Personalised Antimicrobial Dosing in Paediatric Cystic Fibrosis

Sahand Imani
The University of Notre Dame Australia

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Personalised antimicrobial dosing in paediatric cystic fibrosis

Dr. Sahand Imani

*MD, BPharm, MPH, MHLM*

Submitted in partial fulfilment of the requirements for the Master of Medicine/Master of Surgery

School of Medicine
The University of Notre Dame
Sydney, Australia

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Declaration

To the best of the candidate's knowledge, this thesis contains no material previously published by another person, except where due acknowledgement has been made. This thesis is the candidate’s own work and contains no material which has been accepted for the award of any other degree or diploma in any institution.

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research. The proposed research study received human research ethics approval from the Sydney Children’s Hospitals Network Human Research Ethics Committee (2019/ETH11521). Cross-institutional approval was conferred by University of Notre Dame Australia (2021-073S).

Sahand Imani

9th October 2022
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I also extend a heartfelt thank you to Dr Craig Smith for his generous support and wisdom. At many stages of this degree, I benefitted immensely from his practical advice, positive outlook, and confidence in my research. For this, I am eternally grateful.
Abstract

Children with cystic fibrosis (CF) are predisposed to recurrent pulmonary exacerbations throughout their lifetime. This is characterised by an acute worsening of respiratory symptoms in the setting of bacterial infection and results in significant morbidity and mortality. Appropriate antimicrobial therapy is fundamental to management, in particular aminoglycoside antibiotics. Tobramycin is the preferred aminoglycoside of choice, usually administered intravenously for 7 to 14 days.

Tobramycin dosing can be challenging in patients with CF. This is due to the underlying pharmacokinetic derangements (e.g., volume of distribution, organ function) frequently observed in this population. Accordingly, the use of standard dosing (based on age or mg/kg) often results in fluctuating systemic concentrations, impacting safety and treatment efficacy. To optimise therapy, ‘precision dosing’ has become increasingly favoured.

Precision dosing is the concept of dose individualisation to ensure drug concentrations are within therapeutic range. In clinical practice, the two most popular precision dosing strategies used to ascertain drug exposure and calculate the optimal dose are log linear regression (LLR) and Bayesian forecasting (BF). At present, a comparative evaluation of LLR and BF has not been systematically performed and it remains unclear whether one approach offers a meaningful advantage over the other in clinical practice. In this thesis I endeavoured to assess this shortcoming in the literature.

Chapter 1 is an overview of key concepts underlying tobramycin dosing, concentration monitoring and target attainment and outlines existing literature evaluating LLR and BF. Chapter 2 describes a quasi-experimental intervention study conducted to
evaluate clinical and performance outcomes amongst children with CF for whom tobramycin therapy was guided by either LLR or BF at a tertiary children’s hospital. In Chapter 3, I discuss the implications of my study findings as well directions for future research.
List of Abbreviations

AUC$_{24}$: Area under the concentration-time curve during a 24-hour period
BF: Bayesian forecasting
CF: Cystic fibrosis
CFTR: Cystic fibrosis transmembrane conductance regulator
FEV$_1$: Forced expiratory volume in 1 second
IV: Intravenous
LLR: Log-linear regression
MIC: Minimum inhibitory concentration
PD: Pharmacodynamic
PK: Pharmacokinetic
TDM: Therapeutic drug monitoring
List of Publication(s)

Published manuscript in support of thesis


Other contextual works published during the enrolment period of the degree


Chapter 1 - Background and Literature Review

Children with cystic fibrosis (CF) are genetically predisposed to developing recurrent and polymicrobial respiratory infections throughout their lifetime, a major source of morbidity and mortality.¹ Accordingly, these children receive repeated and extended courses of antibiotics to preserve lung function and prolong survival.² However, the pharmacokinetic derangements exhibited secondary to CF make optimising antibiotic therapy challenging.³ Key considerations for antibiotic dosing in children with CF are outlined below.

1.1 Cystic fibrosis

CF is an autosomal recessive condition whereby the gene encoding for the CF transmembrane conductance regulator (CFTR) protein carries a mutation making ion transportation across cell membranes dysfunctional.⁴ This leads to increased mucus viscosity in many organ systems particularly the respiratory tract. This manifests as mucosal dehydration, impaired mucociliary clearance and the inhibition of airway proteases.⁵ These changes hinder innate respiratory defence mechanisms thereby creating an ideal environment for bacterial colonisation/infection and chronic inflammation.

The extra-pulmonary sequelae of CF are also pronounced and influence drug dosing. Changes in the gastrointestinal tract (e.g., dysmotility, poor fat metabolism) alter drug absorption and bioavailability.⁶ Hepatic dysfunction and decreased production of plasma binding proteins increase the drug volume of distribution, as does poor nutritional states and higher lean body mass frequently associated with CF.⁶ In addition, altered expression of metabolising enzymes and occurrence of diabetic
nephropathy can modify drug clearance. Conventional dosing strategies cannot sufficiently account for these pharmacokinetic differences.

1.1.1 Microbiology in CF

During early childhood, the common causative pathogens underlying acute pulmonary exacerbations are *Haemophilus influenzae* and *Staphylococcus aureus*. Over time and with lung disease progression, Gram negative organisms, namely *Pseudomonas aeruginosa*, colonise the airways and become the predominant pathogen. Early eradication and prevention of *P. aeruginosa* colonisation is highly desirable as this bacterium gradually develops several mutations that render it resistant to antibiotics. Once *P. aeruginosa* colonisation has occurred chronic infection and rapid deterioration of lung function will usually follow.

1.2 Aminoglycosides

Due to effectiveness of aminoglycosides in eradicating Gram-negative organisms such as *P. aeruginosa*, they are routinely used in treating CF pulmonary exacerbations. In clinical practice, tobramycin is the aminoglycoside of choice for paediatric patients. However, subtherapeutic drug concentrations increase the risk of therapy failure and pathogen resistance development, whilst excess concentrations pose a risk for toxicity and extend the length of hospital stay. Hence, efforts to optimise tobramycin dosing are important.

1.2.1 Tobramycin Dosing

In Australia, the conventional dose of tobramycin is 10-12mg/kg which is administered once-daily in the morning as an infusion over 30 to 60 minutes. Dosing is then
adjusted accordingly based on measured systemic concentrations to achieve a desired target. Once daily dosing is preferred over twice or three times per day because it is more convenient, has equal efficacy and reduces the risk of nephrotoxicity. The duration of tobramycin therapy for CF pulmonary exacerbations is 7 to 14 days depending on clinical response.

1.2.2 Tobramycin Pharmacokinetics

In CF, the most important factors affecting tobramycin the dose-concentration relationship are body composition and renal function. The malabsorption phenomena, increased metabolic expenditure and reduced food intake mean that children with CF are typically of lean build. As lean tissue contains greater extracellular fluid than adipose tissue, the volume of distribution for hydrophilic antibiotics including tobramycin is increased.

