A pharmacokinetic analysis of tobramycin in patients less than five years of age with cystic fibrosis: Assessment of target attainment with extended-interval dosing through simulation

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A Pharmacokinetic Analysis of Tobramycin in Patients Less than Five Years of Age with Cystic Fibrosis: Assessment of Target Attainment with Extended-Interval Dosing through Simulation

Kevin J. Downes,⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎⁎ ⁃�

Extended interval dosing of tobramycin is recommended for treatment of pulmonary exacerbations in adults and older children with cystic fibrosis (CF), but data are limited in patients less than 5 years of age. We performed a retrospective population pharmacokinetic (PK) analysis of hospitalized children with CF, 5 years of age prescribed intravenous tobramycin for a pulmonary exacerbation from March 2011 to September 2018 at our hospital. Children with normal renal function who had ≥1 tobramycin concentration available were included. Nonlinear mixed effects population PK modeling was performed using NONMEM using data from the first 48 h of tobramycin treatment. Monte Carlo simulations were implemented to determine the fraction of simulated patients that met published therapeutic targets with regimens of 10–15 mg/kg/day once-daily dosing. Fifty-eight patients received 111 tobramycin courses (range 1–9/patient). A two-compartment model best described the data. Age, glomerular filtration rate, and vancomycin coadministration were significant covariates on tobramycin clearance. The typical values of clearance and central volume of distribution were 0.252 L/hr/kg^0.75 and 0.308 L/kg, respectively. No once-daily regimens achieved all pre-specified targets simultaneously in 75% of simulated subjects. A dosage of 13 mg/kg/dose best met the predefined targets of Cmax ≥25 mg/L and AUC24 of 80–120 mg-h/L. Based on our population PK analysis and simulations, once-daily dosing of tobramycin would not achieve all therapeutic goals in young patients with CF. However, extended-interval dosing regimens may attain therapeutic targets in the majority of young patients.

KEYWORDS antibiotics, pediatrics, therapeutic drug monitoring, population pharmacokinetics

Pediatric patients with cystic fibrosis (CF) commonly experience pulmonary exacerbations (PEx) for which they receive antimicrobial therapy. Tobramycin, an aminoglycoside, is commonly used as first-line treatment for patients with CF experiencing a PEx. The CF Foundation recommends extended interval dosing (EID) for tobramycin (and other aminoglycosides) to optimize effectiveness (concentration-dependent killing)
and reduce the likelihood of safety concerns such as nephrotoxicity (1). Although EID has been evaluated and appears effective and safe in patients 5 years of age and older (2), there are limited data to support EID for tobramycin in CF patients less than 5 years of age.

Therapeutic drug monitoring (TDM) can improve both the efficacy and safety of aminoglycosides. These drugs are concentration-dependent antibiotics with post-antibiotic effects (3) but are also associated with a variety of dose- and duration-dependent toxicities including nephrotoxicity and ototoxicity. By monitoring aminoglycoside concentrations, providers can adjust doses to ensure that patients receive therapeutic peak serum drug concentrations and appropriate trough concentrations to potentially minimize toxicity (4). Providers can also use TDM to determine the drug-free interval (DFI)—the duration of time the drug is undetectable—and ensure that the frequency of drug dosing is suitable. Currently, our institution utilizes once-daily dosing (i.e., EID) of tobramycin for patients with CF 5 years of age and older and every 8-h dosing for patients less than 5 years of age given the limited data for tobramycin EID in these younger patients with CF.

The optimal initial dose for tobramycin when using EID in young children is unknown. As such, there are concerns about both over- and under-dosing. Younger patients may clear drug more quickly, putting them at a higher risk of inadequate antibiotic therapy when extended dosing intervals are used. Alternatively, large initial doses could result in high initial tobramycin concentrations and result in toxicity. Therefore, informed dosing guidance for tobramycin in children is important. While Arends and colleagues were the first to specifically evaluate EID in a young CF patient population (5), their study calculated pharmacokinetic (PK) parameters in individual subjects using noncompartmental methods (i.e., algebraic equations) (5). This analytic approach using measured drug concentrations can be subject to bias since it does not account for measurement error or inter- or intra-subject variability.

The primary objective of the current study was to utilize a population PK analysis approach to determine the suitability of empirical tobramycin EID in patients less than 5 years of age. Since TDM can be used to guide dosing during therapy, we sought to evaluate early (within 48 h) PK parameters and assess attainment of CF Foundation-recommended goal tobramycin serum concentrations and DFI through simulations. Secondary objectives of this study were to quantify population PK parameters, including typical values and random inter-individual and residual variabilities, identify important covariates that affect early tobramycin PK, and define drug concentrations attained with EID tobramycin in patients less than 5 years of age with CF. Furthermore, using simulations, we sought to compare target attainment from model predictions to what could be expected in clinical practice using standard TDM approaches.

