Tobramycin Therapeutic Drug Monitoring in Adult patients with Cystic Fibrosis: Clinical-Based Empiric Dosing versus Model-Informed Precision Dosing

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Research Article

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Tobramycin Therapeutic Drug Monitoring in Adult patients with Cystic Fibrosis: Clinical-Based Empiric Dosing versus Model-Informed Precision Dosing

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ABSTRACT

Background:
To inform rational dosing of antibiotics, traditional Therapeutic Drug Monitoring (TDM) with empiric dose adjustment of has been increasingly supplanted by the use of Model-Informed Precision Dosing (MIPD) software.
Our objective was to evaluate a model-informed precision dosing approach specifically designed to individualize empiric tobramycin dosing in adults with cystic fibrosis, and to compare target attainment between both the model-based and the empiric dosing approaches.

Methods:
The BestDose MIPD-software has been used with a published population pharmacokinetic model of tobramycin. To evaluate the MIPD strategy, we used retrospective data from CF adults treated with tobramycin at our local CF center. Empiric dose adjustments from the clinical staff were examined.
Using a simulation-based methodology, individualized tobramycin doses that maximize the probability of attaining a Cmax/MIC ratio of 32 mg/L were retrospectively calculated, and compared with empiric dose adjustments.

Results:
Overall, 101 CF adults were evaluated. Tobramycin Cmax in patients were low (mean of 25.7 ± 5.6 mg/L). The percentage of patients predicted to achieve a Cmax/MIC of ≥ 32 mg/L was low (12.0 %, mean dose of 8.8 ± 1.3 mg/kg) with empiric dose adjustment. TDM with retrospective PK/PD modelling suggest increasing tobramycin dosing in a much larger number of patients (88.0 %, mean dose of 11.6 ± 2.5 mg/kg).

Conclusions:
Tobramycin doses empirically corrected by clinicians after TDM were predicted to be still insufficient to achieve the efficacy target in most CF patients. Meanwhile a model-based dosing approach that individualizes the tobramycin dosing led to significantly improved achievement of expected target exposure levels in CF adults. Prospective clinical evaluation is warranted.

RUNNING TITLE

Tobramycin TDM: Empiric Dosing vs MIPD

KEYWORDS

- Pharmacokinetics (PK)
- Therapeutic Drug Monitoring (TDM)
- Antibiotic therapy optimization
- Bayesian forecasting (BF)
- Model-based adaptive dosing
- Precision medicine

HIGHLIGHTS

- Our study highlighted that maximal concentrations of tobramycin in adult patients with cystic fibrosis were low, given the prespecified PK/PD target.
- Empirically adjusted doses by clinicians after TDM appeared to be still insufficient to achieve this PK/PD target in most patients.
- Larger doses guided by MIPD could increase Cmax/MIC target attainment without significant overexposure.

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1. INTRODUCTION

Tobramycin is a bactericidal concentration-dependent antibiotic widely used for treatment of pulmonary exacerbations in patients with cystic fibrosis (CF) (Flume et al., 2009; Smyth et al., 2014). In these patients, tobramycin is commonly used as first-line treatment of *Pseudomonas aeruginosa* infections, in combination with a beta-lactam. Tobramycin has a narrow therapeutic margin and its pharmacokinetics is prone to large between-subject variability (Akkerman-Nijland et al., 2021). Tobramycin exposure is a determinant of both antimicrobial effect and nephrotoxicity (Prayle et al., 2010).

- A widely accepted pharmacokinetics/pharmacodynamics (PK/PD) target for tobramycin is a peak serum concentration (Cmax) to minimum inhibitory concentration (MIC) ratio of 8 – 10 (Abdul-Aziz et al., 2020; Bland et al., 2018; Drusano et al., 2007).
- Another PK/PD target for tobramycin is the 24h-area under the curve (AUC_{24}) to the MIC ratio. Target values of 30 to 100 have been suggested (Burkhardt et al., 2006; Mouton et al., 2005; Smith et al., 2001).
- Trough concentrations (Cmin) of aminoglycosides have been reported as surrogate markers to minimize ototoxicity and nephrotoxicity (Abdul-Aziz et al., 2020). Two Cmin target values have been suggested for tobramycin : < 0.5 mg/L (Agence française de sécurité sanitaire des produits de santé, 2011) and < 1 mg/L (Abdul-Aziz et al., 2020).

The small therapeutic range, the large between-subject variability, and the predefined concentration-effect relationships are justifications for therapeutic drug monitoring (TDM) of tobramycin.

Since two PK/PD targets have been assessed for tobramycin efficacy, one can assess discrepancies within and between countries about the efficacy surrogate used for tobramycin TDM. Some recent TDM guidelines have recommended the use of both targets (Abdul-Aziz et al., 2020). In a previous study with children, we showed that the Cmax/MIC and the AUC_{24}/MIC targets were not interchangeable and may be associated with discrepancies in dosage requirements (Praet et al., 2021). Moreover, further discrepancies within and between countries remain about the method used for tobramycin TDM. Historically, evidence has suggested that optimizing the ratio of aminoglycoside Cmax/MIC of the infecting organism is best correlated with efficacy (Kashuba et al., 1999; Moore et al., 1987). One must bear in mind that this data is derived from patients without CF. To this end, high-dose extended-interval dosing maximizes the Cmax/MIC ratio concentration-dependent killing (Flume et al., 2009; Ochs et al., 2021). As MIC result is not often available on time, the sole Cmax is a common target considered (Zobell et al., 2016). According to Prescott about the dosing practices in United States, tobramycin peak serum concentration of 25–30 mg/L and a trough value of < 1 mg/L were the most frequent targets (Prescott, 2014). Drusano et al. pointed out that the ratio of AUC_{24}/MIC may be a superior predictor of activity with extended-interval dosing of aminoglycosides (Drusano et al., 2007). The AUC_{24}/MIC index tends to rather be considered in Anglo-Saxon countries. For example, the Australian Therapeutic Guidelines recommend to use AUC-based computerized TDM methods (Avent, Rogers, et al., 2011). But one must remember that MIC testing is often not performed in clinical care, or available several days after start of treatment. Paviour et al. (survey of 73 CF centers) reported that less than 20% of Australian and UK CF centers considered tobramycin MIC for its TDM. Therefore, AUC_{24} alone is routinely utilized to guide dose individualization for tobramycin with CF (Brockmeyer et al., 2020; Paviour et al., 2016). Begg et al. suggested to achieve an AUC between 80 and 100 $mg.l.h^{-1}$ for adult patients (Begg et al., 1995). Finally, as last example of tobramycin TDM heterogeneity, the UK guidelines recommand the sole Cmin monitoring for once-daily tobramycin dosing (« UK Cystic Fibrosis Trust Antibiotic Group. Antibiotic treatment for cystic fibrosis. 3rd ed. London. », 2009).

Conventional TDM of aminoglycosides can be supported by the use of dosing nomograms or log-linear regression (LLR) (Paviour et al., 2016), which allow straightforward adjustment of the dosing interval

with timed drug concentration samples. But these methods are limited as they cannot readily incorporate covariates affecting PK parameters and can be misleading to overexposure or underexposure (Avent, Teoh, et al., 2011). While the LLR approach is limited by its sensitivity to the precise timing of the underlying drug concentrations, the Bayesian forecasting (BF) approach can overcome this sensitivity limitation (Barras et al., 2016). The BF approach applies a population PK model as Bayesian prior and integrates patient's information (drug concentrations and covariates such as age, weight, renal function) to predict the individual pharmacokinetics of a patient, which are then used to estimate AUC_{24} values. The use of Bayesian dosing software to assist aminoglycoside dosing, responding to the concept known as model-informed precision dosing (Darwich et al., 2017; Wicha et al., 2021), was found to be more precise for the estimation of the AUC_{24} (Avent, Teoh, et al., 2011; Gao et al., 2019). Dosage adjustment based on Bayesian forecasting is endorsed as the most sophisticated approach.