In addition, many studies have observed an increase in total body clearance of aminoglycoside antibiotics in CF. The CFTR protein is expressed in the nephrons of the kidney and inactivation of this protein is associated with low-molecular weight proteinuria. Although the precise mechanism is not yet understood, it is hypothesised that the defective CFTR protein somehow causes an increased glomerular filtration rate, increased tubular secretion, and/or decreased tubular reabsorption of tobramycin.

In CF, the combination of a larger volume of distribution and increased renal clearance often means larger doses of tobramycin are required to achieve the desired target concentrations.
1.2.3 Therapeutic Drug Monitoring

For treatment of CF pulmonary exacerbation, tobramycin therapeutic drug monitoring (TDM) is considered standard of care. Following dose administration, blood samples are collected from the patient at timed intervals and tobramycin assays are performed. The measured concentrations are then interpreted within the clinical context and dosing is modified to maintain concentrations within therapeutic range.

Of note, TDM performance can vary between institutions. The number and timing of blood sample collection relies on the concentration targets and dose adjustment strategies adopted at each site and these may differ according to local guidelines. In terms of frequency, TDM is generally performed within 48h of commencing tobramycin therapy and then repeated until desired concentrations are attained. Once targets are attained, ongoing monitoring occurs at the discretion of the overseeing clinician. This is usually prompted by prolonged durations of therapy or change in the patient’s clinical status.

1.2.4 Target Concentrations

Aminoglycosides, including tobramycin, have a concentration-dependent bactericidal effect. That is, the higher the aminoglycoside concentration (relative to the organism’s minimum inhibitory concentration (MIC), the more rapid and extensive the bactericidal eradication.

Historically, a peak tobramycin concentration (C\text{max}) to MIC ratio (C\text{max}/MIC) of ≥10 was regarded as the best predictor of clinical efficacy. This is equivalent to a C\text{max} of ~10 to 20 mg/L, considering the susceptibility cut-off of most Gram-negative
organisms to tobramycin is 1 to 2 mg/L.\textsuperscript{21} Similarly, to reduce the risk of toxicity, the tobramycin trough concentration (C\textsubscript{min}) is monitored with the desired target set at of <2 mg/L.\textsuperscript{21}

However, reliably calculating transient metrics such as C\textsubscript{max}/C\textsubscript{min} in a single patient, for an antibiotic dosed once daily, is difficult. For instance, C\textsubscript{max} measurements have been shown to vary significantly depending on the duration of the tobramycin infusion administered and the timing of blood sample collection.\textsuperscript{21,22} In reported clinical practice, measuring C\textsubscript{max} ranges from blood samples being taken immediately or up to 120min post-infusion.\textsuperscript{21}

Although C\textsubscript{max}/C\textsubscript{min} is still used for monitoring tobramycin at some institutions, the more contemporary metric is a concentration target defined by the 24h-area under the concentrations curve (AUC\textsubscript{24}).\textsuperscript{23} Whereas C\textsubscript{max}/C\textsubscript{min} provide a ‘snapshot’ of systemic drug concentrations, the AUC\textsubscript{24} is an integrated concentration-time profile and measures both the concentration and the duration of tobramycin activity in circulation (Figure 1).\textsuperscript{21,24} Accumulating evidence now supports AUC\textsubscript{24} as the preferred method for tobramycin TDM.\textsuperscript{21} This is also endorsed by the Australian Therapeutic Guidelines.\textsuperscript{25}

Although the AUC\textsubscript{24} is considered to be a more dependable and consistent metric for monitoring tobramycin concentration, it has its limitations.\textsuperscript{26} For instance, the ideal target AUC\textsubscript{24} for efficacy and in particular toxicity is less well-defined. Current best evidence suggests that in CF a tobramycin AUC\textsubscript{24} ≥100 mg/L·h is favourable, but a range between 80 to 125 mg/L has also been reported as acceptable.\textsuperscript{21} Additionally,
the optimal approach for calculating AUC$_{24}$ and adjusting tobramycin doses remains undefined.

![Graph showing concentration targets for tobramycin](image)

**Figure 1:** Illustration of the concentration targets associated with efficacy and toxicity for tobramycin (Note: Figure has been reproduced/adapted from Hodiamont et al. under Creative Commons Licence)

### 1.3 Dose Optimisation Approach

In clinical practice, the two most common approaches for estimating tobramycin AUC$_{24}$ are log-linear regression (LLR) and Bayesian forecasting (BF).$^{17}$ LLR is an equation-based strategy which uses simple first-order pharmacokinetic principles. With LLR, two blood samples are collected, the first at 1 to 2 hours and the second at 8 to 10 hours post-tobramycin infusion.$^{27,28}$ This coincides with the expected peak and mid-dose interval concentrations of tobramycin. The two ‘paired’ concentration data are then entered into a Microsoft Excel spreadsheet embedded with a validated regression equation and the AUC$_{24}$ is then calculated linearly based on the patient’s own drug concentration profile.$^{29}$
Although LLR offers a simple means of calculating AUC\textsubscript{24} with reasonable accuracy, it does have a few shortcomings. Notably, the need for two blood collections can be tedious and more invasive, particularly for children.\textsuperscript{30} Furthermore, each blood sample must be meticulously timed for results to be precise which may be difficult to coordinate in a busy clinical environment.\textsuperscript{31} Erroneous recorded preanalytical information (i.e., time of dose or time of blood collection) has been shown to be a significant source of bias with LLR.\textsuperscript{32} Moreover, LLR is unable to offer dose predictions until the first dose of tobramycin is administered. These elements also render LLR incompatible with the ambulatory management of CF pulmonary exacerbation which is becoming increasingly in demand.\textsuperscript{33}

BF is the more modern and sophisticated method for AUC\textsubscript{24} calculation. It uses specialist software incorporating population pharmacokinetic data and probabilistically determines tobramycin AUC\textsubscript{24} based TDM and how the drug has behaved in prior patients.\textsuperscript{34} With time and accumulation of the patient’s own data the software’s predictive accuracy is further refined. In addition, BF can calculate AUC\textsubscript{24} using only single blood sample able to be collected at any time.\textsuperscript{35} Combined, these features of BF allow for AUC\textsubscript{24} to be calculated with low bias at convenient and opportune times, whilst empowering clinicians to make expedited dosing decisions.\textsuperscript{36} Despite these advantages LLR remains far more frequently used in clinical care in Australia and abroad.\textsuperscript{17}

1.4 Comparison of LLR and BF

In general, when compared to no intervention, TDM-guided aminoglycoside therapy coupled with an appropriate dosing strategy (e.g., LLR or BF) increases target
concentration attainment and improves clinical outcomes.\textsuperscript{37-39} Yet, deciding on which dosing strategy is ideal for tobramycin therapy in the setting of paediatric CF pulmonary exacerbations remains uncertain. To date, very few studies have directly compared LLR and BF.\textsuperscript{32, 40-42} Of these, most were performed using small sample sizes, only examined AUC\textsubscript{24} target attainment or were conducted in controlled research settings.