RESULTS

Study population. Sixty-one patients received 115 tobramycin courses during the study period. Four courses in 3 patients were excluded (two in premature infants, two with no tobramycin concentrations obtained). Thus, 58 patients receiving 111 tobramycin courses were included. Table 1 displays baseline characteristics of the study population during their first course and all courses during the study. The median age of patients at the initiation of therapy was 2.2 years (IQR: 1.2-4). Thirty-five subjects received one tobramycin course during the study period, 13 received two courses, and 10 received three or more courses. Two-hundred twenty-eight tobramycin serum concentrations were collected; 4 concentrations were excluded due to the samples being mistimed. Of 224 tobramycin concentrations included, 53 (23.7%) were reported as BQL. Fig. 1 depicts the distribution of tobramycin serum concentrations in relation to time after dose.

Model development. Due to the timing of TDM sampling in our data set (i.e., peaks and troughs), we utilized prior information from adult CF patients to inform initial parameter estimates for inter-compartmental clearance (Q) and peripheral volume (V2). We identified a published, standard two-stage PK analysis that included rich sampling in 6 adult CF patients treated with 3.3 mg/kg thrice daily tobramycin (6). Because all
model parameters were not reported in this publication, we used WebPlotDigitizer (7) to extract the concentration-time data of each subject in Fig. 2 of this published model (6). We then constructed a data set for analysis in NONMEM, using median population weight for each subject, to derive initial Q and V2 estimates for our model. Given poor estimation of between-subject random effects for Q and V2 during base model development, they were fixed to 0 for these parameters.

**TABLE 1** Characteristics of study population based on first course and all courses of tobramycin

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>First course (n = 58)</th>
<th>All courses (n = 111)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>25 (43%)</td>
<td>46 (41%)</td>
</tr>
<tr>
<td>Age in yr, median (IQR)</td>
<td>2.2 (0.8–3.8)</td>
<td>2.6 (1.2–4)</td>
</tr>
<tr>
<td>Wt in kg, median (IQR)</td>
<td>11.2 (8.2–14.7)</td>
<td>12.4 (9.7–14.8)</td>
</tr>
<tr>
<td>Ht in cm, median (IQR)</td>
<td>85.8 (70.5–95.5)</td>
<td>88.1 (75–98)</td>
</tr>
<tr>
<td>Serum creatinine in mg/dL, median (IQR)*</td>
<td>0.3 (0.2–0.3)</td>
<td>0.3 (0.2–0.3)</td>
</tr>
<tr>
<td>GFR in mL/min/1.73m², median (IQR)*</td>
<td>126 (110–149)</td>
<td>129 (110–148)</td>
</tr>
<tr>
<td>GFR &lt; 90 mL/min/1.73m², n (%)*</td>
<td>3 (5.2%)</td>
<td>6 (5.4%)</td>
</tr>
<tr>
<td>Dose in mg/kg/dose, median (IQR)*</td>
<td>3.2 (3.1–3.3)</td>
<td>3.2 (3.1–3.3)</td>
</tr>
</tbody>
</table>

Concurrent nephrotoxic medications, n (%)tux

<table>
<thead>
<tr>
<th></th>
<th>First course (n = 58)</th>
<th>All courses (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38 (65.5)</td>
<td>70 (63.0)</td>
</tr>
<tr>
<td>1</td>
<td>18 (31.0)</td>
<td>33 (29.7)</td>
</tr>
<tr>
<td>2 or more</td>
<td>2 (3.4)</td>
<td>8 (7.2)</td>
</tr>
</tbody>
</table>

*Among 58 individuals treated, 35 received one course, 13 received two courses, 4 received three courses, 1 received four courses, 2 received five courses, and 1 each received seven, eight, and nine courses.

tAt time of tobramycin initiation.

uxConcurrent nephrotoxic medications included non-steroidal anti-inflammatory medications, acyclovir, vancomycin, piperacillin-tazobactam, ticarcillin/clavulanate, and trimethoprim-sulfamethoxazole.

