AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Bayesian Estimation of Tobramycin Exposure in Patients with Cystic Fibrosis

Michael A. Barras,[a,b*] David Serisier,[c] Stefanie Hennig,[b] Katrina Jess,[c] Ross L. G. Norris[a,b*]

Pharmacy Department, Mater Health Services, South Brisbane, Queensland, Australia[a]; School of Pharmacy, The University of Queensland, Woolloongabba, Queensland, Australia[b]; Respiratory Department, Mater Health Services, South Brisbane, Queensland, Australia[c]

Fixed tobramycin (mg/kg) dosing is often inappropriate in patients with cystic fibrosis (CF), as pharmacokinetics are highly variable. The area under the concentration-time curve (AUC) is an exposure metric suited to monitoring in this population. Bayesian strategies to estimate AUC have been available for over 20 years but are not standard practice in the clinical setting. To assess their suitability for use in clinical practice, three AUC estimation methods using limited sampling were compared to measured true exposure by using intensive sampling tobramycin data. Adults prescribed once daily intravenous tobramycin had eight concentrations taken over 24 h. An estimate of true exposure within one dosing interval was calculated using the trapezoidal method and compared to three alternate estimates determined using (i) a two-sample log-linear regression (LLR) method (local hospital practice); (ii) a Bayesian estimate using one concentration (AUC_1); and (iii) a Bayesian estimate using two concentrations (AUC_2). Each method was evaluated against the true measured exposure by a Bland-Altman analysis. Twelve patients with a median (range) age and weight of 25 (18 to 36) years and 66.5 (51 to 76) kg, respectively, were recruited. There was good agreement between the true exposure and the three alternate estimates of AUC, with a mean AUC bias of <10 mg/liter · h in each case, i.e., −8.2 (LLR), 3.8 (AUC_1), and 1.0 (AUC_2). Bayesian analysis-based and LLR estimation methods of tobramycin AUC are equivalent to true exposure estimation. All three methods may be suitable for use in the clinical setting; however, a one-sample Bayesian method may be most useful in ambulatory patients for which coordinating blood samples is difficult. Suitably powered, randomized clinical trials are required to assess patient outcomes.

Approximately 70,000 patients worldwide have cystic fibrosis (CF) (1), and it is the most common life-threatening genetic disorder. The mortality and morbidity in CF patients are often attributed to *Pseudomonas aeruginosa*-induced pulmonary exacerbations for which intravenous (i.v.) and inhaled antibiotics are used to prevent and treat recurrence (2, 3).

Intravenous tobramycin, an aminoglycoside antibiotic, is a mainstay in the treatment of *Pseudomonas* infection in patients with CF (1, 4). Tobramycin is most commonly administered as a daily i.v. injection in doses ranging from 7 to 15 mg/kg of body weight per day (1, 4, 5). The bactericidal actions of tobramycin are directly linked to drug exposure; however, dosing is complicated, as exposure must be maintained within a narrow therapeutic range (TR) (4–6). Exposures above the TR increase the risk of nephrotoxicity (1) and ototoxicity, of which the latter can be irreversible (1, 7). Exposures below the TR can lead to therapeutic failure, increased antibiotic resistance, and poor patient outcomes (2, 3). To help ensure optimal therapy, a therapeutic exposure must be achieved as quickly as possible (8, 9), preferably after the first dose of a treatment course, which can last up to 14 days (10).

Unfortunately, in CF patients, tobramycin has high between-subject variability in its pharmacokinetic (PK) parameters, such as clearance (CL) and volume of distribution (V) (11, 12). Serum tobramycin concentrations are used to estimate exposure after a given dose, often by the area under the concentration-time curve (AUC). There is consensus that therapeutic drug monitoring (TDM) should be conducted as part of standard practice (1, 4). A target used to assess efficacy for aminoglycosides is the AUC/MIC ratio (13) with an acceptable target range of 70 to 100 mg/liter · h (14, 15), assuming an MIC of 1.