Still to this day, when tobramycin concentrations are available, dose adjustment is most often empirically performed by clinicians, with increase or decrease in the drug dose to correct for under- or overexposure, respectively. However, the ability of empiric dose adjustment to achieve concentration targets has not been thoroughly assessed. Aminoglycoside regimens that are tailored to each patient with the use of drug concentrations and PK-guided dosing have been shown to shorten length of hospital stay (Burton et al., 1991; Destache et al., 1990; van Lent-Evers et al., 1999) and to improve survival rates (Bootman et al., 1979; Whipple et al., 1991) without increasing nephrotoxicity. Performing computerized TDM with the assistance of PK software programs and Bayesian forecasting has proven to be useful in the past (de Velde et al., 2018). To illustrate, when the therapeutic target is not just a concentration but e.g. an AUC, manual dosing recommendation appears precarious. The more robust approach to individualize dosing by TDM is the maximum *a posteriori* (MAP) probability Bayesian fitting procedure. Bayesian forecasting methods use *a priori* pharmacokinetic parameters from a suitable population model and current concentration observations to estimate each patient's pharmacokinetic parameters and drug exposure (Burton et al., 1985, 1991; Hennig et al., 2015). This model-informed precision dosing (MIPD) approach described by Jelliffe et al. (Jelliffe et al., 1998) is implemented in various TDM software programs (Abdulla et al., 2021; Jager et al., 2022), such as the BestDose software (M. N. Neely et al., 2018).

Finally, while tobramycin TDM can be helpful for dose individualization after the first dose, the identification of clinical determinants of drug exposure after initial dosing is relevant.

The objectives of the present study were to:

- Evaluate the attainment of target concentrations of tobramycin before TDM.
- Assess the ability of empiric dose adjustment to achieve target concentrations after TDM.
- Compare the empirically adjusted doses by clinicians to optimal doses calculated by PK modelling (MIPD).
- Identify potential determinants of target attainment and optimal doses.

2. METHODS

2.1. Study population

We performed a retrospective study in our local adult CF center (CRCM Adulte, Lyon Sud, *Hospices Civils de Lyon*, France) that included all adult CF patients who received a once-daily intravenous tobramycin dose for pulmonary exacerbations in 2019 and had TDM. As we performed a retrospective analysis of anonymized data collected in routine care, patient's consent and ethics approval were not required, as stated under the French regulation for clinical research (Michaud & Michaud Peyrot, 2020).

2.2. Data collection

In the center from which data originate, IV tobramycin is administered once-daily over 14 days for treatment of pulmonary exacerbations. Most patients are treated at home. The initial dose is selected by the clinicians. TDM is performed in all patients on a single occasion, on the 3rd (or 4th) day of therapy. Blood sampling is usually performed just before the dose and 0.5 h after end of 30-min infusion, for the determination of Cmin and Cmax values, respectively. As infusion duration and sampling times may differ from theoretical times, those are precisely recorded by nurses. Samples are transported and assayed in a single reference laboratory. Once results are available, the clinicians adjust tobramycin dose if necessary. Cmax target range is 30-40 mg/L and Cmin target is < 0.5 mg/L.
We retrospectively collected TDM data including the initial dose and the dose corrected after TDM, infusion and sampling times, as well as demographic variables including age, sex, height, body weight, serum creatinine and creatinine clearance estimated by the Cockcroft-Gault equation (Cockcroft & Gault, 1976). Tobramycin concentrations were determined using an immunoturbidimetry assay (particle-enhanced turbidimetric immunoassay [PETIA]). The lower limit of quantification (LLOQ) of the technique was 0.2 mg/L. Coefficients of variation calculated for repeatability were less than 4%, so within the acceptance range (<8 to 10%) of our national quality insurance program.

2.3. Pharmacokinetic analysis

In order to retrospectively determine the optimal dose that would have been necessary to achieve concentration targets, we analysed TDM data by using a PK modelling approach.
Tobramycin doses, time and values of measured concentrations, and covariates values from each individual patient were analysed by the BestDose software (M. Neely et al., 2012). Patients data were fitted under a Bayesian framework with the tobramycin population PK model developed with the R package Pmetrics and implemented in the BestDose software (Praet et al., 2021). This is a two-compartment PK model built on a data-rich population PK analysis including 195 paediatric patients who received intravenous tobramycin cures for pulmonary exacerbations. Over half of the paediatric cohort consisted of adolescent patients, with a major proportion over the age of 15 years (one-third of the entire cohort).
The population PK model was externally validated with data obtained from 49 patients not used in the model building process. The predicted and observed concentrations were found to be in good agreement, with little bias and low imprecision.
The relationships between PK parameters and covariates were described according to a linear scale (see **Equation 1** and **Equation 2**).

$$\boldsymbol{CL} = (CL_0 \times CL_{CR} + CL_i) \times BSA \qquad \text{Equation 1}$$

$$\boldsymbol{V1} = V1_0 \times TBW \qquad \text{Equation 2}$$

With: ***CL***, total clearance; CL_0, typical clearance; CL_{CR}, creatinine clearance; CL_i, nonrenal clearance; *BSA*, body surface area; ***V1***, central volume of distribution; $V1_0$, typical central volume of distribution; *TBW*, total body weight.

Of note, in order to be implemented in the BestDose software, a simpler model was derived (*i.e*. model regardless the BSA). This model still provided a fairly good description of the data and thus appeared suitable for model-based TDM of tobramycin in pediatric CF patients. The relationships between PK parameters and covariates are as follows (see **Equation 3** and **Equation 4**):

$$\boldsymbol{Ke} = Ki + Ks \times CL_{CR} \qquad \text{Equation 3}$$

$$\boldsymbol{V1} = V1_0 \times TBW \qquad \text{Equation 4}$$

With: *CLcr*, creatinine clearance estimated by the Cockcroft-Gault equation; ***Ke***, total elimination rate constant; *Ki*, nonrenal elimination rate constant; *Ks*, renal elimination rate constant; *TBW*, actual total body weight; ***V1***, central volume of distribution; $V1_0$, typical central volume of distribution.

For each patient, the joint posterior distribution of individual PK parameters were estimated from the Bayesian inference. Then the individual PK profile of each patient was estimated, including predictions of measured tobramycin concentrations. Model predictive performances (Sheiner & Beal, 1981) were visually evaluated by plotting observed tobramycin concentrations (Cobs) versus individual predicted concentrations (Cpred), as well as numerically by computation of the mean prediction error (ME, in milligrams per liter, see **Equation 5**) as a measure of bias (a systematic upward or downward deviation from the identity line in the goodness-of-fit plot). Precision (the degree of data dispersion around the identity line) was assessed by computation of the root mean square error (RMSE, in milligrams per liter, see **Equation 6**) and the normalized root mean square error (NRMSE, dimensionless, see **Equation 7**) of predictions. The NRMSE has the advantage to be homogenous to a coefficient of variation (CV) while the RMSE rather relates to a standard deviation (SD) (EFSA Panel on Plant Protection Products and their Residues (PPR) et al., 2018).

$$\boldsymbol{ME}\ (mg/L) = \frac{1}{n}\sum_{i=1}^{n}(Cpred_i - Cobs_i) \qquad \text{Equation 5}$$

$$\boldsymbol{RMSE}\ (mg/L) = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(Cpred_i - Cobs_i)^2} \qquad \text{Equation 6}$$

$$\boldsymbol{NRMSE}\ (unitless) = \frac{RMSE}{\bar{Y}} \qquad \text{Equation 7}$$

With: $Cpred_i$, predicted concentration; $Cobs_i$, observed concentration; for the *i*th individual and *n* the total number of observations. $\bar{Y}$ is the mean of the *n* observed tobramycin concentrations.

The two-compartmental model was also used to estimate at day 1 of therapy the tobramycin Cmax at 30 min post-empiric initial dose and the Cmin at 24h exactly. Target values (Abdul-Aziz et al., 2020) were compared to those estimated Cmax (eCmax) and estimated Cmin (eCmin).

