to those from another MCS study of ciprofloxacin against *P. aeruginosa* using PK data from healthy volunteers and MICs from North American susceptibility data (23). PTA using a total  $AUC/MIC$  of  $\geq 125$  was 53% with doses of 400 mg q12h compared to 59% with doses of 400 mg q8h. Obviously, as fractions of isolates in the higher MIC categories increase, so would the benefits of using even higher ciprofloxacin doses or a lower susceptibility breakpoint. This concern was demonstrated in a study by Montgomery et al. which evaluated ciprofloxacin against *P. aeruginosa* using PK and MIC data from adult patients with cystic fibrosis (24). PTA using a total  $AUC/MIC$  of  $\geq 125$  was only 10% with doses of 400 mg q12h and 30% with 400 mg q8h. The authors concluded that with recommended doses, an MIC breakpoint of  $< 0.5$   $\mu\text{g/ml}$  would be more appropriate.

In conclusion, as demonstrated by clinical outcome-based MCSs, the highest recommended ciprofloxacin dose of 400 mg i.v. q8h should be used in the treatment of *P. aeruginosa* infection to improve PD target attainment and clinical cure. However, even this dose appears ineffective if pathogen MICs are 1  $\mu\text{g/ml}$ , warranting the consideration of a lower MIC breakpoint,  $\leq 0.5$   $\mu\text{g/ml}$ .

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