Locally, clinical pharmacists perform tobramycin monitoring and estimate an AUC for dose adjustment by using two blood concentrations and the log-linear regression (LLR) method. However, from a practical point of view, the collection of two blood samples is difficult and time-consuming to coordinate, especially in an outpatient setting, where patients are administered the antibiotic in hospital and are able to leave between blood tests. However, they often fail to present for their second blood sample at the correct time. Bayesian analysis-based software can be used to estimate AUC (16) and has the potential to be more accurate than conventional methods and to allow the collection of samples at unrestricted, patient-preferred times (17).

Bayesian analysis-based programs use embedded population PK models (16–18). The user can input known patient demographics (age, sex, weight, renal function) to allow the estimation of a concentration-time curve based on the population model. As tobramycin concentration data are obtained, these, along with dosing details, can be input to estimate patient-specific PK parameters, which can be used to estimate an exposure metric such as an AUC, maximum concentration (C_{max}), or minimum concentration (C_{min}). Given these individualized values, dosing and moni-

Received 26 May 2016 **Returned for modification** 26 June 2016
Accepted 20 August 2016

Accepted manuscript posted online 29 August 2016

Citation Barras MA, Serisier D, Hennig S, Jess K, Norris RLG. 2016. Bayesian estimation of tobramycin exposure in patients with cystic fibrosis. Antimicrob Agents Chemother 60:6698–6702. doi:10.1128/AAC.01131-16.

Address correspondence to Michael A. Barras, michael.barras@health.qld.gov.au.

* Present address: Michael A. Barras, Pharmacy Department, Royal Brisbane & Women's Hospital, Brisbane, Queensland, Australia; Ross L. G. Norris, Department of Clinical Pharmacology, St. Vincent's Hospital, Sydney, Australia.

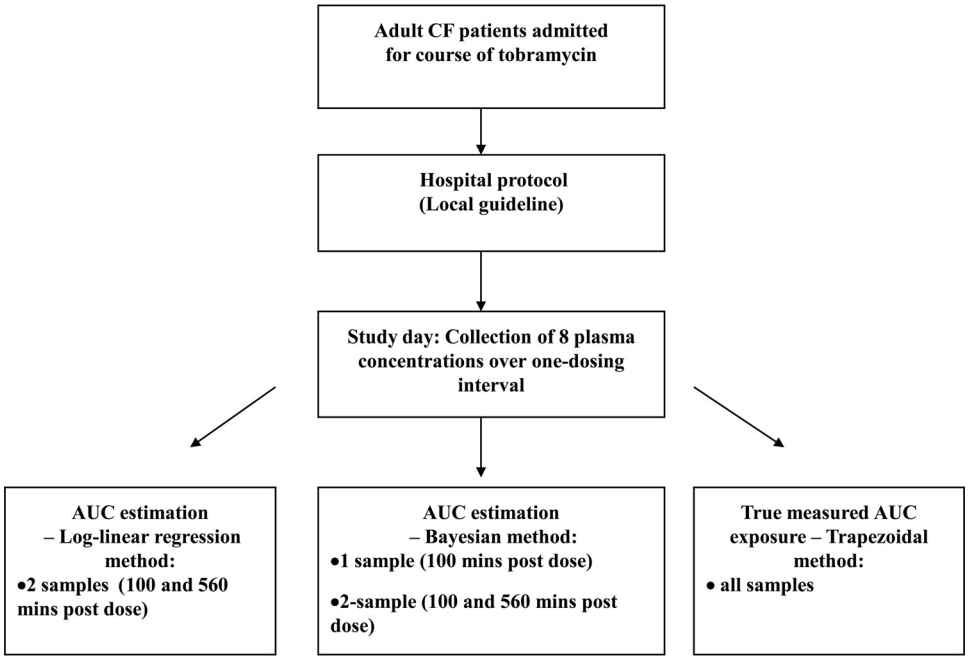

FIG 1 Study flow chart. AUC, area under the concentration-time curve (mg/liter · h); CF, cystic fibrosis.

toring strategies can be personalized in a dynamic way. As subsequent patient data and tobramycin concentrations are collected, further individualization can occur, potentially with the use of only one concentration (17, 19, 20).

