Systematic Comparison of the Population Pharmacokinetics and Pharmacodynamics of Piperacillin in Cystic Fibrosis Patients and Healthy Volunteers

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Respiratory tract infections cause 90% of premature mortality in patients with cystic fibrosis (CF). Treatment of Pseudomonas aeruginosa infection is often very problematic. Piperacillin-tazobactam has good activity against P. aeruginosa, but its pharmacokinetics (PK) in CF patients has not been compared to the PK in healthy volunteers in a controlled clinical study. Therefore, we compared the population PK and pharmacodynamics (PD) of piperacillin between CF patients and healthy volunteers. We studied 8 adult (median age, 20 years) CF patients (average total body weight [WT], 43.1 ± 7.8 kg) and 26 healthy volunteers (WT, 71.1 ± 11.8 kg) who each received 4 g piperacillin as a 5-min intravenous infusion. We determined piperacillin levels by high-performance liquid chromatography, and we used NONMEM for population PK and Monte Carlo simulation. We used a target time of nonprotein-bound concentration above the MIC of 50%, which represents near-maximal bacterial killing. Unscaled total clearance was 25% lower, and the volume of distribution was 31% lower in CF patients. Allometric scaling by lean body mass reduced the unexplained (random) between-subject variability in clearance by 26% compared to the variability of linear scaling by WT. A standard dosage regimen of 3 g/70 kg body WT every 4 h as a 30-min infusion (daily dose, 18 g) achieved a robust (≥90%) probability-of-target attainment (PTA) for MICs of ≤12 mg/liter in CF patients and ≤16 mg/liter in healthy volunteers. Alternative modes of administration allowed a marked dose reduction to 9 g daily. Prolonged (4-h) infusions of 3 g/70 kg WT every 8 h and continuous infusion (daily dose, 9 g), achieved a robust PTA for MICs of ≤16 mg/liter in both groups. Piperacillin achieved PTA expectation values of 64% and 89% against P. aeruginosa infection in CF patients, based on susceptibility data from two German CF clinics.

Cystic fibrosis (CF) is the most common inherited disease in the Caucasian population. Respiratory diseases are the primary cause of mortality (13, 37, 58). About 30% of children aged 2 to 5 years and 51% of adults (aged 26 to 30 years) with CF are infected by Pseudomonas aeruginosa (16). Piperacillin in combination with the beta-lactamase inhibitor tazobactam has good bactericidal activity against gram-positive microorganisms and P. aeruginosa infection in CF patients (40, 43, 53, 62). The combination is frequently used in the empirical treatment of hospital-acquired infections and for treatment of pulmonary exacerbations in CF patients (32). There are reports that P. aeruginosa isolates from non-CF patients show a better susceptibility to anti-pseudomonal agents (27) than isolates from CF patients (54, 68). As P. aeruginosa infection can only be eradicated in the early stage of therapy given to CF patients (8), early aggressive anti-infective treatment against this pathogen is vital (28). Therefore, the probability of successful microbiological outcome for the treatment of P. aeruginosa infection is important.

It is now generally agreed that the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics should be used jointly to predict the probability of successful antibiotic treatment. For this task, population PK in combination with Monte Carlo simulations (MCS) is the method of choice as it combines the variability in bacterial susceptibility with the variability in PK characteristics. However, MCS has not yet been used to determine the PKPD profile of piperacillin in CF patients.

The PKPD profile of piperacillin in CF patients can be affected by altered PK in this patient group (16, 73). Although pronounced differences in clearance and volume of distribution between CF patients and healthy volunteers were reported by some authors (60, 73), other data show smaller differences (24, 45, 64). We are not aware of any PK study of piperacillin in CF patients which included a healthy volunteer control group. Such a comparison would help to explain a possibly altered PK in CF patients. For example, higher clearances in CF patients could diminish the probability of attaining a PKPD target. For beta-lactams, the duration of the nonprotein-bound concentration above the MIC (T > MIC) best predicts the drug-related response (12, 17). A target time of 50% T > MIC was shown to be the target for near-maximal bacterial killing, and a target time of 90% T > MIC correlates best with bacteriostasis.

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for penicillins (12, 17). Based on these targets, the probability-of-target attainment (PTA) can be calculated.

To optimize the PTA for empirical therapy, knowledge of the best descriptors for body size and body composition may be important. There is considerable evidence that body composition influences PK (9, 26, 46, 50, 70), which requires dose adjustment at least for some patient groups. CF patients are often undernourished and have a paucity of adipose tissue. There are reports that lean body mass (LBM) better describes the volume of distribution (44, 60, 70–72) and clearance in CF patients than total body weight (WT) (44). Consequently, Touw et al. (71, 72) proposed to calculate the initial daily dose of tobramycin in CF patients based on LBM rather than on WT. LBM was also proposed for use as the size descriptor for CF patients (55) and has been proposed to be a superior predictor of drug dosage compared to other measures of body size (e.g., WT or body surface area) (46). However, the superiority of dosing according to a size descriptor that accounts for body composition (e.g., LBM) to dosing by WT still needs to be shown (46, 60).

As penicillins are hydrophilic molecules, we expect them to distribute primarily into lean body compartments. For piperacillin, we believed a priori that body size is better described by LBM than by WT, since WT does not account for body composition, whereas LBM does. The two most desirable properties of a size descriptor are the following. (i) It should be able to describe body size (including body composition) and functional capacity for healthy volunteers as well as for undernourished, obese, and “normal” patients. If this was true, e.g., for LBM in CF patients, a physician could administer the same dose in mg/kg of LBM to normal patients and to CF patients. (ii) A size descriptor should reduce the unexplained between-subject variability (BSV) as much as possible. This allows one to select doses in empirical therapy more precisely.

Population PK can directly rank different size descriptors based on their performance for these two criteria and is also a powerful tool with which to compare the PKPD characteristics between CF patients and healthy volunteers. Therefore, our first objective was to compare the PK of piperacillin between CF patients and healthy volunteers via population PK. As our second objective, we studied whether the average differences and the variability in clearance and volume of distribution are better described by LBM than by WT. Our third objective was to study the influence of patient-related differences in PK parameters on PD characteristics of piperacillin given at various dosage regimens.