Considering the existing literature, a study by Hennig et al. revealed LLR and BF function equally well in terms of AUC\textsubscript{24} predictive performance and offer comparable tobramycin dose recommendations for children with CF.\textsuperscript{40} Similar findings were also noted by Barras et al., albeit their study only included twelve CF patients and did not assess all sampling time combinations for LLR.\textsuperscript{41} This latter limitation is pertinent given the variability in sampling time that can exists in clinical practice. If fact, Gao et al. who also analysed AUC\textsubscript{24} estimations in CF patients identified sampling time as a cause of significant bias, noting median relative prediction errors ranging from −34.7 to 45.5\% with LLR.\textsuperscript{32} Most recently, Brockmeyer et al. retrospectively calculated AUC\textsubscript{24} using BF among a group of patients for whom during clinical care tobramycin therapy was guided by traditional LLR.\textsuperscript{42} Here, the authors found the BF estimates of AUC\textsubscript{24} were on average 6.4 mg/L·h higher than the LLR estimates, surmising that one in seven patients treated would have avoided a tobramycin dose increase had BF been used instead, with this increasing toxicity risk.

Although published data comparing LLR and BF continues to build what still remains unknown is whether there are differences in overall patient clinical outcomes when each of LLR or BF are used in a 'real-word' clinical settings. Similarly, theorised
benefits in terms of performance and practicality for each of LLR and BF have not been formally quantified and could be equally valuable. Any observed differences may help delineate superiority/non-inferiority and provide justification for selecting and implementing either method in clinical practice.

Summary

Children with CF pulmonary exacerbations receive IV tobramycin therapy, with dosing guided by either LLR or BF. It remains unclear whether one approach is superior to the other and clinical data is scarce. Knowledge of comparative advantages between LLR and BF may justify selection of either approach, guide clinical practice, and assist with optimising treatment of pulmonary exacerbations. The aim of this thesis is to evaluate clinical and performance outcomes amongst children with CF for whom tobramycin therapy is guided by either LLR or BF.
Chapter 2 – Manuscript *

1. Introduction

Cystic fibrosis (CF) is a life-threatening genetic disorder that affects multiple organ systems, resulting in significant morbidity and mortality.\textsuperscript{43} The most serious consequence of CF is progressive degeneration of lung function secondary to chronic and typically polymicrobial respiratory infections.\textsuperscript{44} Bacteria such as \textit{Staphylococcus aureus}, \textit{Haemophilus influenzae} and \textit{Pseudomonas aeruginosa} opportunistically colonise the airways of CF patients and may lead to intermittent infective exacerbations.\textsuperscript{45} A widely accepted treatment strategy is to administer intravenous (IV) tobramycin, an aminoglycoside antibiotic, once daily for 7 to 14 days, usually in combination with a β-lactam antibiotic.\textsuperscript{11,46,47}

When tobramycin concentrations are too high, there is an increased risk of adverse events including nephrotoxicity and ototoxicity.\textsuperscript{48} Conversely, when concentrations are too low, there is an increased risk of therapeutic failure, antibiotic resistance, and poor clinical outcomes.\textsuperscript{49} As patients with CF often receive numerous and extended courses of tobramycin throughout their lifetime, optimising tobramycin treatment for efficacy and safety is paramount. This relies on maintaining systemic drug concentrations within a narrow target range during each antibiotic course.

CF can significantly alter pharmacokinetic parameters (e.g., volume of distribution, body composition, renal function), impacting drug absorption and clearance.\textsuperscript{50} In this context, conventional dosing of tobramycin (based on age or mg/kg) may result in unpredictable and fluctuating drug concentrations.\textsuperscript{51} To personalise therapy, routine

\* Reference and figure numbers of the manuscript have been amended from the published version for the purposes of the thesis. The published version of the manuscript is contained in the Appendix.
therapeutic drug monitoring (TDM) is required, and doses must be adjusted accordingly toward a pharmacokinetic/ pharmacodynamic (PD/PK) target. The ideal target to use during clinical care is contentious, with discrepancies existing both within and between countries.

Traditionally, the tobramycin PK/PD is defined by a peak (C\text{max}) and trough (C\text{min}) concentration-effect relationship. However, as C\text{max} and C\text{min} are transient compared to overall drug exposure, evidence suggests these indices are less suitable for once-daily dosed tobramycin. In Australia, hospitals have increasingly transitioned towards a PK/PD target defined by the 24h-area under the concentration time curve (AUC\text{24}) relative to the MIC of the bacterium, in keeping with national guidelines. By convention, an MIC of 1 mg/L is assumed during empiric therapy. Accordingly, a tobramycin target AUC\text{24}/MIC of ≥100 mg/L·h is desired for patients with CF.

Two methods that are used to predict AUC\text{24} during tobramycin treatment are log-linear regression (LLR) and Bayesian forecasting (BF). LLR is considered the low-fidelity, prototypical method and has been extensively appraised. It involves collecting two tobramycin concentrations at fixed intervals (relative to dose administration) and estimating AUC\text{24} based on simple pharmacokinetic calculations, assuming a one-compartment distribution model. Although conceptually straightforward, LLR is highly sensitive to the precise timing of sample concentrations. Thus, in busy clinical environments, where accurately timed blood collections are difficult to coordinate, LLR is prone to significant bias.

In contrast, BF entails the use of sophisticated software embedded with population pharmacokinetic data. The pre-existing population covariates are used to prospectively identify individual’s pharmacokinetic parameters for the purposes of
calculating AUC\textsubscript{24}.\textsuperscript{57,58} In addition, elements of sampling and assay method can be integrated to improve accuracy of AUC\textsubscript{24} estimates.\textsuperscript{59} A further benefit of BF is that only a single tobramycin concentration is required. This can be collected at unrestricted and patient preferred times, prior to achieving steady-state drug concentrations.\textsuperscript{41} Granting all this, the LLR approach remains far more commonly used in clinical practice.\textsuperscript{17}

Aside from methodological disparities, what is perhaps more important but remains unknown is whether there are any differences in clinical (e.g. respiratory function) and/or performance outcomes (e.g. practicality, accuracy) when each method is utilised. Adopting evidence into healthcare is often challenging and the effectiveness of promising health interventions can be variable once implemented into practice.\textsuperscript{60} As it stands, BF occupies a transitional space between research and practice with many of its touted benefits not yet systematically appraised at the clinical coalface.\textsuperscript{61} In the setting of paediatric CF, knowledge of comparative advantages between LLR and BF may justify selection of either approach, guide clinical practice, and assist with optimising treatment of pulmonary exacerbations.

We conducted a quasi-experimental pre-post intervention study to evaluate clinical and performance outcomes amongst children with CF for whom tobramycin therapy was guided by either LLR or BF at a tertiary children’s hospital.

2. Methods

2.1 - Setting and Data Source

The Children’s Hospital at Westmead is a paediatric referral hospital in metropolitan Sydney, Australia. At our institution, between the years 2018 to 2019, there was a
transition from LLR (pre-intervention) to a BF (post-intervention) approach for tobramycin dosing in CF patients. We extracted electronic medical records to establish a deidentified database consisting of pre-intervention and post-intervention patients as well their relevant clinical and dosing performance outcome measures.