**FIG 1** Distribution of tobramycin measurements in relation to time after dose. Drug concentrations are log-transformed. Those reported as below limit of quantification are shown in blue and plotted as 0.3 μg/mL (i.e., 1/2 lower limit of quantification). Horizontal line reflects the limit of quantification (0.6 μg/mL).
Clearance (CL) and Q were allometrically scaled for weight to 0.75, normalized to 70-kg, while central (V1) and peripheral (V2) volume parameters were scaled linearly for weight, normalized to 70-kg (8). The results of the covariate selection process are shown in Table S1. Age and eGFR were included in the model a priori, based on prior published models (9). Concomitant receipt of vancomycin was also informative on CL in the forward stepwise approach. When evaluating inter-occasion variability (IOV), the addition of IOV increased the AIC of the model, had no impact on inter-individual random effects on CL and V1, and did not change the point estimates of the model parameters. Additionally, IOV minimally reduced the residual unexplained variability of the model from 33.4% to 32.8% and led to an increase in the percent relative standard error for each parameter estimate, suggesting that inclusion of IOV did not improve model fit. Therefore, IOV was not included in our final model.

The parameter estimates for the final model are shown in Table 2, along with bootstrap estimates (n = 1,000 replications) of parameters with 95% confidence intervals; the NONMEM control stream for the final model is provided in the supplemental materials. Additional bootstrap analyses were performed (n = 500) with stratification by receipt of vancomycin, by age (<1 year, 2–3 years, or 4+ years), and by eGFR (<100, 100–199, 200+ mL/min/m²). In each case, the model parameter estimates were within the 95% confidence intervals of the bootstrap estimates. The associated diagnostic plots for the final model are shown in Fig. 2.

In the final model, the typical value of CL for our population was $0.252 \text{ L/hr/kg}^{0.75}$ (95% CI: 0.233–0.271), $V_1$ was 0.308 L/kg (95% CI: 0.264–0.353), $Q$ was 0.195 L/hr/kg$^{0.75}$ (95% CI: 0.171–0.219), and $V_2$ was 0.096 L/kg (95% CI: 0.081–0.110). Concomitant receipt of vancomycin was associated with a 29.2% (95% CI: 3.7–55.7%) reduction in tobramycin CL, although vancomycin was administered to only 5 patients during 8 tobramycin courses. Visual predictive checks (VPCs) for the final covariate model are shown in Supplement files. The median of the predicted tobramycin concentrations fit closely to the observed data, but the 5th and 95th percentile of the predicted tobramycin concentrations at early time points were lower and higher, respectively, than the observed data (Fig. S1A in the supplemental material), suggesting increased variability within the model. When re-running the VPCs using only the assay error from the quality control runs in the lab (4.3%), we found improved fit at the early sampling times (Fig. S1C). Although there was slight over-prediction of 8-h concentrations, use of assay error only led to fewer predicted BQL concentrations (Fig. S1D) compared to use of residual variability from our derived model (Fig. S1B).

**Target attainment.** Monte Carlo simulations were performed for tobramycin dosing regimens of 10–15 mg/kg once daily. Due to the small number of patients in our original study population who received concomitant vancomycin treatment, all simulated patients did not receive vancomycin. Table 3 reports the proportion of simulated patients achieving the goal parameters of EID.

When assessing attainment of targets determined directly from the Simulation Output approach (i.e., using simulated concentrations and clearance estimates; no residual variability), all simulated patients achieved the $C_{\text{min}}$ goal of <0.6 mg/L. And more than 75% of simulated patients achieved the $C_{\text{max}}$ goal of >25 mg/L with 11–15 mg/kg/day dosing regimens. No EID regimens achieved the AUC target (80–120 mg h/L) in >75% of simulated patients. More than 75% of simulated patients had an AUC >80 mg h/L with dosing of 12–15 mg/kg/day, although an increasing proportion of simulated subjects’ AUC exceeded 120 mg h/L at higher dosages. Across all five targets, a dosage of 13 mg/kg had the highest average target attainment (79.8%), followed by 12 mg/kg (78.5%) and 14 mg/kg (78.4%).