The aim of this study was to evaluate three AUC estimation methods by comparison to true measured exposure, calculated using intensive sampling data, in adult CF patients to assess their suitability for use in clinical practice.

MATERIALS AND METHODS

Figure 1 shows the flow chart for recruitment and data analysis. Data were collected from adult CF patients admitted as inpatients to the Mater Health Service (MHS) Respiratory Unit, Brisbane, Australia, over a 3-month period. On admission, tobramycin was administered as a once daily infusion over 30 min, per hospital protocol. This dose was either 10 mg/kg, based on total body weight, or a dose equivalent to the last dose that was prescribed during the previous admission.

Patients were treated using local dosing and monitoring methods until a suitable day was organized for the patient to participate in a rich sampling protocol. This occurred only after the patient had attained a therapeutic AUC as required by the treating physician, commonly between 70 and 100 mg/liter · h. At the MHS, patients do not have to remain in hospital while on their 10- to 14-day course of i.v. tobramycin and return only for daily dose administration or blood sampling. Local hospital practice is to collect two serum tobramycin concentrations from each patient within one dosing interval: the first is collected 1 to 1.5 h after the commencement of the infusion, and the second is collected at 8 to 12 h after commencement of the infusion. An AUC from 0 to 24 h (AUC_{0-24}) is estimated using an LLR method (21) embedded in a Microsoft Excel-based program, and the dose is adjusted to the TR if necessary.

For this study, a rich sampling strategy was implemented following a morning dose, with eight serum drug concentrations taken over the 24-h dosing interval, i.e., a predose sample and an additional seven samples at 50, 70, 100, 160, 280, 520, and 640 min after the start of infusion (30-min duration) to enable calculation of true tobramycin exposure (AUC_{0-24}) after this dose.

Comparison of AUC estimation methods. AUCs were estimated using four methods (Fig. 1): calculation of a true exposure by use of the traditional trapezoidal method (linear-up log-down) (22), a Bayesian method with either one serum drug concentration (AUC_1) or two serum drug concentrations (AUC_2), and the local hospital method utilizing the LLR method (21). It has been postulated that Bayesian software does not require a minimum number of concentrations to calculate an AUC (20); therefore, an AUC was calculated using one concentration, taken at 520 min postdose. In addition, a two-sample AUC was calculated using concentrations taken at 100 and 520 min postdose. The times were chosen as they match those used at the hospital to estimate an LLR AUC (local method). Previous reports have demonstrated that no additional reliability in the estimation of concentrations is gained by sampling beyond 6 h postdose (11, 19); however, the concentration at 520 min would not compromise the estimation of the AUC and matches local practice. All AUC calculations used the sampling data from the same dosing interval, and no Bayesian optimization using previous patient data occurred before the study day for this study.

Demographic data were summarized using standard statistics. Bland-Altman difference plots were used to compare the AUC of each method to the true AUC (trapezoidal). The mean difference (bias) and upper and lower limits of agreement (95% confidence interval [CI]) were calculated and plotted. The percentage change in bias was reported. Statistical difference was considered at a P value of <0.05 (Tukey's test).

Ethics approval was obtained from the MHS Human Research Ethics Committee. The software TDMx (23) was used for the Bayesian analyses, embedded with the population PK model described by Hennig et al. (6). All statistical and graphical analyses were performed using the software Prism (version 7).

RESULTS

Data were collected from 12 patients with CF. Table 1 shows the demographics of the population. The medians (ranges) for age, weight, and tobramycin dose of the population were 25 (18 to 36) years, 66.5 (51 to 76) kg, and 400 (320 to 640) mg, respectively.

TABLE 1 Patient demographics

Demographic	No. or median (range)
Age, yr	25 (18–36)
Weight, kg	66.5 (51–76)
Height, cm	170 (154–185)
Gender	
Male	7
Female	5
Serum creatinine, μmol/liter	73 (55–92)
Dose at study day, mg	400 (320–640)
Dose, mg/kg	6.3 (5.2–8.4)
Day of therapy for sampling	6 (4–7)

The estimated AUC values using the four methods for each of the 12 patients are shown in Table 2.