Finally for each patient, using the individual PK parameters, the BestDose software was used to derivate at day 4 of therapy after tobramycin TDM:

- the tobramycin exposure level (Cmax, AUC_{24}, Cmin) resulting from the empirically adjusted dose by the clinicians.
- the tobramycin optimal dose that would have fulfilled the Cmax target of 32 mg/L 0.5 h after end of 30-min infusion, considering the USCAST-FDA tobramycin MIC breakpoint of 4 mg/L for *P. aeruginosa* (*USCAST. 2020. Breakpoints. Comparison tables for website V6.0 29Feb2020.pdf*, s. d.) and the lower bound of Cmax/MIC index of 8 – 10 (Abdul-Aziz et al., 2020).
- the tobramycin optimal dose that would have fulfilled the AUC_{24} target of 320 $mg.h.L^{-1}$, considering the USCAST-FDA tobramycin MIC breakpoint of 4 mg/L for *P. aeruginosa* (*USCAST.*

2020. Breakpoints. Comparison tables for website V6.0 29Feb2020.pdf, s. d.) and the lower bound of AUC_{24}/MIC index of 80 – 100 (Abdul-Aziz et al., 2020).

Figure 1 shows the workflow of the comparative dosing adjustment study design.

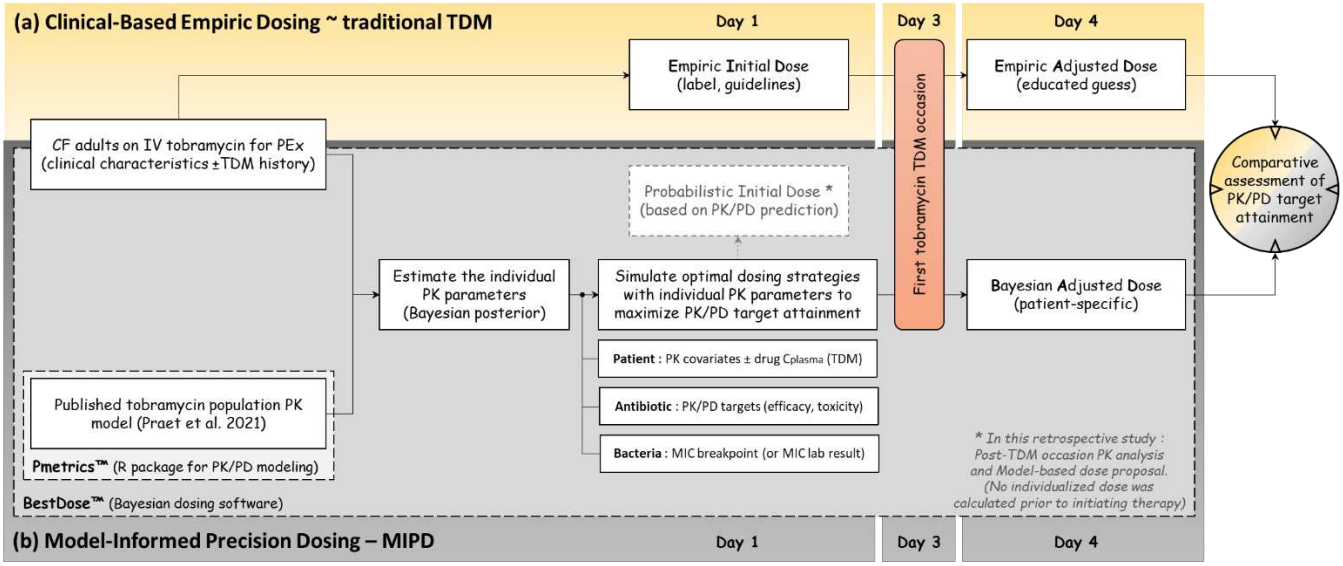

Figure 1. Workflow of the antibiotic dosing adjustment process: parallel between clinical-based empiric dosing versus pharmacokinetic model-informed precision dosing (MIPD). (**a**) As for clinical-based empiric dosing (*i.e*. traditional TDM), tobramycin empiric doses are calculated based on the individual total body weight. The guidelines recommend an initial tobramycin dose of 10 mg/kg/day in the present clinical setting. (**b**) As for model-informed precision dosing – MIPD (*i.e*. model-based TDM), tobramycin regimens are tailored to each patient with the use of a limited number of drug concentrations and PK-guided dosing, through the tobramycin population PK model previously developed (Praet et al., 2021). In the BestDose software, the Bayesian adjusted dose (aiming specific PK/PD target: e.g. Cmax/MIC = 8) is computed using multiple factors: individual covariates values (total body weight, creatinine clearance), tobramycin TDM results (initial dosing, Cmax value, Cmin value) and tobramycin MIC breakpoint for *Pseudomonas aeruginosa* (4 mg/L).

Abbreviations: CF, cystic fibrosis; Cmax, maximum plasmatic concentration ('peak'); Cmin, minimal plasmatic concentration ('residual', 'trough'); Cplasma, plasmatic concentration; IV, intravenous; MIC, minimum inhibitory concentration; MIPD, model-informed precision dosing; PD, pharmacodynamics; PEx; pulmonary exacerbations, PK, pharmacokinetics; TDM, therapeutic drug monitoring.

2.4. Predictors of target attainment and optimal initial dosing

We performed a classification and regression tree (CART) analysis. CART is a nonparametric regression method of data mining and machine learning (Breiman et al., 1984). Basically, CART procedure mutually identifies exclusive and exhaustive subgroups of a population whose patients share common characteristics that influence the dependant (or target) variable of interest. This target variable can either be categorical (*i.e*. classification tree) or continuous (*i.e*. regression tree). CART uses a binary partitioning technique, splitting predictors at nodes into two areas of maximal homogeneities. The apex of the dyadic decision tree is formed by the most significant predictor. A constant value of the predictor is predicted by each area of the tree. More information about this CART method can be found elsewhere (Strobl et al., 2009).

CART was run with the Statistica software (version 13.3, Tibco software, Palo Alto, CA, USA). Classification tree procedure identified the predictors of tobramycin Cmax target attainment (Cmax ≥ 32 mg/L) after an initial tobramycin dose. To do so, the peak was coded as a binary variable. The probability of having this dependent categorical measure achieved was estimated among those within each node, and cut-off values of continuous predictors were provided. Regression tree procedure

identified the predictors of the optimal tobramycin dose (optimal doses computed by the BestDose software after the first TDM occasion). The overall group was split into two subgroups with the most different average optimal dose, using the most powerful predictor of the outcome, namely 'optimal dose'. The average value of the outcome was estimated within each leaf, and cut-off values of predictors at each node were provided.

A total of 19 independent variables were examined as potential predictors of tobramycin peak achievement and optimal tobramycin dose:

- **Sex**,
- **Age** (in years),
- **Height** (in cm),
- Actual total body weight (**TBW**, in kg),
- Serum creatinine (**SCr**, in µM),
- Creatinine clearance (CCR) estimated by the original Cockcroft-Gault equation (**CCR_{CG}**, in mL/min) (Cockcroft & Gault, 1976),
- Glomerular filtration rate (GFR) estimated by the Modified of Diet in Renal Disease equation (**GFR_{MDRD}**, in mL/min/1.73 m²) (Levey et al., 2006),
- GFR estimated by the Chronic Kidney Disease Epidemiology collaboration equation (**$GFR_{CKD\text{-}EPI}$**, in mL/min/1.73 m²) (Levey et al., 2009),
- Body surface area (**BSA**, in m²) estimated by the Boyd equation (Boyd, 1935), body mass index (**BMI**, in kg/m²) (Keys et al., 1972),
- Ideal body weight (**IBW**, in kg) estimated by the Devine equation (Pai & Paloucek, 2000),
- Lean body weight (**LBW**, in kg) estimated by the method from Green and Duffull (Janmahasatian et al., 2005),
- Adjusted body weight (**ABW**, in kg) as calculated by Bauer et al. (Bauer et al., 1983), according to formula : $ABW = IBW + 0.4 \times (TBW - IBW)$ in patients with TBW > IBW, and as TBW otherwise,
- Tobramycin dose (in mg) as well as tobramycin dose adjusted for each body size descriptors: **dose/TBW**, **dose/BSA**, **dose/BMI**, **dose/IBW**, **dose/LBW**, **dose/ABW**.

In order to prevent overfitting, the minimal number of observations per tree leaf was fixed at 10, corresponding about to 10% of the population sample size. The final tree was also submitted to a 5-fold cross validation.