There were substantial differences in target attainment when the TDM approach

### Table 2: Final population PK parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model Estimate</th>
<th>Bootstrap estimates (n = 1,000) Median 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_{\text{CL}}$ (L/hr/70 kg)</td>
<td>6.10</td>
<td>6.09</td>
</tr>
<tr>
<td>$\theta_{\text{AGE}}$</td>
<td>0.136</td>
<td>0.137</td>
</tr>
<tr>
<td>$\theta_{\text{GFR}}$</td>
<td>0.246</td>
<td>0.269</td>
</tr>
<tr>
<td>$\theta_{\text{VAN}}$</td>
<td>0.708</td>
<td>0.752</td>
</tr>
<tr>
<td>$\theta_{\text{V1}}$ (L/70 kg)</td>
<td>21.6</td>
<td>21.5</td>
</tr>
<tr>
<td>$\theta_{\text{Q}}$ (L/hr/70 kg)</td>
<td>4.73</td>
<td>4.72</td>
</tr>
<tr>
<td>$\theta_{\text{V2}}$ (L/70 kg)</td>
<td>6.69</td>
<td>6.09</td>
</tr>
<tr>
<td>$\omega_{1,1}$–CL</td>
<td>0.0296 (17.2% CV)</td>
<td>0.0287</td>
</tr>
<tr>
<td>$\omega_{1,2}$–CL:V1</td>
<td>0.0325 (0.751)b</td>
<td>0.0323</td>
</tr>
<tr>
<td>$\omega_{2,2}$–V1</td>
<td>0.0633 (25.2% CV)</td>
<td>0.0655</td>
</tr>
<tr>
<td>Residual variability</td>
<td>0.333 (57.8% CV)</td>
<td>0.324</td>
</tr>
</tbody>
</table>

*CL, clearance; BSV, between subject variability; Q, inter-compartmental clearance; RSE, relative standard error; V1, central volume; V2, peripheral volume.

Final model parameterized as:

$TV_{\text{CL}} = \theta_{\text{CL}} * (\text{WT/70} ^ {0.75}) * (\text{AGE/2.7} ^ {\theta_{\text{AGE}}}) * (\text{GFR/128} ^ {\theta_{\text{GFR}}}) * (\theta_{\text{VAN}} ^ {\text{VAN}})$

$TV_{\text{V1}} = \theta_{\text{V1}} * (\text{WT/70})$

$TV_{\text{Q}} = \theta_{\text{Q}} * (\text{WT/70} ^ {0.75})$

$TV_{\text{V2}} = \theta_{\text{V2}} * (\text{WT/70})$

Off-diagonal correlation coefficient.

A full block covariance matrix was utilized to define the inter-individual random effects ($\omega$) for CL and V1. Inter-individual random effects fixed to 0 for Q and V2.

Finally control stream and ETA shrinkages values provided in Supplemental Materials.
was assessed (i.e., log-linear regression on simulated concentrations at 3 and 8 h; incorporated assay variability). In general, all targets were less often met using the log-linear approach compared to model expectations. The differences were most significant for \( C_{\text{max}} \) and AUC\(_{24} \) targets. At a dose of 12 mg/kg, 54% fewer simulated subjects met the \( C_{\text{max}} \) target using the log-linear estimation approach compared to the simulation output, while 12% fewer met the AUC\(_{24} \) target of 80–120 mg\( \cdot \)h/L.

**DISCUSSION**

This retrospective, population PK study analyzed the applicability of EID for IV tobramycin in CF patients less than 5 years of age and compared attainment of therapeutic targets in simulated patients according to CF Foundation guidelines (1). Our patient cohort included a wide variety of CF patients in terms of age and prior tobramycin exposures. Our simulations suggest that EID tobramycin would not attain all recommended therapeutic goals in a significant majority (>75%) of patients with CF less than 5 years of age. However, a dosage of 13 mg/kg/day had the highest probability of target attainment across all 5 targets evaluated and would be the optimal EID dosing regimen, according to our simulations. This dose met the \( C_{\text{max}} \) target using the log-linear estimation approach compared to the simulation output, while 12% fewer met the AUC\(_{24} \) target of 80–120 mg\( \cdot \)h/L.

**TABLE 3** Percentage of simulated patients meeting therapeutic targets on day 2 of treatment based on simulated concentrations