The Bland-Altman plots are shown in Fig. 2a to c, and a summary of the bias, percent change in bias, and limits of agreement (95% CIs) between the true exposure and the results of the three estimation methods is shown in Table 3. There was no significant difference in bias relative to the mean of the true measured exposure for any of the three AUC methods, with the mean AUC bias less than 10 mg/liter · h in each case. The AUC_2 method was the least biased. There was a wide range between the lower and upper limits of agreement for all methods; however, the AUC_2 method, with a range of 24.9 mg/liter · h, was the most preferred (change in bias, 1.03%).

When the two Bayesian methods are compared, Fig. 2 shows that the AUC_2 method performs better than AUC_1 method when patient results are farther away from the population average. This is expected, as the Bayesian software will use the prior model rather than the actual data to optimize model parameters. Generally, these results indicate that when estimating a tobramycin AUC, it would be reasonable to use all three methods.

DISCUSSION

Pseudomonas aeruginosa is the most common bacterium to infect the lungs of individuals with CF (1), and tobramycin, given i.v. once daily, is a first-line antibiotic to treat and prevent infection (1, 4, 5, 24). However, the TR for tobramycin is often difficult to achieve with standard dosing and monitoring methods (11, 17, 25), which is hazardous, as toxicity is linked to severe adverse effects such as irreversible nephrotoxicity and ototoxicity (7, 26, 27). CF patients generally require large doses of tobramycin, often for extended periods of time (10 to 14 days), which can increase the risk of toxicities (7, 26, 27). In addition, patients may attend

TABLE 2 Tobramycin AUC by method[a]

Patient	AUC (mg/liter · h) by:			
	Trapezoidal method	LLR method, 2 samples	Bayesian method, 1 sample (AUC_1)	Bayesian method, 2 samples (AUC_2)
1	88.9	104.6	86.8	92.9
2	94.9	100.3	107.6	105.3
3	71.9	92.4	76.1	73.3
4	79.3	97.1	68.7	70.5
5	79.8	74.9	69.0	78.6
6	81.5	88.1	74.6	78.4
7	71.9	97.6	65.2	70.0
8	102.4	111.2	87.9	99.4
9	102.8	92.4	87.8	91.4
10	62.7	59.4	56.1	55.3
11	77.6	87.1	77.6	80.3
12	51.1	57.8	61.4	57.1

[a] AUC, area under the concentration-time curve; AUC_1, sampling at 520 min postdose; AUC_2, sampling at 100 and 520 min; LLR, log-linear regression; trapezoidal method, true exposure calculated using the linear-up log-down trapezoidal method.