(This work was presented in part as part of a meta-analysis [6].)

### MATERIALS AND METHODS

**Subjects.** A total of 34 Caucasian volunteers (8 adult CF patients and 26 adult healthy volunteers) of both sexes participated in the study after they had given their written informed consent. Table 1 shows the demographic data. The subjects’ health status was assessed by physical examination, electrocardiography, and laboratory tests including urinalysis and screening for drugs of abuse. Cystic fibrosis had been confirmed for each patient by standard sweat test and clinical history (including the Shwachman score) prior to inclusion of the patient in the study. Most patients had been treated in the center for more than a decade, and the diagnosis and status were well known and repeatedly confirmed. Patients were studied during an infection-free period. Consumption of alcohol, methylxanthines, and tobacco in any form or of other medication was forbidden from 24 h before the first piperacillin dose was given until the last sample was given. The subjects took no antibiotics during this time period. The subjects fasted overnight and received a standard breakfast at 1 h postdose and a standard lunch at 4 h postdose. Sufficient fluid intake of mineral water was assured during the study. All volunteers were closely observed by physicians for the occurrence of adverse events during the period of drug administration. The study protocol had been approved by the local ethics committee.

**Study design and drug administration.** The study was a single-dose, single-center, open, parallel group study. Each subject received a dose of 4 g piperacillin as a 5-min intravenous infusion, except for one CF patient who received a dose of 3 g piperacillin. All infusions were administered with a BRAUN perfusor (Braun, Melsungen, Germany). The instruments were checked on a daily basis by weighing defined volumes delivered by the perfusor.

**Blood sampling.** All blood samples were drawn from a forearm vein via an intravenous catheter contralateral to the one used for drug administration. Blood samples were drawn immediately before the start of the infusions (0 min), at the end of the infusions (5 min), and at 5, 10, 15, 20, 30, 45, 60, and 90 min and 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 24 h after the end of infusion. The samples were cooled in an ice water bath for 15 min before centrifugation. After centrifugation, all plasma samples were immediately frozen and stored at −70°C until analysis.

**Drug analysis.** Piperacillin concentrations in plasma were determined by high-performance liquid chromatography (HPLC). For determination of piperacillin in plasma, 100 μl of the sample was deproteinated with 200 μl acetonitrile containing an internal standard (mezlocillin). After mixing and centrifugation at 15,000 rpm, 40 μl was injected onto the HPLC system. Piperacillin was determined using a reversed-phase column (LiChrospher model C18, 5 μm [250 by 4.6 mm]), potassium dihydrogen phosphate (pH 6.2)/acetonitrile mobile phase, with a flow of 2 ml/min. Piperacillin level and the internal standard were detected at 220 nm.

The plasma samples were measured against a plasma calibration row. The calibration row in plasma was prepared by a 10:1 dilution of a tested drug-free plasma with a stock solution to obtain the highest calibration level. The other calibration levels were obtained by 1:1 dilution of the highest calibration level or a level of higher concentration with drug-free plasma.

For control of interassay variation, spiked quality controls in plasma were prepared by adding defined volumes of the stock solution or the spiked control of higher concentration to defined volumes of tested drug-free plasma. No interferences were observed for plasma for piperacillin and the internal standard. Calibration was performed by linear regression. Linearity of piperacillin calibration curves in plasma was shown between 0.200 and 150 mg/liter. The quantification limits were identical with the lowest calibration levels. The interday precision and analytical recovery of the spiked quality control standards of piperacillin in human plasma ranged from 3.5 to 9.2% and from 95.0 to 106.9%, respectively.

**Population PK analysis.** (i) **Population model.** We tested one-, two-, and three-compartment disposition models. Drug elimination was described by (i) first-order, (ii) mixed-order (Michaelis-Menten), or (iii) parallel first-order and mixed-order elimination. We assessed these three elimination models for (a) the whole data set, (b) the data from CF patients, and (c) the data from healthy volunteers separately. We discriminated competing models by their predictive performance assessed via visual predictive checks, NONMEM’s objective function, and standard diagnostic plots. For the visual predictive check, we simulated the plasma profiles for at least 2,000 CF patients and 6,500 healthy volunteers for...
each competing model. We calculated the median, the nonparametric 80% prediction interval (10% to 90% percentile), and the nonparametric 50% prediction interval (25% to 75% percentile) from the simulated plasma concentrations. These prediction interval lines were then overlaid on the original raw data. If the model described the data correctly, then 20% of the observed data points should fall outside the 80% prediction interval and 50% of the data should fall outside the interquartile range at each time point. We compared the median predicted concentrations and the prediction intervals with the raw data and tested whether the median and the prediction intervals mirrored the central tendency and the variability of the raw data for the respective model.

(ii) Size models. We studied size models 1 to 5 as follows: (i) no size model; 2, linear scaling by WT; 3, allometric scaling by WT (30, 76, 77); 4, linear scaling by LBM (9, 33); and 5 allometric scaling by LBM. We compared the ability of the size models to describe the differences in the central tendency of PK parameters between CF patients and healthy volunteers. Additionally, we determined by how much the random (unexplained) BSV was reduced by the respective size model relative to the variability of linear scaling by WT.

Our allometric model assumes that the volume of distribution scales linearly (allometric exponent, 1.0) with body size (i.e., WT or LBM), whereas clearance scales slightly less than linearly with body size (allometric exponent, 0.75). The allometric exponent was fixed at 1.0 for all volume terms and at 0.75 for all clearance terms. \( F_{\text{Size}, V} \) and \( F_{\text{Size}, CL} \) are the fractional changes in volume of distribution and clearance, respectively, for the rth subject with WT standardized to a weight, WT, of 70 kg.

\[
F_{\text{Size}, V} = \frac{\text{WT}}{\text{WT}_{\text{STD}}} \\
F_{\text{Size}, CL} = \left( \frac{\text{WT}}{\text{WT}_{\text{STD}}} \right)^{0.75} \\
F_{\text{Size}, LBM} = \frac{\text{LBM}}{\text{LBM}_{\text{STD}}} \\
F_{\text{Size}, CL, LBM} = \left( \frac{\text{LBM}_{\text{STD}}}{\text{LBM}} \right)^{0.75}
\]

The same allometric size model was applied for LBM with a standard lean body mass (LBM, 53 kg).