<table>
<thead>
<tr>
<th>Target</th>
<th>10 mg/kg</th>
<th>11 mg/kg</th>
<th>12 mg/kg</th>
<th>13 mg/kg</th>
<th>14 mg/kg</th>
<th>15 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation output(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} \geq 25 \text{ mg/L} )</td>
<td>65.6</td>
<td>79.1</td>
<td>88.2</td>
<td>93.9</td>
<td>96.8</td>
<td>98.4</td>
</tr>
<tr>
<td>( C_{\text{min}} &lt; 0.6 \text{ mg/L} )</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Time undetectable &lt; 11h</td>
<td>31.2</td>
<td>38.1</td>
<td>44.9</td>
<td>51.5</td>
<td>56.8</td>
<td>62.4</td>
</tr>
<tr>
<td>AUC(_{24} ), 80–120 mg( \cdot )h/L</td>
<td>40.3</td>
<td>56.9</td>
<td>67.9</td>
<td>70.4</td>
<td>66.1</td>
<td>55.7</td>
</tr>
<tr>
<td>AUC(_{24} ), &lt; 120 mg( \cdot )h/L</td>
<td>98.8</td>
<td>96.4</td>
<td>91.4</td>
<td>83.0</td>
<td>72.3</td>
<td>68.5</td>
</tr>
<tr>
<td>TDM approach(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} \geq 25 \text{ mg/L} )</td>
<td>5.9</td>
<td>16.7</td>
<td>34.1</td>
<td>53.3</td>
<td>69.8</td>
<td>82.5</td>
</tr>
<tr>
<td>( C_{\text{min}} &lt; 0.6 \text{ mg/L} )</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Time undetectable &lt; 11h</td>
<td>30.5</td>
<td>37.1</td>
<td>43.6</td>
<td>49.8</td>
<td>55.4</td>
<td>61.1</td>
</tr>
<tr>
<td>AUC(_{24} ), 80–120 mg( \cdot )h/L</td>
<td>24.8</td>
<td>40.3</td>
<td>55.7</td>
<td>65.9</td>
<td>69.6</td>
<td>66.5</td>
</tr>
<tr>
<td>AUC(_{24} ), &lt; 120 mg( \cdot )h/L</td>
<td>99.5</td>
<td>98.5</td>
<td>96.1</td>
<td>91.7</td>
<td>84.9</td>
<td>74.8</td>
</tr>
</tbody>
</table>

\(^a\)Monte Carlo simulations (\( n = 500 \)) performed using study population characteristics (age, weight, GFR) at start of tobramycin course. Target attainment assessed following the second dose. Dark-gray shading indicates >75% target attainment. Light-gray shading indicates 50–75% target attainment. No shading indicates <50% target attainment.

\(^b\)All targets calculated based on log-linear regression of simulated concentrations at 3 and 8 h following the second dose, as is typically performed with clinical TDM. Residual variability set to assay variability from quality control runs (4.3%).
has not been fully evaluated in young children and remains an important question. Based on our simulations, a dosage of 13 mg/kg/dose appears optimal, but prospective studies are needed.

We focused on tobramycin PK in the first 2 days of treatment to determine if EID would be appropriate for empirical use in young children with CF. In older children who receive EID tobramycin at our institution, TDM is routinely performed following the first or second dose, and then weekly during the course of treatment. Our analysis mirrored this approach by examining early PK and assessing target attainment on day 2. Thus, we cannot extrapolate our findings to later time points. Nevertheless, there was a substantial degree of variability between the patients within our study population. As a result, EID regimes with higher dosages obtained \( C_{\text{max}} \) and \( C_{\text{min}} \) concentration targets in greater than 75% of simulated patients. However, similar results were not found for the percent of patients achieving DFI and AUC goals. With extended durations of DFI, patients may have prolonged periods of low tobramycin concentrations that put them at theoretical risk of antimicrobial failure. A large proportion of the simulated patients at higher dosages (14-15 mg/kg/day) who did not meet the AUC24 target did so due to supra-therapeutic AUC24 values (>120 mg*h/L), which could result in elevated risks of tobramycin toxicity.

Importantly, there were substantial differences in target attainment depending on the method used. These were most notable for estimates of \( C_{\text{max}} \) and AUC24, the two parameters that describe tobramycin exposure. In the absence of Bayesian methods, log-linear regression is often used for clinical TDM to estimate PK parameters and target attainment in individual patients (15). Since this approach relies on assumptions of a one-compartment model with linear elimination, \( C_{\text{max}} \) can be grossly underestimated for a two-compartment drug, as we found. The log-linear approach can also lead to significant differences in AUC24 estimates compared to true AUC24 values. It should be recognized that our methods for target attainment assessment in the Simulated Output approach does not perfectly approximate Bayesian methods. And we intentionally omitted residual variability from this approach to more directly assess model predictions. In doing so, our goal was to highlight differences between model predictions and TDM calculations and demonstrate how all of the types of variability (inter- and intra-individual variability, residual variability, and the method for performing PK calculations) create challenges to optimal dosing in clinical practice.