2.2- Selection Criteria

All consecutive patients treated with IV tobramycin for CF pulmonary exacerbations between January 2015 to September 2021 (i.e., immediate three-years pre- and post-intervention period) were included in the study. Only patients treated exclusively with either LLR or BF were considered eligible for inclusion.

2.3- Evaluation of Outcomes

The primary clinical outcomes considered in this study were: (1) hospital length of stay (LOS), (2) rates of unexpected hospital re-admission within the subsequent month following discharge, (3) pulmonary function (with reference to change in forced expiratory volume in the first second (Δ FEV₁) from time of hospital admission to discharge) and (4) rates of acute kidney injury (AKI). The occurrence of AKI was defined in terms of clinical suspicion/diagnosis or a second blood test demonstrating ≥1.5 times increase in baseline serum creatinine at any time during hospital admission. The performance outcomes considered were those relating to tobramycin dosing and pharmacokinetics. These included (5) the number and timing of tobramycin TDM blood samples collected, (6) empiric (initial) dose selection, (7) final maintenance dose prescribed throughout hospital admission and (8) the frequency and precision of target concentration attainment. Given our younger patient demographic with preserved renal function, the tobramycin target AUC₂₄ used at our institution during the study
period was ≥100 mg/L·h. Precision dosing was defined as attaining a tobramycin AUC$_{24}$ within the range of 100 to 110 mg/L·h.

2.4 - Local Practice and Procedures

At our centre, clinical pharmacists working in a CF team (consisting of clinicians, physiotherapists, nutritionists etc.) oversee tobramycin dosing and monitoring. As per local guidelines, tobramycin is administered in the morning as a once daily infusion over 30 mins. An empiric dose of 10-12mg/kg (up to a maximum of 600mg) is typically prescribed. The first AUC$_{24}$ is ideally calculated within 48-hours of commencing therapy, which is then used to guide dose adjustment.

With the LLR method, two blood tobramycin concentrations from each patient are drawn during a dosing interval: the first between 30min to 2-hours and the second between 6 to 10-hours after the infusion. These two ‘paired’ measurements are entered into a Microsoft Excel spreadsheet embedded with first order pharmacokinetic equations described by Hennig et al. 2015. The AUC$_{24}$ is characterised as a mono-exponential curve and the recommended dose is calculated linearly. Using BF, only a single blood tobramycin concentration is collected at any time-point after the infusion is complete. This measurement, along with patient’s demographic and clinical data, is entered into DoseMe© (http://doseme.com.au), an online Bayesian dose individualisation platform. Here, the AUC$_{24}$ is estimated based on the integrated population model.

At our hospital, laboratory MIC testing is often not performed or only made available after several days delay. Importantly, even when testing is performed, the individual MIC measurements may not be sufficiently accurate. Thus, a target MIC of 1mg/L is assumed for Gram-negative organisms treated with tobramycin and, in essence,
AUC\textsubscript{24} alone is used to guide dosing. This strategy remained consistent during the entirety of the study period and is commonly used amongst other hospitals and across different antibiotics.\textsuperscript{21,64}

Regarding lung function assessment, all spirometry testing is performed by a respiratory scientist and conducted at our on-site respiratory laboratory. In general, only patients older than four years of age are considered eligible. A referral from the admitting respiratory physician is required to initiate an assessment. For each referred patient, spirometry is performed ideally twice, once near to time of admission and then once prior to discharge.

Besides the change in dosing strategy from LLR to BF there was no other formal guidance or instruction provided to clinicians overseeing the care of CF patients. The target tobramycin AUC\textsubscript{24} was set to 100 mg/L-h, throughout both study periods and this was standardised in the LLR calculator and DoseMe platform as the default value. In the LLR group dose adjustments were made linearly (i.e., the was dose doubled if the level was half what it should be) and as per DoseMe recommendations in the BF group. Doses were rounded to the nearest 10mg for ease of administration. Dose selection support was provided to admitting teams by a trained CF fellow. The frequency of blood sampling and TDM performance was based on the discretion of each admitting officer.

2.5- Statistical Analysis

Data analyses were performed using JASP© statistical software (Version 0.16) (https://jasp-stats.org/). Continuous variables are reported as mean ± SD or median (IQR), for parametric and non-parametric data, and compared using Student’s T or
Mann–Whitney U tests, respectively. Categorial variables are reported as numbers and/or proportions and compared using χ2 test. Results were deemed statistically significant when the P-value was <0.05. Repeat hospital admissions were noted for a cohort of patients in both the LLR and BF groups and assumed to be independent for the purposes of statistical analysis.

2.6- Ethics

Ethics approval was sought and granted by the Sydney Children’s Hospitals Network Human Research Ethics Committee (2019/ETH11521). Cross-institutional approval was conferred by University of Notre Dame Australia (2021-073S).

3. Results

A total of 376 hospital admissions for CF pulmonary exacerbations were included in the study. Tobramycin therapy was guided by LLR during 66% (n=248) of the admissions whilst BF was utilised in the remaining 34% (n=128). Patient demographics were similar between LLR and BF cohorts in terms of gender ratios, age, weight, and body mass index (Table 1). A homozygous pF508.del genotype was more prevalent in BF group (45%, 57/128) compared to the LLR group (32%, 79/248) (P=0.02). Cystic fibrosis transmembrane conductance regulator (CFTR) modulators were more commonly used during BF (29%, 37/128) as opposed to LLR (3%, 8/248) admissions (P<0.001). Baseline mean FEV1 was ~5% greater amongst those treated with BF (P=0.02). All patients received twice daily airway physiotherapy and nutritional support during each admission.

Sputum and/or bronchial lavage samples were collected at the time of hospital presentation (prior to antibiotic therapy) in 45% (58/128) of the BF admissions and 52% (130/248) of the LLR admissions (P=0.19). In each cohort, ~90% of collected
samples yielded positive cultures ($P=0.78$) (Table 1). *P. aeruginosa* was isolated in 19% (11/58) of cultures in the BF group and 38% (50/130) of cultures from LLR group ($P=0.01$).

With regards to clinical outcomes (Table 2), there were no significant differences found in overall hospital LOS or rates of re-admission for CF pulmonary exacerbations. Overall, patients in both groups had improved lung function at the end of tobramycin treatment, with a comparable mean $\Delta FEV_1$ during hospital admission (LLR= 8.1% versus BF= 7.8%; $P=0.65$). Incidence of AKI was rare with only one diagnosis made in the LLR group.
Table 1: Baseline characteristics

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</tr>
<tr>
<td>Co-administered antibiotic, n (%)</td>
<td></td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>124 (50)</td>
<td>58 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>84 (34)</td>
<td>47 (37)</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>37 (15)</td>
<td>22 (17)</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Creatinine (µmol/L), mean (SD)</td>
<td>47.5 (15)</td>
<td>43.7 (14)</td>
<td>0.08</td>
</tr>
<tr>
<td>FEV₁ (%), mean (SD)</td>
<td>69.7 (19)</td>
<td>74.5 (19)</td>
<td>0.02</td>
</tr>
<tr>
<td>No. of positive cultures</td>
<td>114/130</td>
<td>50/58</td>
<td>0.78</td>
</tr>
<tr>
<td>Isolates:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>50</td>
<td>11</td>
<td>0.01</td>
</tr>
<tr>
<td>S. aureus</td>
<td>60</td>
<td>31</td>
<td>0.36</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>3</td>
<td>1</td>
<td>0.80</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1</td>
<td>0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

LLR- log linear regression; BF- Bayesian forecasting; BMI- Body mass index; CFTR- Cystic fibrosis transmembrane conductance regulator; FEV₁- Forced expiratory volume in the first second.