3. RESULTS

3.1. Study population

Data from 101 adult CF patients who received tobramycin in 2019 were included in our analysis, representing a cumulative total of 153 tobramycin TDM occasions.
Characteristics of the study population are shown in **Table 1**. TDM revealed that tobramycin exposure was below the expected target exposure. Apparent under-dosing and under-exposure were shown with:

- an empiric initial tobramycin dose of 8.8 ± 1.3 mg/kg (against the usual initial dosage of 10 mg/kg advocated for CF patients, (Agence française de sécurité sanitaire des produits de santé, 2011; Paviour et al., 2016; « UK Cystic Fibrosis Trust Antibiotic Group. Antibiotic treatment for cystic fibrosis. 3rd ed. London. », 2009))
- an estimated Cmax at 30 min (eCmax) at day 1 of therapy of 25.7 ± 5.6 mg/L (against the 32 – 40 mg/L advised with the USCAST-FDA tobramycin MIC breakpoint of 4 mg/L and the Cmax/MIC index of 8 – 10 (Abdul-Aziz et al., 2020)).

Table 1. Characteristics of the study population (n = 101).

Variable	Mean ± SD	Min – Max
Number of Male / Female	44 / 56	/
Age (years)	30.9 ± 10.1	18.0 – 61.5
Height (cm)	164.6 ± 8.1	150.0 – 189.0
TBW (kg)	55.1 ± 10.3	36.0 – 90.0
Weight descriptors		
IBW (Devine equation) (kg)	58.4 ± 8.8	43.3 – 83.1
ABW (Bauer et al. method) (kg)	54.0 ± 8.8	36.0 – 80.0
LBW (Green-Duffull method) (kg)	43.8 ± 7.3	30.8 – 65.7
BMI (kg/m²)	20.3 ± 3.1	14.4 – 34.8
BSA (Boyd equation) (m²)	1.59 ± 0.17	1.24 – 2.10
Serum creatinine (µM)	61.1 ± 15.6	27.0 – 136.0
Renal function descriptors		
CCR_{CG} (mL/min)	113.9 ± 27.6	42.0 – 227.4
$GFR_{CKD\text{-}EPI}$ (mL/min/1.73 m²)	119.7 ± 18.6	44.4 – 178.8
Tobramycin cures number per patient		
1 cure (n patients)	101	/
2 cures (n patients)	39	/
3 cures (n patients)	10	/
4 cures (n patients)	3	/
Tobramycin empiric initial dose (mg) at day 1	475 ± 72	300 – 800
Initial dose/TBW (mg/kg)	8.8 ± 1.3	5.6 – 16.7
Initial dose/IBW (mg/kg)	8.2 ± 1.1	5.8 – 11.5
Initial dose/ABW (mg/kg)	8.9 ± 1.2	5.7 – 16.7

Initial dose/LBW (mg/kg)	11.0 ± 1.4	7.0 – 18.6
Time after start of infusion for Cmax dosing (min)	63.7 ± 14.7	12 – 105
Tobramycin measured Cmax (mg/L) at day 3	25.5 ± 6.1	14.0 – 46.2
Cmax ≥ 32 mg/L (%)	16.0	/
Cmax < 32 mg/L with empiric subsequent increase in dosing (%)	27.0	/
Cmax < 32 mg/L without empiric subsequent change in dosing (%)	54.0	/
Predicted Cmax at 30 min (mg/L) at day 3	25.0 ± 6.0	14.0 – 51.7
Model predictive performances (overall)		
Bias (ME, mg/L)	- 0.40	/
Imprecision (RMSE, mg/L)	1,97	/
Imprecision (NRMSE, unitless)	0.11	/
Estimated Cmax at 30 min (eCmax) (mg/L) at day 1	25.7 ± 5.6	13.7 – 44.9
eCmax ≥ 32 mg/L (%)	12.0	/
eCmax ≥ 40 mg/L (%)	1.0	/
32 ≤ eCmax < 40 mg/L (%)	11.0	/
Tobramycin computed AUC_{24} ($mg.h.L^{-1}$) at day 3	95.1 ± 22.6	35.2 – 188.5
$AUC_{24} \geq 320$ $mg.h.L^{-1}$	0	/
$AUC_{24} \geq 400$ $mg.h.L^{-1}$	0	/
$320 \leq AUC_{24} < 400$ $mg.h.L^{-1}$	0	/
Tobramycin measured Cmin (mg/L) at day 3	0.4 ± 0.5	0.2 – 3.5
Estimated Cmin at 24h (eCmin) (mg/L) at day 1	0.24 ± 0.3	0.0 – 1.8
eCmin < 1 mg/L (%)	96.7	/
eCmin < 0.5 mg/L (%)	92.8	/

Values are given as Mean ± SD and Min-Max unless otherwise stated. Variable values are given for the first tobramycin cure. Abbreviations : ABW, adjusted body weight ; AUC_{24}, 24h-area under the concentration-time curve ; BMI, body mass index ; BSA, body surface area ; CCR_{CG}, creatinine clearance estimated by the Cockcroft-Gault equation ; Cmax, maximal concentration ; Cmin, trough concentration ; $GFR_{CKD\text{-}EPI}$, glomerular filtration rate estimated by the CKD-EPI equation ; GFR_{MDRD}, glomerular filtration rate estimated by modification of the diet in renal disease equation ; LBW, lean body weight ; ME, mean prediction error; NRMSE, normalized root mean square prediction error ; SD, standard deviation ; RMSE, root mean square prediction error; TBW, actual total body weight.

3.2. Pharmacokinetic analysis

The tobramycin model fitted very well our data, as shown in **Figure 2A** (*n* = 219 measured concentrations). This is supported by the Bayesian results showing in a high correlation coefficient between observed and predicted serum concentrations (overall $R^2 = 0.994$). **Figure 2B** is a zoom on the Cmin values fitting from Figure 2A.