In a retrospective study of 77 children with CF treated with once-daily tobramycin at a mean dose of 12.5 mg/kg/day, Brockmeyer et al. found that 52% met the AUC24 target of 80–120 mg*h/L after the initial dose based on log-linear regression (15). This is comparable to our analyses, in which 43–44% of simulated patients given 12–13 mg/kg/day met this AUC target with log-linear regression. Brockmeyer also utilized Bayesian forecasting, based on a two-compartment model, to estimate AUC24 for each subject (15). Again, similar to our assessment, estimates of AUC24 using Bayesian methods were higher than with log-linear regression (mean difference of 6.4 mg*h/L) (15). These findings have significant clinical ramifications. Dose adjustments based on log-linear regression estimates of \( C_{\text{max}} \) and AUC24 may lead to over-exposure and added risk of toxicity in some patients. Clinicians therefore need to be cognizant of the limitations of traditional TDM practices.

Notably, we excluded the potential effects of vancomycin co-administration in our simulations. This approach was taken because of the exploratory nature of our evaluation of nephrotoxin exposures on tobramycin CL during model development. Since our study was limited to the first 48 h of tobramycin therapy, and changes in serum creatinine (and thus eGFR) can be delayed following kidney injury, we hypothesized that nephrotoxin co-administration could impair tobramycin CL without noticeable changes in measurable eGFR. Although vancomycin co-administration was associated with a reduction in tobramycin CL in our model, only 5 subjects received concomitant vancomycin. Thus, we did not want to over-estimate vancomycin’s potential effects
and simulated all subjects as having not received this drug. Further studies are needed to explore this novel finding.

Our estimates for CL and central volume are similar to previous studies involving children with CF treated with EID tobramycin. Massie et al. studied 44 children aged 9 months to 20 years given 12 mg/kg/day (16). Based on a one-compartment model, they found that CL and volume of distribution were 0.103 L/h/kg and 0.267 L/kg, respectively (16). Hennig et al. performed a population PK analysis of 35 patients with CF aged 0.5 to 17.8 years treated with 10 mg/kg/day of tobramycin (17). Their two-compartment model estimated median population values for clearance of 6.37 L/h/70 kg and central volume of 18.7 L/70 kg (17), again similar to our model’s estimates (Table 2). However, in a study involving 85 children with CF 5–15 years of age by Touw et al. (18), volume of distribution was larger among recipients of once daily compared to thrice daily therapy (0.401 vs 0.354 L/kg, respectively). Clearance was not reported, but elimination rate did not differ by dosing regimen in this study. (18) So, while the findings of our study are consistent with prior reports (16, 17), it is possible that PK parameters could have differed in our population of young children had they actually been administered EID.

Because TDM concentrations were collected as standard of care, approximately 28% of the tobramycin samples included in our study were reported as BQL. While we attempted to account for this using the validated M3 method described by Beal (19), this may have contributed to increased variability in PK parameters in the model. Omission of BQL data can introduce substantial bias in parameter estimates. In our study, omission of BQL would result in under-estimation of CL since the vast majority of BQL data were trough measurements. The M3 method estimates the likelihood that BQL data are actually below quantification limits and is associated with less bias than omission of BQL data when missing data are during the elimination phase. Thus, despite a substantial amount of BQL data in our study, we believe that our PK parameter estimates are accurate.

Since this study was retrospective and relied on standard-of-care TDM drug concentrations, multiple additional limitations exist, which also may have contributed to variability in the model estimates. First, documentation of the duration of infusion was not a component of standard institutional practice during the study period. However, CHOP utilized standard infusion procedures, including a routine infusion time (30 min), which was assumed to have been used in all cases in PK modeling. Incorrect recording of the timing of tobramycin sampling or administration similarly could have affected the estimated PK parameters in the model. Any tobramycin samples that were deemed to clearly be an error (i.e., concentrations drawn during an infusion, concentrations reported as undetectable within 2 h after the infusion) were not included in the analysis. Second, since our study only included children less than 5 years of age, our findings should not be extrapolated to older children or adults. Although age was included as a covariate on CL in our model, parameterization may be different in individuals beyond our observed age range. Thus, our modeling, simulations, and assessment of target attainment focused on concentrations that would be achieved with empirical tobramycin dosing. Our findings should not be used to inform tobramycin dosing later in treatment courses, since PK (and therefore dosing guidance) may differ over time. Lastly, the number of tobramycin serum samples varied greatly between patients, which could have led to differential patient contribution in the PK model.

