The serum pharmacokinetic profile of intravenous (i.v.) tobramycin administration was characterized for a sample of nine adult patients with cystic fibrosis (CF) who were hospitalized for an acute pulmonary exacerbation. Current recommended i.v. tobramycin dosing protocols are predicted through modeling and simulation to be suboptimal. Empirical tobramycin regimens of $\geq 15$ mg/kg of body weight administered i.v. once daily should be evaluated for adult patients with CF to optimize outcomes.
CL, 3.83 (0.58); $K_{12}$, 1.81 (1.88); and $K_{21}$, 1.13 (0.94). With the use of the population mean parameter values as the measure of central tendency, the overall fit of the models to their respective data after the Bayesian step was good ($R^2 = 0.95$), and the plots of predicted versus observed concentrations showed slopes and intercepts very close to the ideal values of 1.0 and 0.0, respectively (see the supplemental material).

The model-predicted median concentration-time profile for each regimen is illustrated in Fig. 1, and central tendency estimates and related dispersions for AUC at 24 h ($AUC_{24}$) and amount of time below the limit of detection are summarized in Table 1. As illustrated in Fig. 1, the highest concentrations are observed at the end of the 1-h infusion, but postdistribution concentrations (2 h from the start of infusion) are expected to be 20 to 40 mg/liter with regimens of 10 to 20 mg/kg once daily. The probabilities of a positive clinical effect are >80% with ≥10 mg/kg once daily against isolates for which the MIC is ≤1 mg/liter and ≥15 mg/kg against isolates for which the MIC is ≤2 mg/liter (Fig. 2). The mean (SD) probability of effect is 71 (5.0) % with a 20-mg/kg once-daily tobramycin dose against isolates for which the MIC is 2 to 4 mg/liter (23), our study found that the daily AUCs with the simulated 20-mg/kg/day regimen are well below the daily AUCs associated with nephrotoxicity with once-daily administration of aminoglycosides (14).

Our population model and predicted exposure profiles for tobramycin are consistent with previous publications that have evaluated this agent in patients with CF across a dosage range of 7 to 15 mg/kg (9, 10, 16–18). These data suggest that empirical tobramycin dosing strategies that are based on 7- to 10-mg/kg regimens lead to exposures that may be optimal for cases where the MIC for the pathogen is ≤1 mg/liter. However, for bacterial pathogens for which the MIC is 2 to 4 mg/liter, which is often the case in patients with CF, tobramycin doses of 15 to 20 mg/kg/day should increase the probability of clinical response. This higher-dosing strategy should also reduce the probability for emergence of resistance at treatment initiation, when the lung bacterial burden is expected to be at its highest (19). Although the suggested consideration of 15- to 20-mg/kg/day doses may be perceived to be high at first glance, it is important to recognize that all adult CF patients are likely to have undetectable trough concentrations, a marker of clinical safety, and the median $T_{\text{bld}}$ was 2.32 to 3.51 h over the 24-h dosing interval (Table 1). The best evidence to date also demonstrates that the daily AUCs with the simulated 20-mg/kg/day regimen are well below the daily AUCs associated with nephrotoxicity with once-daily administration of aminoglycosides (14). Finally, and most importantly, there are data to suggest that administration of 15- to 20-mg/kg/day doses are safe and well tolerated (20, 21). Patients with CF receive repeated courses of tobramycin during their lifetime. The auditory, vestibular, and renal safety levels of these repeated doses, high doses, and cumulative doses (632 to 7,644 mg/kg) have been documented for this population (20, 21). Aminoglycoside-induced nephrotoxicity is reversible in ≥90% of the cases where the aminoglycoside is discontinued (20–22).

In conclusion, we sought to better quantify the PK and PD of tobramycin among adults with CF hospitalized for an APE. Overall, we found that higher weight-based once-daily doses of tobramycin are likely to be necessary in adult patients with CF for pathogens for which the MIC is 2 or 4 mg/liter. Given that tobramycin MICs for *P. aeruginosa* are frequently ≥2 mg/liter (23), our results suggest that a reevaluation of tobramycin treatment guidelines for this patient population is needed. Use of 15- to 20-mg/kg/day regimens for a shorter duration of 5 to 10 days could theoretically improve the probability of effect over toxicity. This suggestion for future study aligns with the recommendations of a

![FIG 1 Model-predicted median serum concentration-time profile for tobramycin administered on a weight basis once daily in patients with cystic fibrosis, with a horizontal reference line at 2 mg/liter.](http://aac.asm.org/)

![FIG 2 Predicted probability of effect with once-daily weight-based tobramycin dosing in patients with cystic fibrosis by MIC.](http://aac.asm.org/)
systematic review to define optimal treatment duration in patients with CF and of thought leaders in the field of drug dose design (19, 24). As with all simulation studies, validation of our findings is critically important given that multidrug-resistant pathogens that can necessitate the use of tobramycin monotherapy are common in patients with CF. As part of the validations, studies should attempt to delineate the tobramycin targets for efficacy and toxicity since these targets have not been described for patients with CF.

REFERENCES