Note: Repeat hospital admissions were assumed to be independent for the purposes of statistical analysis. Demographic variables have been calculated using total number of admissions as the denominator (LLR = 248, BF =128), unless otherwise specified.

*Baseline creatinine and FEV₁ were not assessed/available for all admissions. Creatinine was available for LLR (n=207, 83%) and BF (n=109, 85%). FEV₁ was available for LLR (n=222, 90%) and BF (n=107, 84%).

**Sputum and/or bronchial lavage samples were not collected/available for all admissions. A microbiology culture was available for LLR (n=130, 52%) and BF (n=58, 45%). Not all microbial isolates are reported.
In terms of performance outcomes (Table 3), patients treated with LLR on average had twice the number of TDM blood samples collected during a single hospital admission (LLR =3.8 versus BF =1.9; \( P<0.001 \)). The TDM samples for LLR were all collected within 10-hours following dose administration, reflecting a bimodal time distribution (Figure 2). With BF, a wider timeframe for TDM sampling was observed, with blood sample collection occurring up to 16-hours post tobramycin dosing. Of all blood samples collected, 35% (86/249) were dedicated entirely to tobramycin TDM (i.e., with no other laboratory test ordered concurrently) in the BF group and 74% (690/933) in the LLR group (\( P<0.001 \)).

The median tobramycin dose prescribed was higher during admissions where BF was used compared to LLR, both during empiric (initial) (430mg versus 390mg; \( P=0.18 \)) and maintenance (400mg versus 395mg; \( P=0.89 \)) therapy. A change from the empiric dose was more frequently observed in the BF group (72%, 92/128) compared to the LLR group (63%, 155/248), although this difference was not statistically significant (\( P=0.07 \)). Compared to the LLR group (18%, 45/248), fewer patients treated with BF (11%, 14/128) required three or more AUC\(_{24}\) calculations performed.

<table>
<thead>
<tr>
<th></th>
<th>LLR ((n=248))</th>
<th>BF ((n=128))</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS (days), mean (SD)</td>
<td>15.1 (4)</td>
<td>16.1 (6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospital readmission, n (%)</td>
<td>12 (5)</td>
<td>5 (4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Acute kidney injury, n (%)</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>0.29</td>
</tr>
<tr>
<td>( \Delta \text{FEV}_1 ) (%), mean (SD)</td>
<td>8.1 (10)</td>
<td>7.8 (8)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

LLR- log linear regression; BF- Bayesian forecasting; LOS-length of hospital stay; \( \Delta \text{FEV}_1 \)- change in forced expiratory volume in the first second from time of hospital admission to discharge.

*Hospital readmission for pulmonary exacerbations of cystic fibrosis within 1 month of discharge.

**Acute kidney injury based on clinical suspicion/diagnosis or second blood test.

***\( \Delta \text{FEV}_1 \) was not available in all patients. Data was available for LLR \((n=222, 90\%)\) and BF \((n=107, 84\%)\).
The mean tobramycin AUC$_{24}$ was higher in the BF group both when the first (BF =106 mg/L·h versus LLR =94.7 mg/L·h; $P<0.001$) and final (BF =102.6 mg/L·h versus LLR = 95.1 mg/L·h; $P<0.001$) calculated AUC$_{24}$ in each admission were considered (Figure 3). The tobramycin target AUC$_{24}$ of ≥100 mg/L·h was more frequently attained during hospital admissions where BF was used (72%, 92/128) compared to LLR (50%, 124/248) ($P<0.001$). A higher proportion of the BF group (39%, 50/128) also achieved an AUC$_{24}$ within the precision range of 100 - 110 mg/L·h, compared to the LLR group (25%, 61/248) ($P=0.004$).

### Table 3: Performance outcomes per admission

<table>
<thead>
<tr>
<th>Tobramycin TDM sampling</th>
<th>LLR (N=248)</th>
<th>BF (N=128)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of samples collected, total</td>
<td>933</td>
<td>249</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. of samples per admission, mean (SD)</td>
<td>3.8 (2)</td>
<td>1.9 (1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>*No. of dedicated samples, (n/total) (%)</td>
<td>690/933 (74)</td>
<td>86/249 (35)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tobramycin dosing</th>
<th>Initial dose</th>
<th>Maintenance dose</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage (mg), median (IQR)</td>
<td>390 (200)</td>
<td>395 (188)</td>
<td>0.18</td>
</tr>
<tr>
<td>Initial vs maintenance dose unchanged, n (%)</td>
<td>93 (38)</td>
<td>36 (28)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

| Tobramycin pharmacokinetics | | |
|-----------------------------|--|--|--|
| No. of AUC$_{24}$ during admission, n (%) | 1 | 131 (53) | 56 (44) | 0.01 |
| 2 | 72 (29) | 58 (45) |
| ≥ 3 | 45 (18) | 14 (11) |

| First AUC$_{24}$ measured (mg/L·h), mean (SD) | 94.7 (26) | 106.0 (31) | < 0.001 |

| Final AUC$_{24}$ measured (mg/L·h), mean (SD) | 95.1 (16) | 102.6 (19) | < 0.001 |

| Target attainment during admission, n (%) | AUC$_{24}$ ≥100 mg/L·h | 124 (50) | 92 (72) | < 0.001 |

| AUC$_{24}$ = 100 to 110 mg/L·h | 61 (25) | 50 (39) | 0.004 |

** LLR - log linear regression; BF - Bayesian forecasting; TDM – Therapeutic drug monitoring; AUC - area under the curve.

* A dedicated sample is one that is collected for the purposes of TDM only, with no other laboratory test ordered concurrently.

** Maintenance dose is defined as the final dose of tobramycin prescribed during the admission, after any dose adjustments occurred.

*** Includes patients with at least two AUC$_{24}$ estimates during a hospital admission, LLR (n=117, 47%) and BF (n=72, 56%).
**Figure 2:** Post-dose collection time (hrs) of all tobramycin blood samples (levels) from patients in the log-linear regression (LLR) (n=933) and Bayesian forecasting (BF) (n=249) groups.