Overall, EID regimens optimize tobramycin efficacy while potentially lessening toxicity risk in subjects 5 years and older. Based on our population PK analysis and simulations, EID regimens may not achieve all recommended pharmacokinetic targets for younger children with CF. However, certain doses of EID can optimize the effectiveness and safety of tobramycin in patients less than 5 years of age while achieving targets in most individuals. Use of TDM will be paramount to ensure that appropriate dosing regimens are administered during prolonged courses, but clinicians should recognize that traditional TDM practices using log-linear regression methods underestimate the true PK of Tobramycin in Young Children with CF.
C_{\text{max}}$ and $\text{AUC}_{24}$ in patients. Prospective studies will be needed to validate our findings and specifically evaluate the safety and effectiveness of these regimens in CF patients less than 5 years of age.

**MATERIALS AND METHODS**

**Study design.** This was a retrospective, observational study of children with CF less than 5 years of age prescribed intravenous (IV) tobramycin therapy for a PEx. All hospitalized children who received IV tobramycin therapy for standard-of-care treatment between March 1, 2011, and September 1, 2018 at CHOP and had at least one tobramycin concentration measurement performed for TDM were eligible for inclusion. Patients with renal impairment, defined as an estimated glomerular filtration rate (eGFR) $<60 \text{ mL/min/1.73m}^2$ calculated by bedside Schwartz equation (20), who received extracorporeal membrane oxygenation (ECMO), with a postmenstrual age of less than 44 weeks, or who received concurrent nebulized tobramycin were excluded. The clinical team determined tobramycin dosing regimens and timing of tobramycin concentration measurements for TDM. The hospital formulary-recommended starting dose for patients less than 5 years of age at CHOP was 3.3 mg/kg/dose IV every 8 h given as a 30-minute infusion. Peak and trough measurements were routinely obtained following the third dose.

Patients were included into the study for all tobramycin treatment courses received during the study period. Since we were interested in empirical tobramycin dosing for this study, only drug concentrations obtained within the first 48 h of tobramycin therapy were included. The CHOP Institutional Review Board approved of this study with a waiver of informed consent.

**Data collection.** Electronic medical records were reviewed for collection of demographic and biometric characteristics, serum creatinine, concurrent medications, tobramycin dosing information, and tobramycin concentrations. Data were collected in Excel (Microsoft Corp., Redmond, WA). Tobramycin concentrations were performed in the CHOP Chemistry Laboratory (CLIA-certified) using competitive immunoassay (VITROS Chemistry Products TOBRA Reagent, Ortho-Clinical Diagnostics, Inc., Rochester, NY) throughout the study period. The lower limit of quantification of this assay was 0.6 mg/L.

**Data analysis.** (i) **Base model.** Population PK analyses were conducted using nonlinear mixed-effects modeling with NONMEM v7.4 and the PDx-Pop v5.2.1 interface (ICON plc. Dublin, Ireland).

With prior knowledge on the compartmental disposition of tobramycin (9), we sought to develop a 2-compartment model with first-order elimination. Since our study relied on TDM peak and trough data, we recognized that the current study design would not support estimation of parameters for the known tobramycin 2-compartment pharmacokinetic model disposition. Given that, a literature review identified published extensively sampled tobramycin PK data that could serve to support estimation of the current pediatric population PK model parameters and covariance terms (6). This prior information was quantified by estimating the population PK model parameters for the literature data and served to inform prior distributions for less well-informed model parameters (e.g., $Q$, $V_2$). The prior knowledge was formally incorporated in the current analysis by utilizing a penalized likelihood function with parametric specification of informative prior distributions on selected parameters from the literature model, and estimation of maximum $a$ posteriori probability (MAP) Bayesian population PK parameters given the current TDM data set, as has been described previously (21).

Between-subject variability was modeled using exponential variability, which assumes log-normal distribution of between subject variability around a parameter. A full block covariance matrix was utilized to define the between-subject random effects. Residual variability (RV) was estimated using a proportional error model. Model selection was driven by the data and based on various goodness of fit indicators, including comparisons based on the minimum objective function value (OFV), visual inspection of diagnostic scatterplots, and evaluation of estimates of population fixed and random effect parameters.

(ii) **Handling of BQL data.** Omission of below quantification limit (BQL) data can introduce substantial bias in parameter estimates (22, 23), particularly when there is a large amount of missing data ($>10\text{-}15\%$). To minimize bias associated with BQL data, we developed models using the M3 method described by Beal (19).