For linear scaling by WT or LBM, all exponents were set to 1.0.

(iii) Between-subject variability model. We estimated the BSV values for clearance and volume of distribution by assuming a log-normal distribution for the PK parameters. The \( \eta_{\text{SV}} \) is the log scale difference of the individual PK parameter estimate from its mean for the rth subject. The \( \eta_{\text{SV}} \) is assumed to be a normally distributed random variable with the mean of zero and a standard deviation (SD) BSV. The BSV was estimated as variance, but we report the square root of the estimate, which we expressed these values as a percentage, as this is an approximation to the apparent coefficient of variation of a normal distribution on a logarithmic scale. The variance of the \( \eta_{\text{SV}} \) is the unexplained (random) BSV. The individual PK parameters were calculated as follows (parameters explained below):

\[
\text{CL} = \frac{\text{CL} \times F_{\text{Size}, CL} \times F_{\text{Size}, CL, LBM} \times \exp(\eta_{\text{SV}, CL})}{\text{WT}_{\text{STD}}}
\]

CL is the individual estimate for total clearance for the rth subject. The \( \eta_{\text{SV}, CL} \) is \( \eta_{\text{SV}} \) of CL for the rth subject. The CL is the group estimate for total clearance of a healthy volunteer with standard body size (i.e., WT, 70 kg or an LBM of 53 kg). The FCYCLBM is the disease-specific scale factor of CF patients and is calculated as the average total clearance in CF patients divided by the average total clearance in healthy volunteers after accounting for body size. If this scale factor is 1.0, CF patients and healthy volunteers of the same body size have identical group estimates. We also used a disease-specific scale factor for volume of distribution at steady state (FCYCLBM).

(iv) Observation model and computation. We described the residual unidified variability by a combined additive and proportional error model for plasma concentrations. We used the first-order conditional estimation (FOCE) method with the interaction estimation option in NONMEM version V, release 1.1 (NONMEM Project Group, University of California, San Francisco, CA) (3) for all population PK modeling.

(v) Noncompartmental analysis and descriptive statistics. We used WinNonlin Professional (version 4.0.1; Pharsight Corp., Mountain View, CA) for noncompartmental analysis and descriptive statistics.

(vi) Nonparametric bootstrap. We used nonparametric bootstrap resampling with 2,000 replicates for each size model (19, 52) to quantify the uncertainty in our PK parameter estimates. Each replicate contained observations from 8 randomly selected CF patients and 26 randomly selected healthy volunteers from the original raw data set (subjects could be drawn multiple times). We derived the median and nonparametric 90% confidence intervals (5% to 95% percentile) from the 2,000 estimated PK parameter sets for each parameter of our population PK model.

(vii) Monte Carlo simulation. We used a PKPD target of 50% \( T_{\text{F}, \text{MIC}} \) for near-maximal bactericidal activity and 30% \( T_{\text{F}, \text{MIC}} \) for bacteriostasis for piperacillin. A target of about 50% \( T_{\text{F}, \text{MIC}} \) was required to achieve a reduction in bacterial counts by 2 log_{10} at 24 h, and a target of 30% was required for bacteriostasis at 24 h for penicillins in the animal infection models studied by Craig and Drusano (12, 17). We studied a range of MICs, from 0.5 to 128 mg/liter, and assumed a fixed protein binding of 30% for piperacillin (piperacillin sodium and tazobactam sodium [Zosyn] product information, revised 5 April 1999; Lederle Laboratories, Pearl River, NY) (63). We assumed the same protein binding of 30% for piperacillin in CF patients and in healthy volunteers, as the protein binding is similar for CF patients and healthy volunteers for most drugs including various beta-lactams (55, 60). An altered protein binding in CF patients is not expected to affect the unbound plasma concentrations substantially for a drug with low protein binding like piperacillin.

We studied the following dosage regimens: (i) continuous infusion of 9 g/70 kg WT per day, (ii) prolonged (4-h) infusion of 3 g/70 kg WT every 8 h (dally dose, 9 g), and (iii) short-term (30-min) infusion of 3 g/70 kg WT every 4 h (dally dose, 18 g). We used NONMEM to simulate each dosage regimen at steady state in the absence of residual error and predicted profiles for 9,600 CF patients and 10,400 healthy volunteers with the same demographic data as the subjects in our study for each dosage regimen. The \( T_{\text{F}, \text{MIC}} \) values and the PTA were calculated by linear interpolation between simulated data points (frequent sampling) with Perl scripts written by the first author. These Perl scripts were validated for all studied dosage regimens for this and several other studies in comparison to WinNonlin Pro (version 4.0.1). We used the population mean PK parameter estimates and the variance-covariance matrix representing the BSV provided by NONMEM for MCS and assumed that the dose, duration of infusion, and timing of infusion had no variability. We used the clearance and volume notation of our population PK model during both the estimation and the MCS. The diagonal elements of the variance-covariance matrix are the variances (on a natural log scale; see description above) of the individual random terms \( \eta_{\text{SV}} \) of the respective PK parameter. These variance terms can be obtained as the square of the apparent coefficient of variation for the BSV reported for our final population PK model. We included the covariance between the volume of the central and the volume of the peripheral compartment in the variance-covariance matrix. We did not include the variability of the intercompartmental clearance, as this term was difficult to estimate. The predictive performance of our final population PK model was assured via visual predictive checks. The PTA was derived by calculating the fraction of subjects who attained the PKPD target at each MIC. The PKPD breakpoint was defined as the highest MIC for which the PTA was at least 90%. We also provided the breakpoints for a PTA of at least 95% or 99%. Additionally, we ran simulations based on the individual PK parameter estimates and covariates (WT and LBM) from the eight CF patients in our study to compare various dosing algorithms based on our studied size models.