**Figure 3:** Tobramycin area under the curve (AUC_{24}) estimates using log-linear regression (LLR) and Bayesian forecasting (BF) methods. Minimum target AUC_{24} (100 mg/L·h) is represented by the dashed line. The mean AUC_{24} is represented by ‘x’. The differences in mean (SD) AUC_{24} between the 2 groups in each category - First AUC_{24} measured (LLR= 94.7 (26) versus BF = 106.0 (31), P <0.001) and Final AUC_{24} measured (LLR= 95.1 (16) versus BF = 102.6 (19)), P <0.001.
A subset of patients (n=44) contributed data to both LLR and BF phases. A pairwise comparison was performed for this cohort evaluating outcomes from their last LLR admission against those of their first BF admission. In this analysis, with a small sample size, no meaningful conclusions could be drawn (data not presented).

4. Discussion

The recurrence of pulmonary exacerbations and associated decline in FEV$_1$ is regarded as the most significant predictor of mortality from CF.$^{65}$ Thus, optimising the treatment of CF pulmonary exacerbations is paramount, particularly antibiotic therapy. Dosing of antibiotics in patients with CF is challenging given the inherent pharmacokinetic variability associated with the condition, poor intrapulmonary penetration of systemic antibiotics, and the potential for antimicrobial resistance and drug toxicity. In this setting, utilising TDM coupled with a suitable dosing method is now considered standard of care in enabling individualised, efficacious, and safe therapy.$^{66}$

A consensus on the ideal dosing approach for use in daily practice remains elusive. In our literature review, we were unable to identify any published studies equating patient outcomes during pharmacotherapy guided by LLR and BF. This is despite the longstanding use of both these approaches for drug dosing of antimicrobials and in other therapeutic areas including oncology and transplantation.$^{67,68}$ To the best of our knowledge, our study is the first to systematically compare patient clinical outcomes with LLR and BF methodologies during antibiotic therapy. We attempted to mitigate confounding by assessing a relatively homogenous cohort of paediatric patients with CF pulmonary exacerbations treated with once daily IV tobramycin.
With regards to homogeneity of the study cohorts, we note that a small difference (~5%) in mean baseline FEV\(_1\) was detected between the LLR and BF groups, yet clinical interpretation of this was difficult. On the one hand, this could imply greater baseline disease severity in the LLR group, in keeping with higher rates of *Pseudomonas* colonisation. On the other, the BF group exhibited higher rates of pF508.del homozygosity which typically indicates poorer lung function.\(^{69}\) Additionally, the prevalence CFTR modulator use was greater in the BF group, consistent with recent changes in clinical practice.\(^{70}\) This represents a further potential confounder given the efficacy of these agents in improving baseline FEV\(_1\) (by ~ 3 to 7%) and suspected interaction with airway microbiome.\(^{71,72}\) Overall, it is likely that the difference in baseline FEV\(_1\) simply reflects the inherent variability of spirometry testing.\(^{73}\)

In our evaluation of clinical outcomes, we did not find any significant difference in hospital LOS or readmission when LLR or BF were used. Likewise, there was no difference in rates of AKI, which was seldom diagnosed in both cohorts. To account for this, it is likely that the risk of nephrotoxicity for all study patients was mitigated in the first instance by the routine use of TDM (during target concentration attainment) and once-daily tobramycin dosing.\(^{74}\) The recognised incidence of aminoglycoside-induced AKI is also ordinarily low in paediatric patients.\(^{75}\) Thus, our results may have differed if adult populations, exposed to long-term accumulative doses, were considered. Finally, we found that the changes in FEV\(_1\) pre- and post-tobramycin treatment were comparable between the BF and LLR groups. This is particularly important given that FEV\(_1\) has been validated as a surrogate measure of risk of death and quality of life in CF and is regarded as the most meaningful clinical outcome.\(^{76}\)
In terms of performance outcomes, our results demonstrate that BF can halve the number of blood collections required during each admission compared to LLR. A major limitation of LLR is that it requires two blood samples. The sample collections must also be meticulously timed for results to be accurate, which is often difficult to coordinate during a hospital admission. Of note, the repeated venepunctures with LLR can be particularly invasive and a source of psychological distress for paediatric patients. With BF, timing of collections is flexible and can be aligned with daily pathology rounds in most instances. Additionally, the option of opportunistic sampling is easier to facilitate as TDM samples can be coupled with other blood draws, as shown in our study. Moreover, it is reasonable to assume that minimising the number of collections using BF can also offer significant cost benefits over time.

Considering dosing and pharmacokinetics parameters, several studies have demonstrated that LLR and BF can predict tobramycin AUC\textsubscript{24} with similar accuracy. In contrast, Avent \textit{et al.} found that in a cohort of patients with febrile neutropenia, treatment with gentamicin (another aminoglycoside antibiotic) guided by BF resulted in more frequent and precise attainment of target drug concentrations compared to LLR. This, in part, may be attributed to the fact that the majority of the referenced tobramycin studies were conducted in controlled research settings, using small samples sizes (n<15). Thus, the seemingly comparable predictive performance of LLR and BF could in fact differ once implemented in larger numbers in daily clinical practice.
In view of this, at our institution, we found that patients for whom dosing was guided by BF achieved the desired target tobramycin concentrations more frequently (72%) compared to LLR (50%) during their admission. Accordingly, BF patients also received greater median doses of tobramycin (both empirically and for maintenance) and had higher rates of dose adjustment. Regarding the latter, frequency of dose adjustments with BF were likely assisted by the relatively easier performance of repeat AUC<sub>24</sub> calculations. Additionally, BF offered greater precision of target attainment (defined as an AUC<sub>24</sub> between 100 to 110 mg/L·h) compared to LLR at rates of 39% and 25%, respectively.

The limitations of this study are that it was conducted at a single site using a pre-post intervention study design and was not a formal randomised controlled trial. Theoretically, this renders the study susceptible to bias (namely performance bias) such as differences in laboratory services and clinicians overseeing TDM decisions. Reassuringly, there were no official changes to hospital guidelines during the study period to influence dose selection and the differences in median tobramycin dose prescribed for initial and maintenance therapy were not statistically significant. A maturation effect is also conceivable where the outcomes of interest were naturally impacted over time by the improvements in CF targeted therapies, likely accelerated gain in clinician experience or conversely, the progression of disease. For instance, the use of CFTR modulators increased during the study period. Additionally, the CF clinic at our hospital was gradually restructured to facilitate single room visits as a means of strengthening infection control. Such evolving practices could plausibly explain the decrease in rates of Pseudomonas colonisation noted over time. Nonetheless, our study reflects real world clinical care at a large paediatric hospital.
and so its findings can be relevant to other specialised institutions caring for children with CF.

Regarding assessment of clinical outcomes, in particular hospital LOS, it is valuable to note that treatment of CF pulmonary exacerbations is protocolised in many hospitals, including ours. Although this may influence the minimum hospital LOS, we assume that if significant differences in clinical efficacy did in fact exist between LLR and BF, then admission lengths would have been prolonged accordingly. Furthermore, we were unable to compare other potentially relevant clinical outcomes such as occurrence of ototoxicity. Diagnosing ototoxicity is largely reliant on audiometric evaluation which is not routinely performed at our institution.