(iii) **Covariate selection.** Initially, covariate-parameter relationships were explored graphically and any correlations between covariates noted. Covariate model selection was then conducted by a stepwise backward elimination technique starting with a full covariate model, which was carefully constructed to avoid inclusion of colinear or correlated covariates. Based on previous population PK studies of children with CF treated with tobramycin (9), covariates included prior patient age and eGFR (calculated using Schwartz equation) on $CL$ (20). Age was evaluated as a Hill function on $CL$, as well as an exponential covariate normalized to the population median. eGFR was allowed to vary over the first 48 h of therapy if creatinine was measured more than once over this time frame. No covariates were tested on volume parameters due to the absence of associations in published pediatric models aside from weight (9). During backwards elimination, a critical change in OFV of $\geq 6.63$ for the FOCE method (nominal $\alpha = 0.01$, df = 1) was used to determine covariate inclusion.

Following this initial covariate evaluation process, we then performed an exploratory covariate analyses to assess the effects of concurrent nephrotoxic medication treatment on tobramycin $CL$. The influence of vancomycin, ticarcillin/clavulanate, trimethoprim-sulfamethoxazole, piperacillin-tazobactam, and NSAID co-administration was evaluated using a forward selection process (a reduction in OFV of $\geq 6.63$ for inclusion). Each nephrotoxin exposure was dichotomized (Y/N) as a time-varying covariate, allowing it to vary over the course of tobramycin. We further explored the influence of nephrotoxin exposures as a class effect by grouping agents together as: none vs 1 agent, and 0–1 vs $\geq 2$ agents.

(iv) **Inter-occasion variability (IOV).** To account for multiple treatment courses for the same patient over different hospitalizations, we assessed occasion-specific random effects on the structural model parameter of $CL$. We defined an occasion as a unique hospitalization per subject; if a patient received multiple
treatment courses during a single hospitalization, only the first treatment course was included. We compared the impact of inclusion of IOV on model fit (AIC) between the final covariate model with and without IOV, evaluated the influence of IOV on the fixed and random effects parameter estimates, and examined its impact on residual unexplained variability.

(v) Model performance. Model selection was determined by evaluating goodness-of-fit diagnostic plots, comparisons of the minimum objective function value (OFV), Akaike information criterion (AIC), and precision of parameter estimates. Visual predictive checks (VPCs) were performed to assess the fit of the final covariate model. 100 VPC simulations were obtained from the observed data. Observed tobramycin data was plotted along with the 95th, 50th and 5th percentiles for the simulated data sets. Data was plotted as time after dose (TAD) versus concentration. RStudio v3.6.3 (RStudio, Inc., Boston, MA) was used for descriptive statistics and graphical evaluations.

(vi) Simulations. Monte Carlo simulations were performed using NONMEM and PDx-Pop v5.2.1 to project concentrations achieved with EID dosing of 10–15 mg/kg/day. Simulations were based on relevant characteristics (e.g., age, weight, eGFR, etc.) of our study population at the start of their tobramycin course and the final PK model estimates. A total of 500 simulations were run for each subject in the study population, generating 29,000 simulated subjects, using two approaches. First, random residual variability was fixed to 0 to allow our simulations to reflect only random between subject PK variability within the population. Second, we included the random residual variability from our population PK model to better reflect variability present within a clinical sample observation context.

(vii) Target attainment. Using the simulation output, we then determined how often simulated subjects met the following a priori goal parameters set forth by the CF Foundation for EID (1): tobramycin peak (Cmax) concentration of \( \geq 25 \) mg/L, tobramycin trough (Cmin) concentration of \( < 0.6 \) mg/L, DFI of \( < 11 \) h, and a 24-h area under the curve (AUC24) of 80–120 mg*h/L. Since increased tobramycin exposure is associated with nephrotoxicity, we further determined the proportion of simulated subjects with an AUC24 > 120 mg*h/L. Target attainment was assessed following the 2nd EID dose in two ways. First, using the simulations with zero residual variability, Cmax, Cmin, and DFI targets were determined directly from the simulated concentrations, while AUC24 was calculated using the equation, AUC24 = daily dose/CL, using each simulated subject’s dose and CL estimates. This equation assumes drug is at steady-state, which we felt was a reasonable assumption for patients receiving EID. This approach is called the “Simulation Output” approach in results below. Second, using the simulations that incorporated residual variability based on assay error from lab quality control runs only (4.3%), we performed log-linear regression on simulated concentrations at 3 and 8 h to calculate AUC24, Cmax, Cmin, and DFI targets. The equations used for this approach are shown in the Supplemental Materials. The log-linear approach is used clinically for TDM at many institutions (15), including ours, so this approach was called the TDM approach. The results of these two methods demonstrate differences between model expectations and clinical calculations in a real-world setting.

SUPPLEMENTAL MATERIAL
Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.5 MB.

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REFERENCES