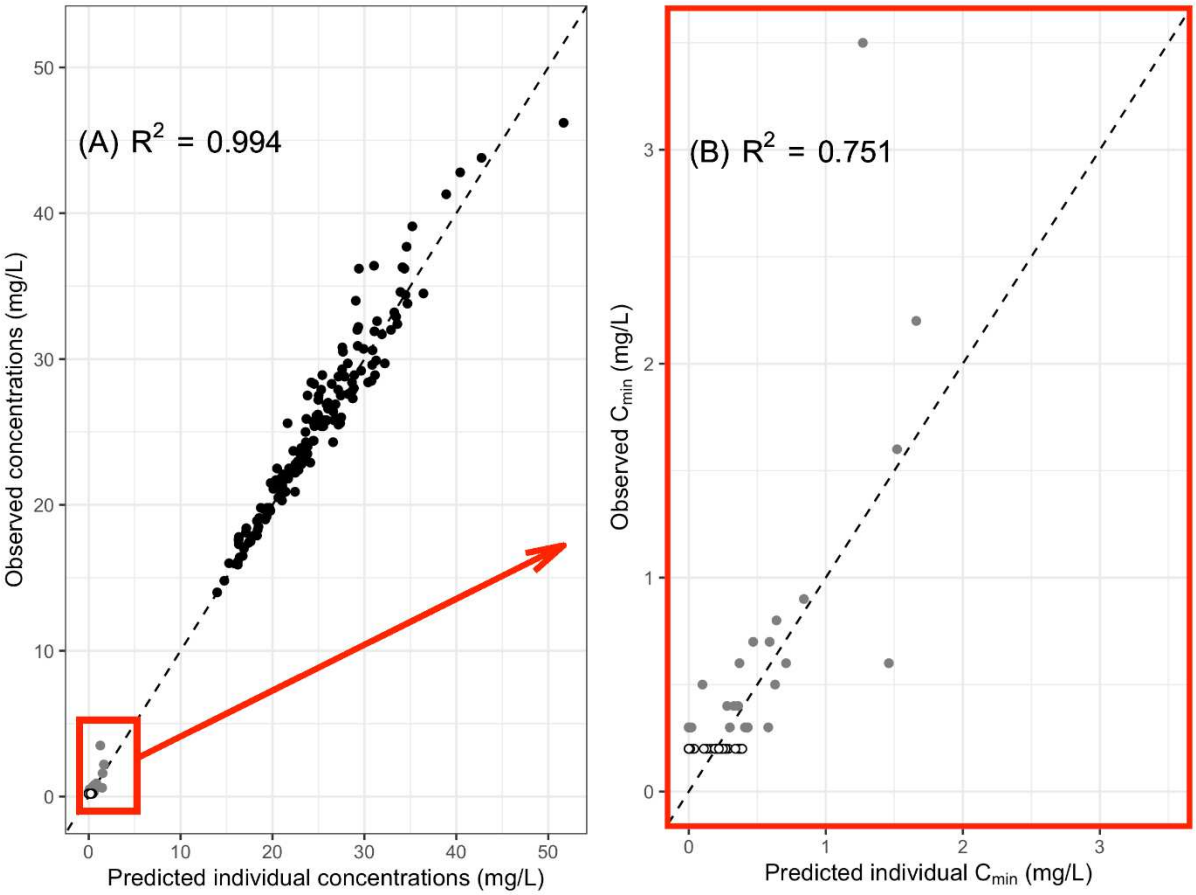

Figure 2. (**a**) Goodness-of-fit of the pharmacokinetic model for the entire dataset. Observed tobramycin concentrations (y axis) are plotted against the individual model predictions (Bayesian estimates). (**b**) Zoom of Figure 2A for the Cmin values. The dashed line represents the identity line (y = x). Black dots represent the Cmax, grey dots represent the Cmin above the LLOQ, white dots represent the Cmin below the LLOQ.
Abbreviations : LLOQ – Lower limit of quantification.

Predictive performances were acceptable, with satisfactory accuracy (little bias: ME = – 0.40 mg/L) and low imprecision (RMSE = 1,97 mg/L, NRMSE = 0.11) of model-based individual predictions. NRMSE is expected not to exceed the upper limit of 0.5 (50%). ME, RMSE and NRMSE were assessed separately from one sampling occasion to the next.

The post-TDM tobramycin dose modifications carried out by the clinicians (empirically adjusted doses) and performed by Bayesian forecasting (model-based adjusted doses), with the respective concentrations, are summarized in **Table 2** along with the empiric initial dosing. The model-based adjusted dose was computed by the BestDose software to target Cmax = 32 mg/L 0.5 h after end of 30-min infusion.

Table 2. Comparison of the tobramycin empiric initial dosing at day 1 of therapy with the post-TDM empiric adjusted dosing and the Bayesian adjusted dosing targeting Cmax = 32 mg/L 0.5 h after end of 30-min infusion.

Variable	Value for dataset					
	Empiric Initial Dosing		**Empiric Adjusted Dosing**		**Bayesian Adjusted Dosing [b]**	
	Mean ± SD	Min – Max	Mean ± SD	Min – Max	Mean ± SD	Min – Max
Tobramycin dose (mg)	475 ± 72	300 – 800	479 ± 71	300 – 800	629 ± 143 [b]	350 – 1075 [b]
Dose/TBW (mg/kg)	8.8 ± 1.3	5.6 – 16.7	8.8 ± 1.3	5.6 – 16.7	11.6 ± 2.5 [b]	6.0 – 20.7 [b]
Cmax (mg/L)	25.7 ± 5.6 [a]	13.7 – 44.9 [a]	25.8 ± 5.0	13.7 – 45.0	32 (target)	/
Cmin (mg/L)	0.24 ± 0.3 [a]	0.0 – 1.8 [a]	0.28 ± 0.3	0.0 – 1.98	0.35 ± 0.4	0.0 – 2.29
Dose modification compared to the empiric initial dose (day 1 of therapy)						
Average difference (mg)	/	/	6.0 ± 23.1	- 75.0 – 50.0	162.8 ± 137.6	- 100.0 – 575.0
Average difference (mg/kg)	/	/	0.1 ± 0.4	- 1.4 – 1.1	2.9 ± 2.5	-1.8 – 11.1
Dose unchanged (% patients)	/	/	63.0 %	/	2.0 %	/
Dose decrease (mg) [% patients]	/	/	- 37.5 ± 17.7 [10.0]	- 75 – - 25	- 37.5 ± 24.3 [10.0]	- 100 – - 25
Dose increase (mg) [% patients]	/	/	36.1 ± 12.7 [27.0]	25 – 50	189.2 ± 124.7 [88.0]	25 – 575

Values are given as Mean ± SD and Min-Max unless otherwise stated. Values are given for the first tobramycin cure.

[a] eCmax and eCmin (Cmax estimated at 30 min post-dose and Cmin estimated at 24h exactly by the BestDose software at day 1 of therapy).

[b] Post-TDM Bayesian adjusted dose computed by the BestDose software to target Cmax = 32 mg/L 0.5 h after end of 30-min infusion.

Abbreviations: Cmax, maximal concentration; Cmin, trough concentration; SD, standard deviation; TBW, actual total body weight.

The apparent initial tobramycin under-dosing (mean of 8.8 ± 1.3 mg/kg) at day 1 of therapy was not significantly corrected with the empiric adjusted dosing post-TDM (mean of 8.8 ± 1.3 mg/kg). Subsequent tobramycin peaks certify the inefficiency of the empiric dosing adjustment, with an estimated initial mean Cmax of 25.7 ± 5.6 mg/L and a post-empiric adjusted Cmax of 25.8 ± 5.0 mg/L. The higher dosing (mean of 11.6 ± 2.5 mg/kg) proposed by the Bayesian forecasting method to meet target Cmax = 32 mg/L 0.5 h after end of 30-min infusion is not tainted by excessive trough concentrations (mean Cmin of 0.35 ± 0.4 mg/L).

Boxplots for all measured or fitted tobramycin doses (empiric initial dose, empirically adjusted dose, Bayesian adjusted dose), their respective Cmax and their respective Cmin are shown in **Figure 3**. Figure 3 displays for the first tobramycin cure (n = 101), which is representative compared to the total number of cures (n= 153). (See **Figure A1** in annex, inter-cures boxplots).

Notches on the boxplots represent the 95% confidence intervals of the median of the displayed variable (y-axis). Notches can be used to compare groups: if notches of two boxes do not overlap, it suggests that both medians can be assumed significantly different.

Differences between empiric initial doses (EID) and adjusted doses (EAD, BAD) were statically assessed. As data to compare depend on each other (same patients), a nonparametric test on two paired samples, *i.e*. a Wilcoxon signed-rank test, was performed. The significance level was set at 0.025 (instead of 0.05) in order to control the risk in relation to the number of tests (two tests with the same reference value, namely EID).

Mean tobramycin doses of the empiric initial dosing (EID) and the empirically adjusted dosing (EAD) do not significantly differ (**Figure 3a**). Accordingly, the mean respective Cmax do not substantially differ (**Figure 3b**). Pharmacokinetic modelling with Bayesian adjusted dosing (BAD) delivers significantly higher doses compared to EID to meet the Cmax target, with very little increase in Cmin (**Figure 3c**). It is worth to note that the tobramycin doses of the BAD shows a greater variability than empiric doses (EID and EAD). This supports the idea that BAD better accounts for interindividual variability.