To determine the clinical relevance of the differences in the PTA between CF patients and healthy volunteers, we calculated the expected PTA for various MIC values and the PTA were calculated by

\[
T_{\text{F}, \text{MIC}} = \frac{\text{MIC}}{\text{MIC}_{\text{MIC}}}
\]

FIG. 1. Average plasma concentrations of piperacillin for CF patients and healthy volunteers after a single 5-min intravenous infusion of 4 g piperacillin. We did not calculate the average concentration if fewer than three observations were quantifiable at the respective time point. Therefore, data for CF patients are shown only up to 4 h after the end of infusion (see Fig. 2).
distributions (i.e., the PTA expectation value [48]). We calculated the PTA expectation value by multiplying the PTA at each MIC by the frequency of how often this MIC occurred in the respective MIC distribution. The individual products at each MIC are summed up and the sum is the PTA expectation value for the respective MIC distribution. The PTA expectation value is the probability of target attainment in a specific target population (e.g., CF patients) with infections caused by bacteria from a specific MIC distribution (ideally the MIC distribution of each local hospital). If achieving the PKPD target is the primary determinant of successful treatment, the PTA expectation value can be interpreted as the probability of successful treatment of a CF patient at the local hospital with empirical therapy.

We calculated the PTA expectation value based on published MIC distributions. These values comprised susceptibility data for *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* from the 2002 MYSTIC program in North America (35) and in South America (34), *Pseudomonas aeruginosa* data from the Hartford Hospital, Connecticut (36), and data for nonmucoid and mucoid *Pseudomonas aeruginosa* isolates from CF patients in Freiburg, Germany (62), and Leipzig, Germany (65).

### RESULTS

**Noncompartmental analysis.** Figure 1 shows the average plasma concentrations of CF patients and healthy volunteers after a 5-min infusion of 4 g of piperacillin. Table 2 lists the results of the noncompartmental analysis. These parameters were not scaled by any size descriptor. Total clearance was 25% lower in CF patients, and the volume of distribution at steady-state was 31% smaller in CF patients than in healthy volunteers. CF patients had higher peak concentrations. The terminal-half life was 34% shorter, and the mean residence time was 17% shorter in CF patients than in healthy volunteers.

**Population PK analysis.** The visual predictive check indicated a very good predictive performance for the two- and three-compartment models with first-order elimination. The one-compartment model had insufficient predictive performance. The objective function was 253 points better for the two- than for the one-compartment model. All models with mixed-order elimination or with parallel first-order and mixed-order elimination provided no statistically significant ($P < 0.05$, log-likelihood ratio test) improvement in the objective function. This was observed for the analysis of the whole data set, for analysis of data in CF patients, and for analysis of data in healthy volunteers separately. For all our models studied, the first-order elimination was estimated to account for more than 95% of total clearance, indicating a limited degree of

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**TABLE 2.** Unscaled PK parameters derived via noncompartmental analysis for CF patients and healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range) value</th>
<th>CF patients</th>
<th>Healthy volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total clearance ($\text{liter} \cdot \text{h}^{-1}$)</td>
<td>8.78 (6.39–12.1)</td>
<td>11.7 (6.25–14.5)</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution at steady state (liter)</td>
<td>8.13 (5.16–10.8)</td>
<td>11.8 (9.06–30.6)</td>
<td></td>
</tr>
<tr>
<td>Peak concentration ($\text{mg} \cdot \text{liter}^{-1}$)</td>
<td>767 (408–1044)*</td>
<td>446 (272–721)</td>
<td></td>
</tr>
<tr>
<td>Terminal half-life (h)</td>
<td>0.69 (0.34–1.19)</td>
<td>1.05 (0.49–7.52)</td>
<td></td>
</tr>
<tr>
<td>Mean residence time (h)</td>
<td>0.85 (0.66–1.03)</td>
<td>1.02 (0.79–3.49)</td>
<td></td>
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</tbody>
</table>

* Normalized to a dose of 4 g piperacillin, since one CF patient received a dose of 3 g instead of 4 g. Only four CF patients had a blood sample drawn directly at the end of the infusion. The other four CF patients had blood draws 5 to 12 min after the end of infusion. The peak concentrations provided here are calculated based on the highest observed concentration for all eight CF patients. Therefore, the true peak concentrations at the end of the infusion for CF patients were probably higher than the value shown here.

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**FIG. 2.** Visual predictive check based on 8,000 simulated CF patients and 26,000 simulated healthy volunteers for plasma concentrations for the two-compartment model based on allometric scaling by LBM (see Table 3). The plots show the raw data, the 80% prediction interval (10 to 90% percentile), and the interquartile range (25 to 75% percentile). Ideally, 50% of the raw data points should fall inside the interquartile range at each time point, and 80% of the raw data should fall inside the 80% prediction interval.
saturation. As the two-compartment model with first-order elimination had highly sufficient predictive performance and as models with saturable elimination yielded no improvement, we selected a two-compartment model with first-order elimination as our final structural model.

Figure 2 reveals the highly sufficient predictive performance for the final model, as the central tendency of the observations was well captured by the median of the simulated concentrations and as the 80% prediction interval (10 to 90% percentile) described the variability of the observations well. Ideally, 10% of the observations should fall outside the 80% prediction interval on each side and at each time point. The final estimates for this model are shown in Table 3. The disease-specific scale factors $FCYF_{CL}$ and $FCYF_{VSS}$ shown in Table 4 are the ratios of group estimates between CF patients and healthy volunteers after accounting for body size (functional capacity).

A value of 1.0 for FCYF means that a CF patient and a healthy volunteer of the same size have the same group estimate for the respective PK parameter. A value above (or below) 1.0 means that CF patients have a higher (or lower) estimate for the respective PK parameter than healthy volunteers of the same size.

We distinguished the different size models by (i) their estimates for the disease-specific scale factors FCYF and (ii) their ability to reduce the unexplained (random) BSV in clearance and volume of distribution. CF patients had a 27% lower total clearance and a 40% lower volume of distribution compared with healthy volunteers, when no size descriptor was included (Table 4, size model 1). For all other size models, the $FCYF_{VSS}$ value was close to 1.0 (range, 0.924 to 0.999). However, total clearance was estimated to be 20% larger in CF patients than in healthy volunteers for linear scaling by WT and to be 12% larger for linear scaling by LBM. For allometric scaling by WT or LBM, total clearance was estimated to be similar (range, 1.00 to 1.06) for both subject groups. Linear or allometric scaling by LBM reduced the unexplained BSV by about 30% for clearance and about 14% for volume of distribution of the central compartment relative to linear scaling by WT (Table 5). We selected allometric scaling by LBM as our final covariates for the disease-specific scale factors FCYF and (ii) their ability to reduce the unexplained (random) BSV in clearance and volume of distribution.