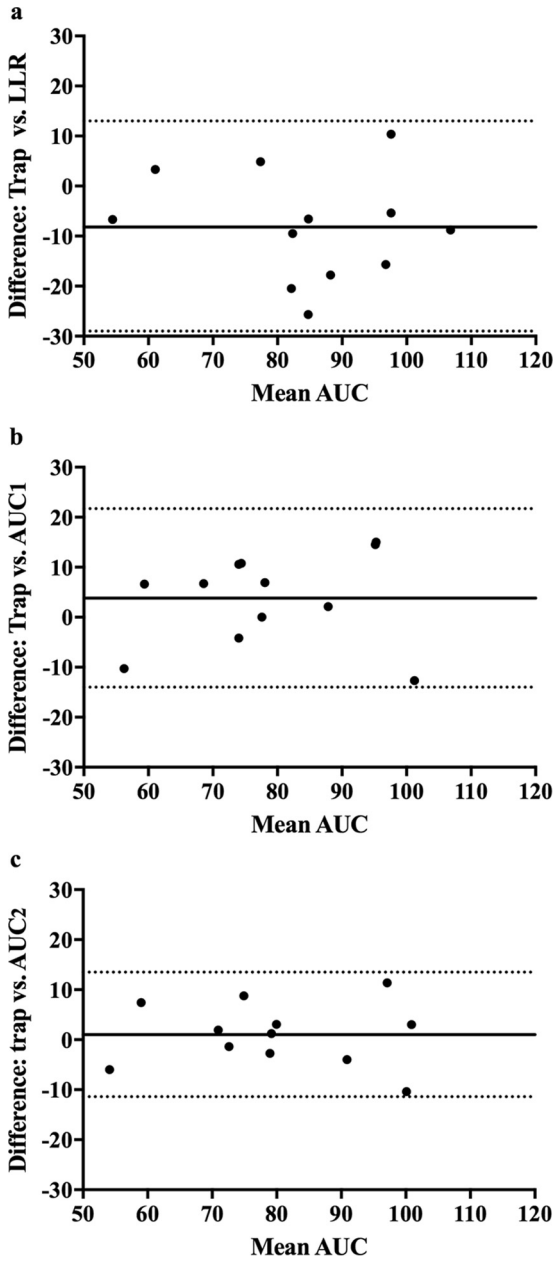

FIG 2 Bland-Altman plots with mean difference (solid lines) and upper and lower limits of agreement (95% confidence intervals) (dashed lines). (a) Trapezoidal method versus LLR method; (b) trapezoidal method versus AUC_1 method; (c) trapezoidal method versus AUC_2 method. AUC, area under the concentration-time curve (mg/liter · h); trap, calculation of the true exposure (AUC) via the trapezoidal method; LLR, log-linear regression method. The Bayesian method used one serum concentration (AUC_1) or two serum concentrations (AUC_2).

TABLE 3 Summary of bias and limits of agreement (95% confidence intervals) from Bland-Altman analysis[a]

Methods of AUC estimation	Mean difference (bias) (% change in bias)	SD	Upper 95% limit	Lower 95% limit	Range
Trap vs LLR	−8.2 (10.5)	11.0	13.0	−29.0	42.0
Trap vs AUC_1	3.8 (3.9)	9.1	21.7	−14.0	35.7
Trap vs AUC_2	1.0 (1.03)	6.3	13.5	−11.4	22.9

[a] Except for % change in bias, all values are in mg/liter · h. Trap, calculation of the true exposure (AUC) via the trapezoidal method; LLR, log-linear regression method; AUC_1 and AUC_2, Bayesian method using one and two serum concentrations, respectively.

hospital at regular intervals, during which i.v. tobramycin may be administered to reduce the *Pseudomonas* inoculum and prevent further acute exacerbations. There is ongoing concern about toxicity due to the repetitive nature of tobramycin exposure (4).

Bayesian methods have been used in the TDM of drugs for over 20 years; however, they are still not a commonly used strategy in the clinical setting, in particular in Australia and the United Kingdom (16, 28, 29). This may be attributed to a lack of one or more of the following: the availability of licensed software, the availability of skilled users, an understanding of Bayesian principles, and validation in a clinical setting. Certainly, local clinicians have expressed the lack of validation in a clinical setting. Bayesian monitoring methods have gained importance in the CF population due to the narrow TR and the sufficient unexplained interpatient variability and low intrapatient variability in PK parameters (and response) (11). In addition, tobramycin distribution may be better described using two-compartmental PK (30). As such, fixed-dosing, traditional nomograms (31) and PK software that use noncompartmental models should be used with caution if only one or two serum concentrations are available (17).

As the use of the AUC method for monitoring tobramycin exposure is growing (4, 14), a number of dose prediction software programs are available (16–18, 31). However, they can be unpalatable, as they often lack networking capabilities, use databases that are not compatible with hospitals' information technology (IT) systems, or have little readily accessible IT support. The new Bayesian method-based software used in this analysis can be accessed from the Internet (http://www.tdmx.eu/Resources/) free of charge.

Our study has shown that the Bayesian estimation of AUC is similar to the local method using LLR with two concentrations. Other studies have shown the superiority of Bayesian dosing and monitoring methods over traditional methods for aminoglycoside exposure estimation (17, 18, 25). Recently, Hennig et al. (17), compared Bayesian estimation to LLR and nomogram methods for the dosage adjustment of tobramycin in children with CF. The LLR method and Bayesian forecasting methods showed negligible bias but imprecision of 20% in predicting subsequent observed concentrations. The Bayesian methods were recommended as the first line for dose adjustment. However, this study had no measure of total exposure for comparison. Our study is the first in which true tobramycin exposure was used as a comparator and allows a robust evaluation of Bayesian methods.