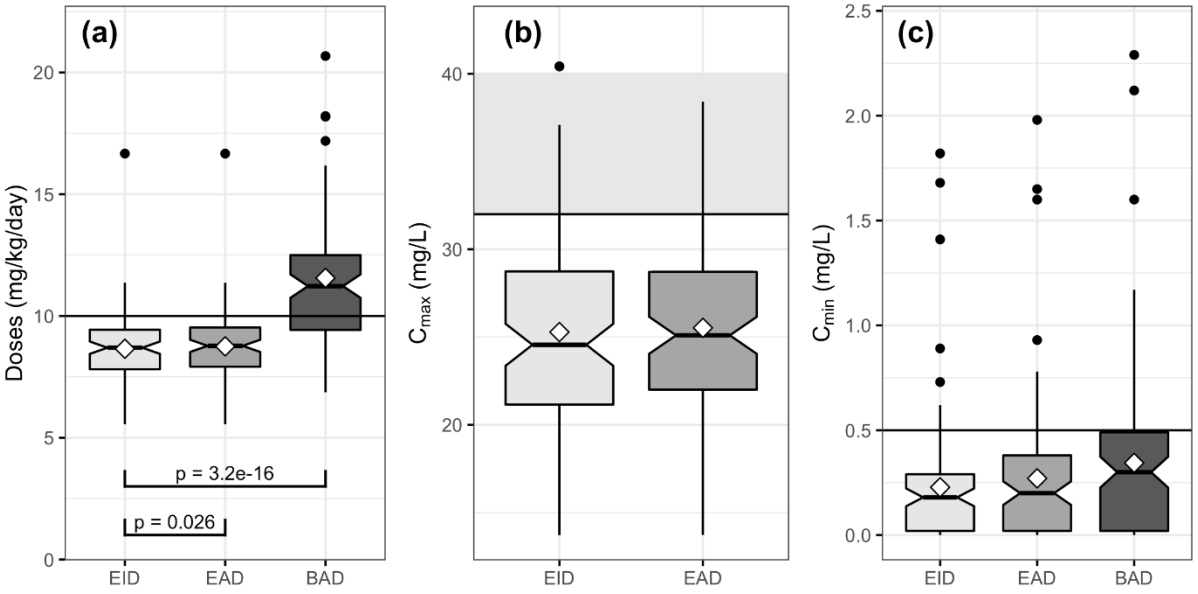

Figure 3. Boxplots with notches for the entire cohort of adult patients with cystic fibrosis (*n* = 101). Values are given for the first tobramycin cure. (**a**) Tobramycin doses per total body weight (mg/kg/day) corresponding to the empiric initial dosing (EID, in light grey), the empirically adjusted dosing (EAD, in grey) and the Bayesian adjusted dosing with the BestDose software (BAD, in dark grey). The horizontal black solid line is the guidelines recommended tobramycin dose (10 mg/kg/24h). (**b**) Tobramycin Cmax values (mg/L) corresponding to the empiric initial dosing (EID, in light grey) and the empirically adjusted dosing (EAD, in grey). The horizontal black solid line is the efficacy Cmax target of 32 mg/L, considering the Cmax/MIC threshold of 8 and the USCAST-FDA tobramycin MIC breakpoint of 4 mg/L for *Pseudomonas aeruginosa*. The shaded area delimits the [min=32 mg/L; max=40 mg/L] range corresponding to the Cmax/MIC index range of 8 to 10. (**c**) Tobramycin Cmin values (mg/L) corresponding to the empiric initial dosing (EID, in light grey), the empirically adjusted dosing (EAD, in grey) and the Bayesian adjusted dosing with the BestDose software (BAD, in dark grey). The horizontal black solid line is the toxicity Cmin target (0.5 mg/L). All the boxplots provide five summary statistics: the median (horizontal black segment), two hinges (lower and upper box limits delimited by 25% and 75% quantiles) and two whiskers (from the bottom to top vertical black segments delimited by the upper and the lower hinges + or – 1.5-fold the interquartile range). All outlying value are individually represented as black dots. White diamonds stand for mean values. Notches on the boxplots represent the 95% confidence intervals of the median of the exposed variable (y-axis). Notches can be used to compare groups: if notches of two boxes do not overlap, it suggests that both

medians can be assumed significantly different. Differences between empiric initial doses (EID) and adjusted doses (EAD, BAD) were statically assessed using a Wilcoxon signed-rank test (p-values < 0.025 were considered significant).
Abbreviations: BAD, Bayesian adjusted dosing; Cmax, maximal concentration; Cmin, trough concentration; EAD, empirically adjusted dosing; EID, empiric initial dosing.

After the tobramycin TDM occasion (day 3 – predicting day 4), the model-based adjusted doses computed by the BestDose software aiming for AUC_{24} = 320 mg.h.L^{-1} were higher than the ones aiming for Cmax = 32 mg/L 0.5 h after end of 30-min infusion. Indeed, aiming for AUC_{24} = 320 mg.h.L^{-1}, the average model-based adjusted dose was of 1674 ± 481 mg (30.7 ± 8.4 mg/kg). Subsequent mean though concentration corresponding to this AUC_{24} target was of 0.79 ± 0.8 mg/L.

3.3. Predictors of target attainment and optimal initial dosing

The classification tree identified the initial dose (ID) of tobramycin in mg/kg (ID/TBW) as the primary predictor of Cmax target attainment (Cmax ≥ 32 mg/L), with a cut-off value of 9.5 mg/kg. The overall target attainment rate (TAR) was 11.9% (*n* = 101).
In subgroup with ID/TBW ≤ 9.5 mg/kg (TAR = 3.9 %, *n* = 78), the secondary predictor of target attainment was the dose/BMI ratio. Overall, patients with ID/TBW > 9.5 mg/kg showed the highest proportion of tobramycin peak target attainment (TAR = 39.1 %, *n* = 23). No secondary predictor of target attainment was identified for subgroup with ID/TBW > 9.5 mg/kg.

The regression tree of determinants of tobramycin optimal dose is shown in **Figure 4**. The primary determinant was LBW. Patients (*n* = 13) with a LBW superior to the cut-off value of 53.9 kg present a mean initial optimized dose of 812 ± 109 mg. In patients with LBW ≤ 53.9 kg, the secondary determinant was ABW.

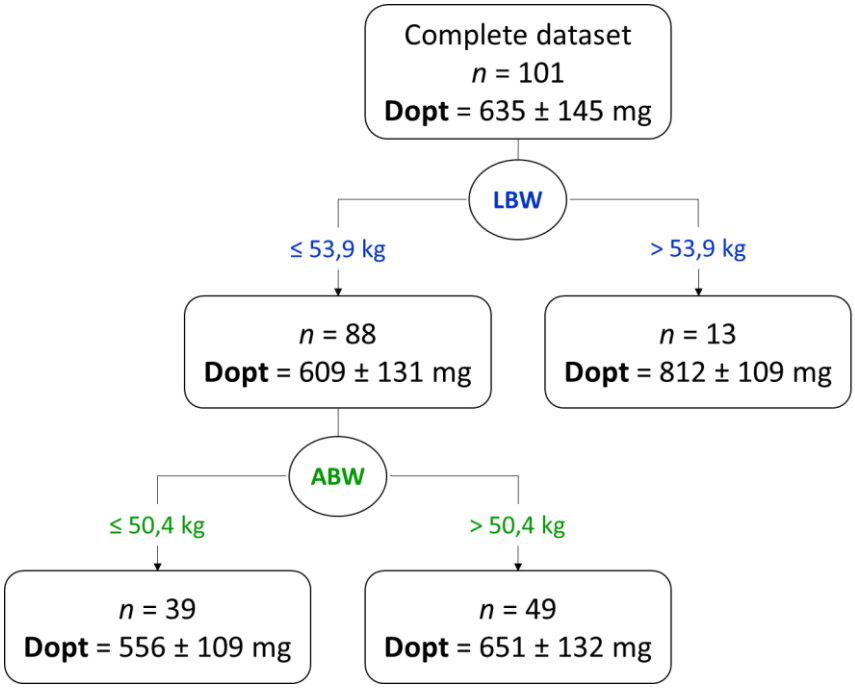

Figure 4. Regression tree of determinants of the optimal tobramycin dose (for Cmax ≥ 32 mg/L) at day 3 (Results of this regression tree at day 3 are projectable to day 1).
Abbreviations: ABW, Adjusted Body Weight ; Dopt, optimal tobramycin dose; LBW, Lean Body Weight.

4. DISCUSSION

Therapeutic drug monitoring of aminoglycosides is critical to prevent under- and overdosing due to narrow therapeutic window and the large between-subject variability in PK parameters in CF population. Thus, during treatment with aminoglycosides, TDM is needed to evaluate drug exposure and to individualize the dose for each patient (Hennig et al., 2008). Through combination of concentration data from limited sampling of individuals with distribution data from a similar patient population, Bayesian forecasting approach allow dosage adjustments driven by individualized predictions.