<table>
<thead>
<tr>
<th>TABLE 3. PK parameter estimates for the two-compartment model based on allometric scaling by LBM</th>
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<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>CL (liter h⁻¹)</td>
</tr>
<tr>
<td>VSS (liter)</td>
</tr>
<tr>
<td>V1 (liter)</td>
</tr>
<tr>
<td>V2 (liter)</td>
</tr>
<tr>
<td>CLc (liter h⁻¹)</td>
</tr>
<tr>
<td>TK0 (fixed) (min)</td>
</tr>
<tr>
<td>CVc (%)</td>
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<tr>
<td>SDc (mg/liter)</td>
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<tr>
<th>TABLE 4. Ratio of CF patients/healthy volunteers group estimates for clearance and volume of distribution for different size models⁴</th>
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<tbody>
<tr>
<td>Size model</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>No size model</td>
</tr>
<tr>
<td>WT linear scaling</td>
</tr>
<tr>
<td>WT allometric</td>
</tr>
<tr>
<td>LBM linear scaling</td>
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<tr>
<td>LBM allometric</td>
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</table>

a Apparent coefficients of variation (CV) for between-subject variability. 
b Medians and nonparametric 90% confidence intervals (CI; 5% to 95% percentile) from 2,000 nonparametric bootstrap replicates. Each replicate included data for eight CF patients and 26 healthy volunteers who were randomly drawn from the original dataset (with replacement). 
c Derived from model estimates, not an estimated parameter. 
d Group estimate for a subject of standard body size (LBM, 53 kg). 
e Coefficient of correlation for the random variability between V1 and V2, r = −0.80. The median and 90% confidence interval for r(V1, V2) from bootstrap was −0.81 (−0.59 to −0.94). CL, total clearance; VSS, volume of distribution at steady state; V1, volume of distribution for the central compartment; V2, volume of distribution for the peripheral compartment; CLc, intercompartmental clearance between the central and the peripheral compartment; TK0, duration of zero-order input (not estimated). CVc is the proportional and SDc is the additive residual error component for the plasma concentrations.
ate model, as this model explained the differences in average clearance between both subject groups and as this model reduced the unexplained BSV similarly to linear scaling by LBM. Monte Carlo simulation. CF patients achieved slightly shorter $f_{T > MIC}$ values than healthy volunteers (see Fig. 3). Therefore, CF patients had slightly lower PTAs, which resulted in PKPD breakpoints similar to those of healthy volunteers for the studied dosage regimens (Fig. 4). The PKPD breakpoints for PTAs of at least 90%, 95%, or 99% are shown in Table 6 for the targets of $f_{T > MIC} \geq 30\%$ and $f_{T > MIC} \geq 50\%$. Continuous infusion of 9 g/70 kg WT per day and 4-h infusion of 3 g every 8 h (daily dose, 9 g) regimens achieved slightly higher or

FIG. 3. Median and prediction intervals (1 to 99% percentile) of the $f_{T > MIC}$ at steady state in CF patients and healthy volunteers after continuous infusion of 9 g/70 kg WT per day (dashed line, ▲), after a 4-h infusion of 3 g/70 kg WT every 8 h (continuous line, □), or after a 30-min infusion of 3 g/70 kg WT every 4 h (continuous line, ●). The curve for the 4-h infusion was shifted to the right by 6% in the MIC for easier identification of the corresponding prediction intervals (1 to 99% percentile). The 1 and 99% percentiles for the continuous infusion were omitted for clarity. After continuous infusion, all simulated CF patients achieved a $f_{T > MIC}$ of 100% at an MIC of 8 mg/liter, and all healthy volunteers had a $f_{T > MIC}$ of 100% at an MIC of 12 mg/liter.

FIG. 4. Probability of target attainment for different dosage regimens of piperacillin at steady state. Importantly, Vinks et al. (75) found a clearance of 24.4 ± 11.7 liter/h (average ± standard deviation) in CF patients for continuous infusion of 16 g piperacillin/2 g tazobactam over 24 h. We found a clearance of 11.3 liter/h (10.4% CV for between-subject variability). The PTA versus MIC profiles shown in this figure are based on our population PK model (see Table 3). As the clearances from the work of Vinks et al. (75) were about two times larger and more variable than our clearances, the PTA curves for continuous infusion in CF patients would be shifted by a factor of about 2 to 4 toward lower concentrations in these plots if one used the data from Vinks et al. for simulation.
TABLE 6. PKPD breakpoints for various dosage regimens of piperacillin for PTA of at least 90%, 95%, or 99%.

<table>
<thead>
<tr>
<th>Dosage regimens</th>
<th>PKPD breakpoints (mg/liter) for PTA of at least 90%/95%/99%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target: $T_{\geq \text{MIC}} \geq 50%$</td>
</tr>
<tr>
<td></td>
<td>CF patients</td>
</tr>
<tr>
<td>Daily dose, 9 g/70 kg WT</td>
<td>24/24/24</td>
</tr>
<tr>
<td>4-h infusion of 3 g every 8 h</td>
<td>16/12/12</td>
</tr>
<tr>
<td>Continuous infusion based on data from Vinks et al.</td>
<td>24/24/24</td>
</tr>
<tr>
<td>Daily dose, 18 g/70 kg WT</td>
<td>32/32/24</td>
</tr>
</tbody>
</table>

- *a* Representing bacteriostasis at 24 h.
- *b* Bacterial killing by 2 log10 at 24 h.

Importantly, Vinks et al. (75) found a clearance of 24.4 ± 11.7 liter/h (average ± SD) in CF patients for a continuous infusion of 16 g piperacillin/2 g tazobactam over 24 h. We found a clearance of 11.3 liter/h (10.4%), geometric mean (coefficient of variation for between-subject variability). We ran an MCS of 10,000 CF patients and a continuous infusion of 9 g piperacillin per day based on the average ± SD clearance of 24.4 ± 11.7 liter/h reported by Vinks et al. (75) for continuous infusion in CF patients. We assumed an average protein binding of 30% (fixed) for piperacillin in CF patients. The lower breakpoints for the data from Vinks et al. are a consequence of the fact that the clearances from Vinks et al. are about two times larger and more variable than our clearances.