Learning about the patient is the strength of a Bayesian approach. The clinician gains a better knowledge of each patient's true PK response; i.e., the clinician "learns" about the patient, the true benefit of a Bayesian system. This is in contrast to the local LLR method, which assumes a one-compartment PK model for tobramycin. As no prior PK parameters are included, two blood concentrations are required at every monitoring occasion.

The practical difficulties when using LLR for tobramycin TDM is that patients and phlebotomy staff have to present on two occasions for blood collection, which is often difficult to coordinate. As a consequence, pathology results are seldom available during work hours, which is problematic for medical and pharmacy staff. Dose individualization may be compromised, which delays the time to TR and thus increases the risk of unwanted patient outcomes. In addition, regular dose adjustments result in further blood sampling, which is costly to the hospital and cumbersome for staff and patients. A one-concentration AUC means that patients are not required to remain as inpatients and adds to the argument of the cost-effectiveness of a coordinated TDM approach (32).

Finally, as intrapatient variability is low in CF patients (33), an accurate estimation of a patient's PK parameters after one hospital stay aids dose selection in the future. Currently, a 10-mg/kg fixed dose is often administered to patients on admission. Our results suggest that an ideal method for monitoring would be to use a two-sample method for the first dosing interval, which allows optimization of the patient's PK parameters, and then a one-sample method thereafter. A prospective evaluation of this hypothesis is required.

There are limitations to our study, notably with the generalizability of results. We had a small sample size ($n = 12$), limited by funding and time; however, this prospective study provides important data to design adequately powered investigations. A large comparative study may allow the investigation of relevant patient outcomes, such as disease progression, lung function, time to exacerbation, and drug toxicity (nephrotoxicity or ototoxicity). Unfortunately, few data exist demonstrating the benefits of a Bayesian dosing and monitoring approach using tobramycin for clinical outcomes, and we cannot make clinical assumptions using a small sample. Finally, the population PK model embedded in the software was developed from patients with CF and therefore should be used only in this population.

Conclusion. An AUC approach for the dosing and monitoring of tobramycin is advocated practice in CF populations. Both Bayesian and LLR estimation methods of tobramycin AUC are equivalent to a true exposure estimate. However, Bayesian estimation using a single serum concentration may be a more practical method. Suitably powered, randomized clinical trials are required to assess patient outcomes.

ACKNOWLEDGMENTS

Financial support from a JP Kelly research grant, Mater Health Services (MHS), is gratefully acknowledged. We acknowledge the support of the staff of the MHS Pharmacy Department and the medical and nursing staff of the MHS Adult Respiratory Unit. In addition, we thank Peter O'Rourke and the staff of the Statistics Department of the Queensland Institute of Medical Research for their assistance with data analysis.

This paper is in memory of coauthor David Serisier, who tragically died during the data analysis phase of this research. We were all in awe of his outstanding skills as a clinician and researcher. He will be sadly missed.

REFERENCES

1. **Ratjen F, Brockhaus F, Angyalosi G.** 2009. Aminoglycoside therapy against Pseudomonas aeruginosa in cystic fibrosis: a review. J Cyst Fibros **8**:361–369. http://dx.doi.org/10.1016/j.jcf.2009.08.004.