Additionally, the apparent pharmacokinetic and dosing advantages of BF found in the study did not impact overall clinical outcomes. Optimising antibiotic therapy is a continuum, and it is likely that the peaks of clinical benefit are achieved once routine TDM is coupled with LLR guided dosing, particularly at a specialised centre where services are regularly appraised. Importantly, BF did result in better target AUC\textsubscript{24} attainment, assuming that both a two-sample LLR and one-sample BF estimate are equally reflective of true tobramycin exposure. Hence, on theoretical grounds, there would be at least a marginal gain in clinical benefit using BF, but one that may only become apparent in a larger and better powered study. Nevertheless, the clear practical advantages, convenience and potential cost-savings derived, provide sufficient support for BF to be advocated as a preferred method for precision drug dosing.
5. Conclusions

The use of LLR and BF for the dosing of IV tobramycin during CF pulmonary exacerbations results in comparable (non-inferior) clinical outcomes amongst paediatric populations. However, BF can significantly reduce the number of blood collections required during each admission, improve dosing accuracy, and provide more reliable target concentration attainment. Based on the study findings, BF can be considered as superior to LLR in terms of performance and practicality. Future prospective studies can validate our findings, aim to assess patient/parent satisfaction, and attempt to formally analyse the potential cost-benefits associated with implementing a BF approach.
Chapter 3 - Implications and Future Direction

Children with CF experience intermittent episodes of infective pulmonary exacerbations throughout their lifetime. A widely accepted treatment strategy is to administer IV tobramycin. However, the inherent pharmacokinetic variability (e.g., body composition, organ function) associated with the condition make antibiotic dosing in these patients challenging, especially when using standard dosing regimens to achieve appropriate systemic drug concentrations. TDM and precision dosing is now standard of care to ensure efficacy and safety. Two methods of aiding precision dosing are LLR and BF.

I have conducted a quasi-experimental pre-post intervention study to evaluate clinical and performance outcomes amongst children with CF for whom tobramycin therapy was guided by either LLR or BF at a tertiary children’s hospital. To date, no direct comparison between the two methodologies has been undertaken, despite the use of both methodologies not only for antimicrobials but also other therapeutic areas including oncology and transplantation.

The findings of our research demonstrate that LLR and BF result in comparable clinical outcomes. However, BF can significantly reduce the number of blood collections required during each admission, improve dosing accuracy, and provide more reliable target concentration attainment in CF children. These findings can be informative for clinicians and institutions treating this special paediatric population and offers an evidence base to guide management.

Now, it is important to note that several comparisons between LLR and BF remain unstudied and present opportunities for future research. Of these, an understanding
of cost-effectiveness with LLR and BF is perhaps most pertinent. BF invariably incurs a higher operational cost than the low-fidelity LLR, both in terms of software subscription fees as well as requirements for clinical expertise and staff training.\textsuperscript{61} Whether these costs can off-set by the savings made from reduced blood sample collection and processing is yet to be clearly determined. In the absence of open-source software or additional government funding, cost could present a significant barrier for adoption of BF into clinical care.

Additionally, patient satisfaction is a further consideration. As highlighted in our study, BF can halve the number of venepunctures required for tobramycin TDM and dosing. Presumably among paediatric groups this would be favourable. However, formally quantifying the psychological impact of needle-related distress on CF children and their parents who are likely to frequent the healthcare system on an ongoing basis over their lifetime will be valuable.\textsuperscript{82} Insights into reducing needle-related distress may help improve compliance with management and reduce treatment refusal.

Lastly, it is accepted that tobramycin AUC\textsubscript{24} estimates derived from both a two-sample LLR, and a one-sample BF method adequately reflect true tobramycin exposure. This premise was adopted in our study but is largely supported by the work of Barras \textit{et al.}\textsuperscript{41} Further clinical data in this regard, ideally gathered in a prospective manner, is welcomed. Similarly, it is generally assumed that the timing of sample collection with BF is inconsequential for the accuracy of AUC\textsubscript{24} estimates. However, only sampling up to 10 hours post-tobramycin dose has been formally evaluated.\textsuperscript{32,41} Although in our study only a small portion of samples used for BF was collected beyond 10 hours post-
dose, research investigating the impact of sample timing on AUC\textsubscript{24} accuracy at all ends of the dosing interval is desirable.

Overall, when selecting the most appropriate precision dosing approach, each hospital must first assess the requirements of its TDM service more broadly.\textsuperscript{61} Institutions will inevitably differ in terms of patient volume, demographic and case mix. For centres that only cater to very few CF patients, predominantly treat adult patients or perform TDM infrequently, LLR may be preferable as it eliminates the need for sophisticated software and offers equivalent clinical outcomes.\textsuperscript{61} Conversely, in specialised centres who care for a high volume of CF patients, are well-funded and have PK expertise available on-site, BF is likely to be more suitable as it allows better individualisation of dosing.

References


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Personalized tobramycin dosing in children with cystic fibrosis: a comparative clinical evaluation of log-linear and Bayesian methods

Sahand Imani1,2, Dominic A. Fitzgerald3,4, Paul D. Robinson3,4, Hiran Selvadurai3,4, Indy Sandaradura5,6,7,† and Tony Lai8,9

1 School of Medicine, University of Notre Dame Australia, Sydney, NSW 2010, Australia; 2 The Children’s Hospital at Westmead, Sydney, NSW 2145, Australia; 3 Department of Respiratory Medicine, The Children’s Hospital at Westmead, Sydney, NSW 2145, Australia; 4 Discipline of Child and Adolescent Health, Sydney Medical School, University of Sydney, Sydney, NSW 2145, Australia; 5 Faculty of Medicine, Westmead Clinical School, University of Sydney, Sydney, NSW 2145, Australia; 6 Centre for Infectious Diseases and Microbiology, Westmead Hospital, Sydney, NSW 2145, Australia; 7 Department of Infectious Diseases and Microbiology, The Children’s Hospital at Westmead, Sydney, NSW 2145, Australia; 8 Department of Pharmacy, The Children’s Hospital at Westmead, Sydney, NSW 2145, Australia

*Corresponding author. E-mail: indy.sandaradura@health.nsw.gov.au
†Both authors contributed equally and shared senior authorship.

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Background: Children with cystic fibrosis (CF) pulmonary exacerbations receive IV tobramycin therapy, with dosing guided by either log-linear regression (LLR) or Bayesian forecasting (BF).

Objectives: To compare clinical and performance outcomes for LLR and BF.

Patients and methods: A quasi-experimental intervention study was conducted at a tertiary children’s hospital. Electronic medical records were extracted from January 2015 to September 2021 to establish a database consisting of pre-intervention (LLR) and post-intervention (BF) patient admissions and relevant outcomes. All consecutive patients treated with IV tobramycin for CF pulmonary exacerbations guided by either LLR or BF were eligible.