It should be noted that these PKPD breakpoints were derived based on data from eight CF patients.

similar breakpoints for the $T_{\geq \text{MIC}} \geq 50\%$ target compared to that of the 30-min infusion at the much higher dosage of 18 g/day (3 g every 4 h). Dosing based on allometric scaling by LBM or WT increased the PKPD breakpoints by about 10 to 30% compared to the mg/kg WT dosage selection for our three studied piperacillin dosage regimens (data not shown).

The PTA expectation values for CF patients and healthy volunteers with the same demographic data as the subjects in our study are shown in Table 7. Although the daily doses of 9 g and 18 g were studied in these dosage regimens, PTA expectation values differed only by 3.2% or less between the three dosage regimens in each subject group. The maximum difference in PTA expectation values between CF patients and healthy volunteers was 5.5%. We also calculated the PTA expectation values shown in Table 7 for bacteriostasis (target, $T_{\geq \text{MIC}} \geq 30\%$). For continuous infusion, we obtained the same PTA expectation values for the bacteriostasis target as for the near-maximal killing (target, $T_{\geq \text{MIC}} \geq 50\%$). The PTA expectation values for prolonged and short-term infusion were slightly higher (median, 4.5%; range, 0.2 to 14.8%) for the bacteriostasis target than for the near-maximal killing target (comparison within the same dosage regimen).

PTA expectation values were lower for susceptibility data from South America (86% for *E. coli* and 71% for *K. pneumoniae*) than for data from North America (97% for *E. coli* and 94% for *K. pneumoniae*). Differences in PTA expectation values between different regions were more pronounced for *P. aeruginosa*. The PTA expectation values were about 93% for the MIC distribution from the Hartford Hospital, 82% for the 2002 MYSTIC data from North America, and only 43% for the 2002 MYSTIC data from South America. For *P. aeruginosa* isolates from CF patients in two German CF clinics, the PTA expectation values were about 89% for Leipzig and about 65% for Freiburg. The PTA expectation values for the nonmucoid and mucoid strains were similar.

**DISCUSSION**

Medical advances have led to tremendous improvements in the life expectancy and quality of life for CF patients during the last 70 years. In the 1930s, the average life expectancy of CF patients was only a few months. The median survival age of CF patients increased to 14 years in 1969 and to 31.3 years in 1996 in the US (13). The probability of surviving 40 years was even 83.3% in 1995 in Denmark for a diagnosed CF patient (23). This improved life expectancy seems to correlate with early treatment of *P. aeruginosa* (23), as it is almost impossible to eradicate this pathogen once a chronic infection is estab-

TABLE 7. Expectation values for the probability of target attainment for CF patients and healthy volunteers

<table>
<thead>
<tr>
<th>Source</th>
<th>Pathogen (no. of isolates)</th>
<th>PTA expectation value (%) results for three dosage regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Continuous infusion (9 g/70 kg WT/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CF</td>
</tr>
<tr>
<td>MYSTIC 2002, North America (35)</td>
<td><em>P. aeruginosa</em> (427)</td>
<td>82.2</td>
</tr>
<tr>
<td></td>
<td><em>E. coli</em> (433)</td>
<td>97.3</td>
</tr>
<tr>
<td></td>
<td><em>K. pneumoniae</em> (288)</td>
<td>94.3</td>
</tr>
<tr>
<td>MYSTIC 2002, South America (34)</td>
<td><em>P. aeruginosa</em> (233)</td>
<td>43.2</td>
</tr>
<tr>
<td></td>
<td><em>E. coli</em> (98)</td>
<td>85.6</td>
</tr>
<tr>
<td></td>
<td><em>K. pneumoniae</em> (92)</td>
<td>71.3</td>
</tr>
<tr>
<td>Hartford, CT (36)</td>
<td><em>P. aeruginosa</em> (557)</td>
<td>92.7</td>
</tr>
<tr>
<td>Isolates from CF patients</td>
<td><em>P. aeruginosa</em>, nonmucoid strains (229)</td>
<td>64.5</td>
</tr>
<tr>
<td>Freiburg, Germany (62)</td>
<td><em>P. aeruginosa</em>, mucoid strains (156)</td>
<td>65.5</td>
</tr>
<tr>
<td>Leipzig, Germany (65)</td>
<td><em>P. aeruginosa</em> (38)</td>
<td>88.6</td>
</tr>
</tbody>
</table>

- *a* Based on the PKPD target for near-maximal killing ($T_{\geq \text{MIC}} \geq 50\%$) and published MIC distributions (see Materials and Methods for details).
- *H*, healthy volunteers; CF, CF patients.
lished. Early aggressive treatment was shown to prevent or delay chronic *P. aeruginosa* infection significantly (21, 29) and resulted in a probability of >80% for still not having developed a chronic *P. aeruginosa* infection 7 years after the first isolation of this pathogen in the respective patient (22).

European experts strongly recommend the use of local susceptibility patterns for the treatment of *P. aeruginosa* infection (16). As the time required to identify *P. aeruginosa* and to assess its antibiotic susceptibility from a sputum culture is about 3 to 4 days, efficacious empirical therapy is very important. Data for the effectiveness of intravenous antibiotic treatment in CF patients are rather sparse, and large randomized controlled trials are required (11, 20, 41).

MCS offers a tool to overcome this shortage of data. A PKPD target like near-maximal bactericidal activity is used as surrogate marker for successful clinical outcome in an MCS. More specifically, MCS allows one to identify the dose and mode of administration with the highest PTA for treatment of a specific patient population against target pathogens, with a specific susceptibility pattern. MCS has been shown to be a very useful tool in rational dose selection for phase II/III clinical trials (18). Mouton et al. (49) used MCS to compare the PKPD profile of ceftazidime between CF patients, intensive care patients, and healthy volunteers.