2. **Cohen-Cymberknoh M, Shoseyov D, Kerem E.** 2011. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. Am J Respir Crit Care Med **183:**1463–1471. http://dx.doi.org/10.1164/rccm.201009-1478CI.
3. **Ratjen F, McColley SA.** 2012. Update in cystic fibrosis 2011. Am J Respir Crit Care Med **185:**933–936. http://dx.doi.org/10.1164/rccm.201202-0306UP.
4. **Prayle A, Smyth A.** 2010. Aminoglycoside use in cystic fibrosis: therapeutic strategies and toxicity. Curr Opin Pulm Med **16:**604–610. http://dx.doi.org/10.1097/MCP.0b013e32833eebfd.
5. **Prescott W, Nagel J.** 2010. Extended-interval once daily dosing of aminoglycosides in adult and pediatric patients with cystic fibrosis. Pharmacotherapy **30:**95–108. http://dx.doi.org/10.1592/phco.30.1.95.
6. **Hennig S, Standing JF, Staatz CE, Thomson AH.** 2013. Population pharmacokinetics of tobramycin in patients with and without cystic fibrosis. Clin Pharmacokinet **52:**289–301. http://dx.doi.org/10.1007/s40262-013-0036-y.
7. **Mulheran M, Degg C, Burr S, Morgan D, Stableforth D.** 2001. Occurrence and risk of cochleotoxicity in cystic fibrosis patients receiving repeated high-dose aminoglycoside therapy. Antimicrob Agents Chemother **45:**2502–2509. http://dx.doi.org/10.1128/AAC.45.9.2502-2509.2001.
8. **DeGrado JR, Cios D, Greenwood BC, Kubiak DW, Szumita PM.** 2014. Pharmacodynamic target attainment with high-dose extended-interval tobramycin therapy in patients with cystic fibrosis. J Chemother **26:**101–104. http://dx.doi.org/10.1179/1973947813Y.0000000107.
9. **Martinez MN, Papich MG, Drusano GL.** 2012. Dosing regimen matters: the importance of early intervention and rapid attainment of the pharmacokinetic/pharmacodynamic target. Antimicrob Agents Chemother **56:**2795–2805. http://dx.doi.org/10.1128/AAC.05360-11.
10. **Plummer A, Wildman M.** 2013. Duration of intravenous antibiotic therapy in people with cystic fibrosis. Cochrane Database Syst Rev **5:**CD006682.
11. **Hennig S, Norris R, Kirkpatrick CM.** 2008. Target concentration intervention is needed for tobramycin dosing in paediatric patients with cystic fibrosis—a population pharmacokinetic study. Br J Clin Pharmacol **65:**502–510. http://dx.doi.org/10.1111/j.1365-2125.2007.03045.x.
12. **Matthews I, Kirkpatrick C, Holford N.** 2004. Quantitative justification for target concentration intervention—parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. Br J Clin Pharmacol **58:**8–19. http://dx.doi.org/10.1111/j.1365-2125.2004.02114.x.
13. **Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A.** 2007. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis **45:**753–760. http://dx.doi.org/10.1086/520991.
14. **Soulsby N, Bell S, Greville H, Doecke C.** 2009. Intravenous aminoglycoside usage and monitoring of patients with cystic fibrosis in Australia. What's new? Intern Med J **39:**527–531. http://dx.doi.org/10.1111/j.1445-5994.2008.01787.x.
15. **Kirkpatrick CM, Duffull SB, Begg EJ.** 1999. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. Br J Clin Pharmacol **47:**637–643.
16. **Avent ML, Rogers BA, Cheng AC, Paterson DL.** 2011. Current use of aminoglycosides: indications, pharmacokinetics and monitoring for toxicity. Intern Med J **41:**441–449. http://dx.doi.org/10.1111/j.1445-5994.2011.02452.x.
17. **Hennig S, Holthouse F, Staatz CE.** 2015. Comparing dosage adjustment methods for once-daily tobramycin in paediatric and adolescent patients with cystic fibrosis. Clin Pharmacokinet **54:**409–421. http://dx.doi.org/10.1007/s40262-014-0211-9.
18. **Duffull SB, Kirkpatrick CM, Begg EJ.** 1997. Comparison of two Bayesian approaches to dose-individualization for once-daily aminoglycoside regimens. Br J Clin Pharmacol **43:**125–135.