If Bayesian methods are currently considered to be the gold standard in TDM, only a few studies have evaluated the effectiveness of conventional TDM (clinical-based empiric dosing) versus a model-informed precision dosing tool in achieving PK/PD targets for aminoglycosides. Van Lent-Evers et al. assessed the benefits of a pharmacy-based and active model-based TDM of aminoglycosides in a multicenter 18-month study. Patients with guided 'active' TDM (dosage optimization by subsequent Bayesian adaptive control) showed better target attainment (significantly higher doses with correspondingly higher Cmax and lower Cmin) compared to the control group (non-guided TDM) (van Lent-Evers et al., 1999). Mortality was significantly decreased in the active group versus the control group among patients with documented infections upon admission. Burton et al. demonstrated the accuracy of a Bayesian dosing method in attaining desired peak and trough serum aminoglycoside concentrations and reported that the Bayesian method was more accurate and less biased than the routine physician dosing (Burton et al., 1985). In a randomized controlled trial performed by Burton et al. (dosing based on physician choice versus dosing based on Bayesian program), a reduction in length of hospital stay and a potential reduction in costs was found when Bayesian aminoglycoside dosing was put into practice (Burton et al., 1991).

Clinicians largely rely on their own expertise when making a decision about dose adjustment. Several population PK models for aminoglycosides allowing Cmax, Cmin and AUC determination have been developed, but only a few are actually used in routine practice for dose individualization. Application of population PK models and Bayesian forecasting to assist the prescriber in choosing the best individual tobramycin dose were finely assessed in this paper.

This study examined a Cmax/MIC based management approach for tobramycin at a single adult CF center. The inner historical Cmax target aimed is of 30 mg/L. Our findings highlight how tobramycin dosing in adult with CF is challenging.

After standard starting doses, only 12.0 % patients at day 1 of therapy achieved the target Cmax = 32 mg/L 0.5 h after end of 30-min infusion (considering the USCAST-FDA tobramycin MIC breakpoint of 4 mg/L for *P. aeruginosa* and the lower bound of Cmax/MIC index of 8 – 10 (Abdul-Aziz et al., 2020)). Mean estimated Cmax and mean estimated Cmin at day 1 of therapy were of 25.7 ± 5.6 mg/L and 0.24 ± 0.3 mg/L, respectively. Even if prior literature demonstrated significant PK interindividual variability of tobramycin in patients with CF, hence supporting the need for tobramycin TDM, the mean initial doses (8.8 ± 1.3 mg/kg/day) were substantially lower than the dose preconized in guidelines (10 mg/kg/day). Furthermore, even after empiric dose individualization by clinicians, 84 % of patients could still not achieve a target Cmax of 32 mg/L at the time of the first TDM cycle. Mean Cmax and mean Cmin at day 3 of therapy were of 25.8 ± 5.0 mg/L and 0.28 ± 0.3 mg/L, respectively. This means that the empirically adjusted dosing (8.8 ± 1.3 mg/kg/day) does not significantly differ from the mean tobramycin doses of the empiric initial dosing.

We retrospectively examined a MIPD approach with a Bayesian dosing software, namely BestDose, to propose optimal and individualized tobramycin doses for our CF patients. The framework and the clinical utility of a Bayesian forecasting approach to guide antibiotic dose individualization in patients with CF has been well described (Wicha et al., 2021). Like previous investigations on predictive abilities of Bayesian forecasting software in aminoglycosides dosing (Böttger et al., 1988; Burton et al., 1985; Duffull et al., 1997), we similarly conclude to good predictive performances of our tobramycin PK model for tobramycin dose adjustment, specially implemented in the BestDose software (Praet et al.,

2021). Hereby the population PK model provided a precise and unbiased fit to our observed tobramycin concentrations, so that it can be used to reliably predict tobramycin PK in adult patients with CF. The tobramycin population PK model used for this study and embedded in the BestDose software (Praet et al., 2021), is currently employed for post-TDM tobramycin dosing adjustment in our local adult CF center (CRCM Adulte, Lyon Sud, Hospices Civils de Lyon, France). From our study population, retrospective Bayesian forecasting suggests much larger dosage increases (mean tobramycine doses of 11.6 ± 2.5 mg/kg/day) to fulfill the Cmax target of 32 mg/L. Noteworthy, such tobramycin increased regimens were not marred by excessive trough concentrations (mean Cmin of 0.35 ± 0.4 mg/L). Our study emphasizes the discrepancy between the tobramycin doses required to achieve Cmax/MIC and AUC_{24}/MIC targets. The model-based adjusted doses required to reach the AUC_{24} target of 320 mg.h.L^{-1} (mean of 30.7 ± 8.4 mg/kg/day) were much higher than those required to achieve the Cmax target, at the cost of subsequent higher though concentrations (mean Cmin of 0.79 ± 0.8 mg/L). Thus, reaching the AUC_{24}/MIC objective would only be conceivable for MICs below 4 mg/L.

Our classification and regression tree analysis support the value of a higher initial dose of tobramycin. Indeed, our results support the use of a mean tobramycin dose of 635 mg to optimize the attainment of Cmax ≥ 32 mg/L after the first dose in CF patients. LBW was identified as the main predictor of the optimal dose of tobramycin. Interestingly, TBW was not a predictor of tobramycin optimal dose, what would support the need for alternative dosing approaches (Boidin et al., 2018; Goutelle et al., 2022). The alternative body weight-derived metrics identified as determinants (LBW, ABW) may be considered in future studies on personalized tobramycin dosing. Our classification tree corroborates the minimum dose of tobramycin recommended by the guidelines in CF (Agence française de sécurité sanitaire des produits de santé, 2011). However, this same result could also support the need to increase the initial doses of tobramycin. Indeed, the patient group with initial dose/TBW greater than 9.5 mg/kg (leaf showing the highest proportion of tobramycin peak target attainment) displayed low target attainment – barely 40%.

We identified an initial dose that would have optimized target attainment for Cmax. However, this dose was based on TDM results and cannot be precisely determined *a priori*. Traditional TDM cannot be performed to individualize the first dose. On the contrary, it is possible with MIPD to determine an *a priori* optimized dose for a specific patient (probabilistic initial dose, based on PK/PD prediction) (Wicha et al., 2021). Despite the use of TDM become widespread, clinicians still face with challenges in adequately adjusting dosing regimens for each patient to achieve target exposures, illustrated here with the example of tobramycin. The individual optimal dose remains difficult to predict with empiric TDM. Wherever possible, MIPD approaches should be used, as they can streamline the traditional TDM process for aminoglycosides. Prospective clinical trials are required to assess the benefit of precision dosing, and ultimately strengthen its implementation in clinical practice. As one could expect, optimal dosing of tobramycin is strongly influences by the MIC. The variability of tobramycin MIC breakpoints for *Pseudomonas aeruginosa* remains an issue in this context, with a 4-fold difference between USCAST and CLSI breakpoints. Obviously, Cmax/MIC target can be better achieved with conventional dosages when a lower MIC breakpoint, such as the USCAST reference of 1 mg/liter, is used. Also a choice was made on the sustained target values of PK/PD Cmax/MIC and AUC_{24}/MIC in the simulations: lower target values may be acceptable as suggested elsewhere (Bland et al., 2018). Thus, lower doses and exposure to tobramycin may be sufficient, while also considering that tobramycin is not administered alone but in combination with a beta-lactam in CF patients.

This work has several limitations, including its retrospective design. Our dosing suggestions are based on calculations only and have not been validated clinically. Data were collected during routine patient care. Thus errors may have occurred in sampling documentation and data collection. Also, our simulations are based on MIC breakpoints, which may be viewed as worst-case microbiological situations. Local microbiology data can be used for precision dosing decisions, while keeping in mind the limited accuracy of MIC determinations (Mouton et al., 2018). Anyway, our results are valuable in

supporting model-based dose optimization of tobramycin for CF patients with *P. aeruginosa* infection. Clinical trials would be necessary to further confirm the proposed dosing approach.