Knowledge of the PK in the relevant patient population (e.g., in CF patients) is a prerequisite to applying an MCS, since MCS combines the patient-specific PK parameters and their variability with the specific susceptibility data from a local hospital. PK studies in CF patients often comprise a very heterogeneous patient population with considerable differences in age, weight, body composition, and disease state. To determine the influence of those disease-specific factors on the PK, it is important to compare the PK of healthy volunteers and CF patients within the same study. Population PK is a powerful concept for studying the influence of these factors on the PK in CF patients quantitatively. Our population PK analysis aimed at estimating the differences in average PK parameters between CF patients and healthy volunteers as well as the PK parameter variability. Our final model had an excellent predictive performance for the average plasma concentration time profiles of piperacillin as well as their variability (see Fig. 2). Therefore, we used it to compare the PD characteristics between both subject groups via MCS. Our MCS was based on data from 34 subjects in total (8 CF patients and 26 healthy volunteers). We had frequent plasma samples and used population PK to describe the PK of piperacillin in both subject groups.

Our results for the PK parameters of piperacillin in healthy volunteers were well within the range of those from other authors (2, 4, 39, 69). The literature data for the PK of piperacillin in CF patients are sparse. The data reported show a rather wide variability in PK parameters. None of the piperacillin studies in CF patients included a healthy volunteer control group which makes it difficult to interpret the differences in the observed results between studies. The average terminal half-life of piperacillin is between 0.54 and 0.89 h in children and adolescents with CF (14, 31, 32, 42, 56) and 1.2 ± 0.9 h in adult (age, 25.8 ± 3.6 years) CF patients (75). We determined a median terminal half-life of 0.69 h (range, 0.34 to 1.19 h) in our adult CF patients (age, 21.1 ± 3.8 years), which is well within the range of half-lives reported by other authors.

For CF patients, the volume of distribution was reported to be 0.4 liter/kg (32) in children, 0.64 liter/kg (14, 31) and 0.17 liter/kg in juveniles and young adults (14, 56), respectively, and 0.296 ± 0.11 liter/kg (75) in adult CF patients. Differences by a factor of 3.8 (maximum/minimum) for volume of distribution are unlikely to be caused by an altered body composition (e.g., between young and adult CF patients). This large range could in part be due to the use of noncompartmental analysis which is less powerful than population PK. We determined a volume of distribution at steady state of 0.181 ± 0.034 liter/kg WT and a volume of distribution during the terminal phase of 0.229 ± 0.100 liter/kg WT, both by noncompartmental analysis. Our estimates were at the lower end of the ranges of values reported in the literature. Total clearance was reported to be about 0.43 liter/h/kg in children aged 5 years (32), 0.497 liter/h/kg in children aged 8 to 16 years (14, 31), and 0.188 liter/h/kg in juveniles and young adults of ages of 12 to 21 years (14, 56). Although higher clearances in liter/h/kg are often observed for younger (and smaller) patients compared to adults, a difference by a factor of 2.6 between the two, i.e., juveniles and adults, CF patient groups seems large. Vinks et al. (75) found a clearance of 0.23 ± 0.04 liter/h per kg LBM after intermittent treatment of adult CF patients. Our total clearance of 0.24 ± 0.04 liter/h per kg LBM (see Table 1 and Table 2) is in good agreement with the data from Vinks et al. (75).

The differences in PK parameters between CF patient groups reported by various authors (14, 31, 56) underline the need to include a healthy volunteer control group to compare the PK for CF patients to the PK for healthy volunteers. Some of those large differences might also be due to inadequate scaling of CF patients for body size. Our CF patients had a 39% lower WT than the healthy volunteers (see Table 1). The LBM was 34% lower in CF patients. Our noncompartmental analysis showed a 31% smaller unscaled volume of distribution at steady state and a 25% lower unscaled total clearance in CF patients than those of healthy volunteers (see Table 2).

Our population PK analysis aimed at ranking the different size models according to (i) their ability to describe the average differences between CF patients and healthy volunteers and (ii) their ability to reduce the unexplained BSV in clearance and volume of distribution. In the absence of a size descriptor (Table 4, size model 1), CF patients had a 27% lower clearance and a 40% lower volume of distribution, because they were smaller. Size models 2 to 5 estimated FCYFVSS close to 1.0 (range, 0.924 to 0.999). Linear scaling of clearance by WT or LBM overaccounted for the fact that our CF patients were smaller. CF patients had a 20% higher clearance expressed as liter/h/kg (linear scaling by WT), probably because WT ignores the fact that our CF patients were leaner than our healthy volunteers. For the allometric size models, the estimates were close to 1.0 (range, 1.00 to 1.06). Therefore, the two allometric size models explained the differences in average volumes of distribution and average clearance between CF patients and healthy volunteers.

Besides the ability of the various size models to describe the differences in average PK parameters, we studied the ability of these models to reduce the unexplained BSV. This is important in empirical therapy, as target concentrations can be attained.
more precisely if the unexplained BSV is reduced by a body size descriptor. Linear and allometric scaling by LBM (see Table 5) reduced the unexplained BSV by about 30% for clearance and about 14% for volume of the central compartment relative to that of linear scaling by WT. Thus, allometric scaling by LBM described the differences in average clearance and volume of distribution and reduced the unexplained BSV relative to that of linear scaling by WT. This result seems reasonable, because LBM accounts for body composition whereas WT does not.

We used the population PK model based on allometric scaling by LBM to calculate the PTA in CF patients and healthy volunteers and to compare the PKPD breakpoints. The elimination in our final model was nonsaturable, although there are data which support a saturable component of piperacillin elimination (4, 69, 75). We systematically compared models with first-order, mixed-order (Michaelis-Menten), and parallel first-order and mixed-order elimination for the whole data set and for the data of each subject group separately. Inclusion of a saturable elimination did not result in a statistically significant improvement in the objective function. More importantly, the first-order (nonsaturable) clearance component accounted for more than 95% of total clearance at low concentrations, indicating a small degree of saturation for all studied models. However, our study assessed the PK of piperacillin only at one dose level after a short-term infusion. Based on the Michaelis-Menten constants reported by Vinks et al. (75) and Lodise et al. (39), plasma concentrations in our study remained above the average Michaelis-Menten constants for about 2 h or less. This is probably the reason why our study had a low power to detect the saturable elimination of piperacillin. Most (4, 69, 75) reports in literature showing a saturable elimination of piperacillin studied more than one dose level, collected serial urine samples, or studied more than one dosage regimen.