19. **Massie J, Cranswick N.** 2006. Pharmacokinetic profile of once daily intravenous tobramycin in children with cystic fibrosis. J Paediatr Child Health **42:**601–605. http://dx.doi.org/10.1111/j.1440-1754.2006.00944.x.
20. **Barras M, Alraman H, Kirkpatrick C, Harris M, Dakin C, Jess K, Pilbeam M, Norris R.** 2011. Bayesian optimisation of tobramycin dosing in paediatric patients with cystic fibrosis. J Pharm Pract Res **41:**183–187. http://dx.doi.org/10.1002/j.2055-2335.2011.tb00857.x.
21. **Begg EJ, Barclay ML, Duffull SB.** 1995. A suggested approach to once-daily aminoglycoside dosing. Br J Clin Pharmacol **39:**605–609. http://dx.doi.org/10.1111/j.1365-2125.1995.tb05719.x.
22. **Riviere JE.** 2011. Comparative pharmacokinetics. Principles, techniques and application, 2nd ed. Wiley-Blackwell, Chichester, United Kingdom.
23. **Wicha SG, Kees MG, Solms A, Minichmayr IK, Kratzer A, Kloft C.** 2015. TDMx: a novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine. Int J Antimicrob Agents **45:**442–444. http://dx.doi.org/10.1016/j.ijantimicag.2014.12.010.
24. **Doring G, Conway S, Heijerman H, Hodson M, Hoiby N, Smyth A, Touw D.** 2000. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. Eur Respir J **16:**749–767. http://dx.doi.org/10.1034/j.1399-3003.2000.16d30.x.
25. **Avent ML, Teoh J, Lees J, Eckert KA, Kirkpatrick CM.** 2011. Comparing 3 methods of monitoring gentamicin concentrations in patients with febrile neutropenia. Ther Drug Monit **33:**592–601. http://dx.doi.org/10.1097/FTD.0b013e31822c78e9.
26. **Al-Aloul M, Miller H, Alapati S, Stockton P, Ledson M, Walshaw M.** 2005. Renal impairment in cystic fibrosis patients due to repeated intravenous aminoglycoside use. Pediatr Pulmonol **39:**15–20. http://dx.doi.org/10.1002/ppul.20138.
27. **Bertenshaw C, Watson A, Lewis S, Smyth A.** 2007. Survey of acute renal failure with cystic fibrosis in the UK. Thorax **62:**541–545. http://dx.doi.org/10.1136/thx.2006.067595.
28. **Norris RL, Martin JH, Thompson E, Ray JE, Fullinfaw RO, Joyce D, Barras M, Jones GR, Morris RG.** 2010. Current status of therapeutic drug monitoring in Australia and New Zealand: a need for improved assay evaluation, best practice guidelines, and professional development. Ther Drug Monit **32:**615–623. http://dx.doi.org/10.1097/FTD.0b013e3181ea3e8a.
29. **Paviour P, Hennig S, Staatz CE.** 2016. Usage and monitoring of intravenous tobramycin in cystic fibrosis in Australia and the UK. J Pharm Pract Res **46:**15–21. http://dx.doi.org/10.1002/jppr.1145.
30. **Bloomfield C, Staatz CE, Unwin S, Hennig S.** 2016. Assessing predictive performance of published population pharmacokinetic models of intravenous tobramycin in pediatric patients. Antimicrob Agents Chemother **60:**3407–3414. http://dx.doi.org/10.1128/AAC.02654-15.
31. **Mohan M, Batty K, Cooper J, Wojnar-Horton R, Ilett K.** 2004. Comparison of gentamicin dose estimates derived from manual calculations, the Australian 'Therapeutic Guidelines: Antibiotic' nomogram and the SeBA-GEN and DoseCalc software programs. Br J Clin Pharmacol **58:**521–527. http://dx.doi.org/10.1111/j.1365-2125.2004.02201.x.
32. **Touw DJ, Neef C, Thomson AH, Vinks AA, Cost-Effectiveness of Therapeutic Drug Monitoring Committee of the International Association for Therapeutic Drug Monitoring and Clinical Toxicology.** 2005. Cost-effectiveness of therapeutic drug monitoring: a systematic review. Ther Drug Monit **27:**10–17. http://dx.doi.org/10.1097/00007691-200502000-00004.
33. **Alghanem S, Paterson I, Touw DJ, Thomson AH.** 2013. Influence of multiple courses of therapy on aminoglycoside clearance in adult patients with cystic fibrosis. J Antimicrob Chemother **68:**1338–1347. http://dx.doi.org/10.1093/jac/dkt035.