5. CONCLUSION

In this study, we have assessed the benefits of a model-based adaptive TDM (Bayesian dosing adjustment) of tobramycin in adult patients with CF with a retrospective analysis of data from 101 adult CF patients. Our results underline that 12.0 % of patients achieved a target Cmax ≥ 32 mg/L after empiric initial dosing (mean of 8.8 mg/kg/day). Initial dose to the total body weight (ID/TBW) was the primary predictor of Cmax target attainment. Initial tobramycin dose < 9.5 mg/kg/day was associated with extremely poor target attainment. Our results also highlight that empirical dose adjustments by clinicians failed to achieve concentrations targets in most patients. This is supported by the dose adjustments guided by PK modelling that revealed significantly higher. In addition, none of the patients achieved a target AUC_{24} ≥ 320 $mg.h.L^{-1}$ after empiric initial dosing. Cmax and AUC_{24} targets of tobramycin are not consistent in terms of dosage requirements. Furthermore, our results suggest that current tobramycin dosage recommendations (10 mg/kg/day) are not optimal to treat CF exacerbations, as illustrated by poor target attainment. Pharmacokinetic modelling suggested that dosing could be safely increased to 11.6 mg/kg/day to target a Cmax of 32 mg/L 0.5 h after end of 30-min infusion. Therefore, model-informed precision dosing (MIPD – *i.e*. Active model-based TDM) could be advantageously employed for early dose optimization and hasten therapeutic response. With the perspective of an individualized medicine, a complementary prospective clinical assessment of personalized tobramycin dosing would enhance to promote Bayesian forecasting approaches as a relevant decision-making support.

ANNEXES

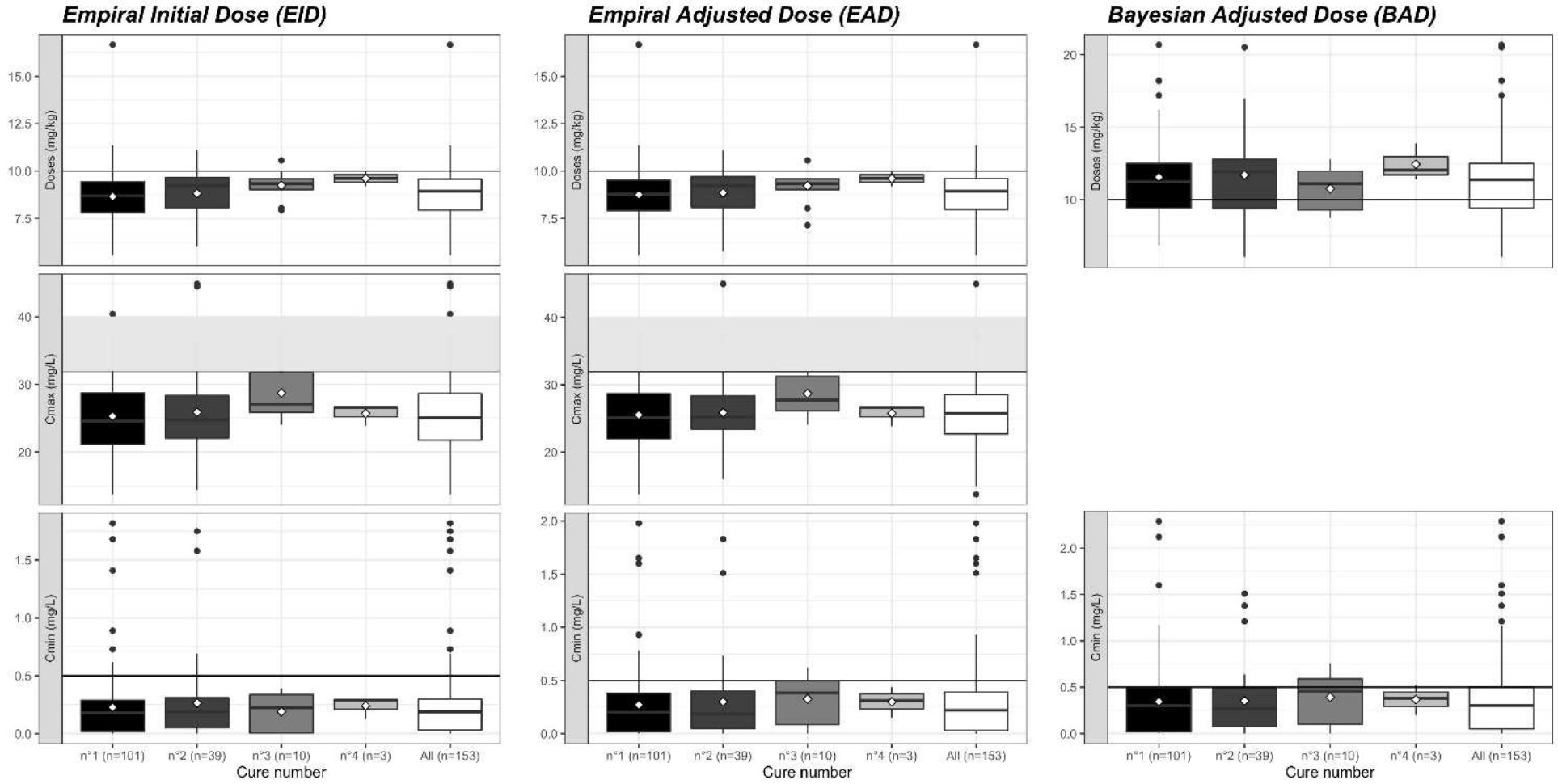

Figure A1. Inter-cures boxplots. Values are given for the first tobramycin cure (n = 101), the second tobramycin cure (n = 39), the third tobramycin cure (n = 10), the fourth tobramycin cure (n = 3) and the total cures number (n = 153).

Abbreviations: BAD, Bayesian adjusted dosing; Cmax, maximal concentration; Cmin, trough concentration; EAD, empirically adjusted dosing; EID, empiric initial dosing.

ABBREVIATIONS

ABW – Adjusted body weight. Calculated according to Bauer et al. (Bauer et al., 1983) in this study.
AUC_{24} – 24h-area under the concentration-time curve (daily area).
AUC_{24}/MIC – 24h-area under the concentration-time curve to the Minimum inhibitory concentration.
BF – Bayesian forecasting.
BMI – Body mass index.
BSA – Body surface area. Estimated by the Boyd equation (Boyd, 1935) in this study.
BAD – Bayesian adjusted dosing.
CART – Classification and regression tree.
CCR – Creatinine clearance.
CCR_{CG} – CCR estimated by the Cockcroft-Gault equation.
CF – Cystic fibrosis.
CI 95% – Confidence interval at 95%.
CL – Total clearance.
CL_0 – Typical clearance.
CL_{CR} – Creatinine clearance.
CL_i – Nonrenal clearance.
CLSI – Clinical and Laboratory Standards Institute.
Cmax – Maximum plasmatic concentration ('peak').
Cmax/MIC – Maximum plasmatic concentration to the Minimum inhibitory concentration.
Cmin – Minimal plasmatic concentration ('residual', 'trough').
Cobs – Observed concentration.
Cpred – Predicted concentration.
ID/TBW – Initial dose to the Total body weight.
ID/BMI – Initial dose to the Body mass index.
Dopt – Optimal dose.
EAD – Empirically adjusted dosing.
ECOFF – Epidemiological cut-off value.
EID – Empiric initial dosing.
EUCAST – European Committee on Antimicrobial Susceptibility Testing.
GFR – Glomerular filtration rate.
$GFR_{CKD\text{-}EPI}$ – GFR estimated by the chronic kidney disease epidemiology collaboration.
GFR_{MDRD} – GFR estimated by the modification of diet in renal disease equation.
IBW – Ideal body weight. Estimated by the Devine equation (Pai & Paloucek, 2000) in this study.
IV – Intravenous.
LBW – Lean body weight. Estimated by the Green and Duffull method (Janmahasatian et al., 2005) in this study.
LLR – Log-linear regression.
LLOQ – Lower limit of quantification.
MAP – Maximum *a posteriori*.
MIC – Minimum inhibitory concentration.
MIPD – Model-Informed Precision Dosing.
ME – Mean prediction error (bias).
NPAG – Nonparametric adaptive grid algorithm.
NRMSE – Normalized root mean square prediction error (precision).
PD – Pharmacodynamics.
PEx – Pulmonary exacerbations.
PK – Pharmacokinetics.
RMSE – Root mean square prediction error (precision).
SCr – Serum creatinine.
SD – Standard deviation.

664 TAR – Target attainment rate.
665 TDM – Therapeutic drug monitoring.
666 TBW – Total body weight.
667 T1/2 – Half-life.
668 USCAST – United States Committee on Antimicrobial Susceptibility Testing.
669 Vd – Distribution volume.
670 V1 – Central volume of distribution.
671 $V1_0$ – Typical central volume of distribution.
672

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674

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678

679 ## TRANSPARANCY DECLARATION

680

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684

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