We could show by exhaustive MCS based on data for healthy volunteers that the differences between a saturable and nonsaturable elimination model for piperacillin were small for the dosage regimens and MIC distributions reported in our study (data available on request). Therefore, the PKPD breakpoints and PTA expectation values from our linear (nonsaturable) PK model are adequate for the studied dosage regimens and dose levels, since the PK of piperacillin appears as “pseudolinear” for the studied dosage regimens, although it is truly nonlinear. Vinks et al. (75) found a clearance of 24.4 ± 11.7 liter/h in CF patients for a continuous infusion of 16 g piperacillin/2 g tazobactam over 24 h. Our clearance in CF patients was 11.7 liter/h with a range of 6.25 to 14.5 liter/h (see Table 2). As the clearances reported by Vinks et al. are about twice as large as and more variable than our clearances, we found PKPD breakpoints of about 4 to 6 mg/liter for a continuous infusion of 9 g/day in CF patients, when we used the clearances from Vinks et al. for MCS (see Table 6). The CF patients in the study from Vinks et al. (75) were treated for an acute exacerbation of their chronic P. aeruginosa infection by piperacillin-tazobactam. Our patients had no acute infection and received piperacillin without tazobactam. This may have contributed to the differences between our results and the study from Vinks et al. (75). The results for short-term infusion of piperacillin were similar to those in the study by Vinks et al.

CF patients had only slightly lower PTAs (see Fig. 4), which resulted in PKPD breakpoints similar to those of healthy volunteers. Figure 4 contains no confidence intervals for the PTA. The expected width of confidence intervals for the PTA versus MIC plot for MCS of beta-lactams was studied as a function of sample size by Bulitta et al. (5). We studied continuous infusion and prolonged (4-h) infusion every 8 h at a daily dose of 9 g/70 kg WT as well as short-term (30-min) infusion every 4 h at a daily dose of 18 g/70 kg WT. Remarkably, continuous and prolonged infusions achieved the same PKPD breakpoint for near-maximal killing of about 16 mg/liter at a 50% lower daily dose than short-term infusions (see Table 6). Our PKPD breakpoint is in good agreement with the PKPD breakpoint determined via MCS by Lodise et al. (39), with the breakpoint of 16 mg/liter for susceptibility specified by the BSAC (1) and with the DIN breakpoints (15) of ≤4 mg/liter for susceptibility and >32 mg/liter for resistance. Importantly, the breakpoint specified by the Clinical and Laboratory Standards Institute (CLSI) is ≤64 mg/liter for susceptibility of P. aeruginosa to piperacillin and piperacillin-tazobactam (10). As chronic infection by P. aeruginosa in CF patients causes a high risk for morbidity and mortality, the CLSI breakpoint for piperacillin against P. aeruginosa seems inappropriately high for CF patients. The CLSI breakpoint of ≤16 mg/liter for susceptibility of Enterobacteriaceae to piperacillin and piperacillin-tazobactam agrees more closely with our PKPD breakpoints.

The dose reduction from 18 g (intermittent treatment) to 9 g daily (prolonged and continuous infusion) underlines the benefit of prolonged and continuous infusion with regard to drug acquisition costs and a possibly lower risk for adverse events. There are also clinical data showing that continuous infusion yields comparable or superior clinical efficacy for piperacillin in non-CF patients (25, 38, 57). Vinks et al. (74) showed the clinical effectiveness of continuous infusion of ceftazidime in CF patients.

Early aggressive treatment of P. aeruginosa infection in CF patients may require very high piperacillin doses that carry an increased risk for adverse events. Dosages of up to 900 mg/kg daily divided into six doses (equivalent to 63 g for a 70-kg patient) were administered to CF patients aged 12 years or less (59). A distinct serum sickness-like adverse reaction was observed for 32% of these patients, and its incidence appeared to be correlated with the piperacillin dose. Adverse events after piperacillin treatment in CF patients were also reported by other authors (51, 61, 66, 67).

As the options for efficacious antipseudomonal treatment become increasingly fewer due to the emergence of resistance, prolonged infusion of piperacillin seems to be an appealing option which can combine a high probability for clinical success and a possibly lower risk for adverse events secondary to considerably lower daily doses.

To determine the clinical relevance of the observed PTAs, we calculated the PTA expectation values for various MIC distributions. The PTA expectation values differed only slightly (<5.5%) between CF patients and healthy volunteers for the studied MIC distributions. The PTA expectation values for E. coli and K. pneumoniae from the 2002 MYSTIC data in North America as well as for the P. aeruginosa data at the Hartford Hospital were robust (>92%) for all three studied dosage regimens (see Table 7). Secondary to a decreased susceptibility of the P. aeruginosa isolates in the 2002 MYSTIC data, PTA
expectation values were only 82% in North America and 43% in South America. When we studied MIC distributions in German CF patients, the PTA expectation values for *P. aeruginosa* were between 64 and 89%. These differences underline the importance of using the MIC distribution of each local hospital to calculate PTA expectation values for successful empirical treatment against each pathogen (16).

In conclusion we found a 25% lower unscaled total clearance and a 31% lower volume of distribution at steady state in CF patients than in healthy volunteers, because our CF patients were smaller. Allometric scaling by WT or LBM explained the differences in average clearance and volume of distribution better than linear scaling by WT. Linear scaling by WT predicted clearance in CF patients to be 20% higher than in healthy volunteers, probably because WT does not account for body composition. Linear or allometric scaling by LBM reduced the unexplained (random) BSV by about 30% for clearance and by about 14% for volume of the central compartment relative to linear scaling by WT. This is important for achieving target concentrations more precisely in empirical therapy. Large clinical studies are warranted to show a higher probability of successful clinical outcome for dose selection in CF patients based on LBM. The PKPD breakpoint for near-maximal bactericidal activity was 16 mg/liter in CF patients and in healthy volunteers for a dosage of 3 g/70 kg WT every 8 h given as a prolonged (4-h) infusion. The PTA expectation values were between 64% and 89% for *P. aeruginosa* isolates from CF patients in two German CF clinics. Clinical trials are warranted to compare the clinical cure rates and adverse events between prolonged infusion at a 50% lower daily dose and short-term infusion at the full daily dose.

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