Results: A total of 376 hospital admissions (LLR= 248, BF = 128) for CF pulmonary exacerbations were included. Patient demographics were similar between cohorts. There were no significant differences found in overall hospital length of stay, rates of re-admission within 1 month of discharge or change in forced expiratory volume in the first second (Δ FEV₁) at the end of tobramycin treatment. Patients treated with LLR on average had twice the number of therapeutic drug monitoring (TDM) blood samples collected during a single hospital admission. The timeframe for blood sampling was more flexible with BF, with TDM samples collected up to 16 h post-tobramycin dose compared with 10 h for LLR. The tobramycin AUC₀₋₂₄h target of ≥100 mgL/h was more frequently attained using BF (72%; 92/128) compared with LLR (50%; 124/248) (P<0.001). Incidence of acute kidney injury was rare in both groups.

Conclusions: LLR and BF result in comparable clinical outcomes. However, BF can significantly reduce the number of blood collections required during each admission, improve dosing accuracy, and provide more reliable target concentration attainment in CF children.

Introduction

Cystic fibrosis (CF) is a life-threatening genetic disorder that affects multiple organ systems, resulting in significant morbidity and mortality. The most serious consequence of CF is progressive degeneration of lung function secondary to chronic and typically polymicrobial respiratory infections. Bacteria such as Staphylococcus aureus, Haemophilus influenzae and Pseudomonas aeruginosa opportunistically colonize the airways of CF patients and may lead to intermittent infective exacerbations. A widely accepted treatment strategy is to administer IV tobramycin, an aminoglycoside antibiotic, once daily for 7 to 14 days, usually in combination with a β-lactam antibiotic.

When tobramycin concentrations are too high, there is an increased risk of adverse events including nephrotoxicity and ototoxicity. Conversely, when concentrations are too low, there is an increased risk of therapeutic failure, antibiotic resistance and poor clinical outcomes. As patients with CF often receive numerous and extended courses of tobramycin throughout their lifetime, optimizing tobramycin treatment for efficacy and safety is paramount. This relies on maintaining systemic drug
concentrations within a narrow target range during each anti-
bacterial course.

CF can significantly alter pharmacokinetic parameters (e.g.,
volume of distribution, body composition, renal function),
impacting drug absorption and clearance.\textsuperscript{9} In this context, conven-
tional dosing of tobramycin (based on age or mg/kg) may result
in unpredictable and fluctuating drug concentrations.\textsuperscript{10} To per-
sonalize therapy, routine therapeutic drug monitoring (TDM) is re-
quired, and doses must be adjusted accordingly toward a phar-
macokinetic/pharmacodynamic (PK/PD) target.\textsuperscript{11} The ideal
target to use during clinical care is contentious, with discrepan-
cies existing both within and between countries.\textsuperscript{12}

Traditionally, the tobramycin PK/PD is defined by a peak ($C_{\text{peak}}$)
and trough ($C_{\text{trough}}$) concentration-effect relationship. However, as
$C_{\text{peak}}$ and $C_{\text{trough}}$ are transient compared with overall drug exposure,
evidence suggests these indices are less suitable for once-daily
dosed tobramycin.\textsuperscript{13} In Australia, hospitals have increasingly
transitioned towards a PK/PD target defined by the $AUC_{0-24h}$ rela-
tive to the MIC for the bacterium, in keeping with national guide-
lines.\textsuperscript{14,15} By convention, an MIC of 1 mg/L is assumed during
empirical therapy. Accordingly, a tobramycin target $AUC_{0-24h} /$
MIC of ≥100 mg·h·L$^{-1}$ is desired for patients with CF.\textsuperscript{15,16}

Two methods that are used to predict $AUC_{0-24h}$ during tobramycin
treatment are log-linear regression (LLR) and Bayesian fore-
casting (BF). LLR is considered the low-fidelity, prototypical
method and has been extensively approved.\textsuperscript{16,17} It involves col-
cecting two tobramycin concentrations at fixed intervals (relative
to dose administration) and estimating $AUC_{0-24h}$ based on simple
PK calculations, assuming a one-compartment distribution mod-
el.\textsuperscript{16,18} Although conceptually straightforward, LLR is highly sensi-
tive to the precise timing of sample concentrations. Thus, in busy
clinical environments, where accurately timed blood collections
are difficult to coordinate, LLR is prone to significant bias.\textsuperscript{19,20}

In contrast, BF entails the use of sophisticated software em-
bedded with population PK data. The pre-existing population cov-
arates are used to prospectively identify individuals’ PK
parameters for the purposes of calculating $AUC_{0-24h}$.\textsuperscript{21,22} In addi-
tion, elements of sampling and assay method can be integrated
to improve accuracy of $AUC_{0-24h}$ estimates.\textsuperscript{23} A further benefit of
BF is that only a single tobramycin concentration is required. This
can be collected at unrestricted and patient-preferred times,
prior to achieving steady-state drug concentrations.\textsuperscript{24} Granting
all this, the LLR approach remains far more commonly used in
clinical practice.\textsuperscript{13,25}

Aside from methodological disparities, what is perhaps more
important but remains unknown is whether there are any differ-
ces in clinical (e.g., respiratory function) and/or performance
outcomes (e.g., practicality, accuracy) when each method is uti-
lized. Adopting evidence into healthcare is often challenging
and the effectiveness of promising health interventions can be
variable once implemented into practice.\textsuperscript{25} As it stands, BF occu-
pies a transitional space between research and practice with
many of its touted benefits not yet systematically appraised at
the clinical coalface.\textsuperscript{26} In the setting of paediatric CF, knowledge
of comparative advantages between LLR and BF may justify se-
lection of either approach, guide clinical practice, and assist
with optimizing treatment of pulmonary exacerbations.

We conducted a quasi-experimental pre–post intervention
study to evaluate clinical and performance outcomes amongst
children with CF for whom tobramycin therapy was guided by ei-
ther LLR or BF at a tertiary children’s hospital.

Methods

Setting and data source

The Children’s Hospital at Westmead is a paediatric referral hospital in
metropolitan Sydney, Australia. At our institution, between the years
2018 and 2019, there was a transition from LLR (pre-intervention) to
BF (post-intervention) approach for tobramycin dosing in CF patients.
We extracted electronic medical records to establish a deidentified data-
base consisting of pre-intervention and post-intervention patients as well
their relevant clinical and dosing performance outcome measures.

Selection criteria

All consecutive patients treated with IV tobramycin for CF pulmonary ex-
acerbations between January 2015 to September 2021 (i.e. immediate
3 years pre- and post-intervention period) were included in the study.
Only patients treated exclusively with either LLR or BF were considered eli-
gible for inclusion.

Evaluation of outcomes

The primary clinical outcomes considered in this study were: (1) hospital
length of stay (LOS); (2) rates of unexpected hospital re-admission within
the subsequent month following discharge; (3) pulmonary function (with
reference to change in forced expiratory volume in the first second (FEV1)
from time of hospital admission to discharge); and (4) rates of acute
kidney injury (AKI). The occurrence of AKI was defined in terms of clinical
suspicion/diagnosis or a second blood test demonstrating ≥1.5 times in-
crease in baseline serum creatinine at any time during hospital
admission.\textsuperscript{27}

The performance outcomes considered were those relating to tobra-
mycin dosing and pharmacokinetics. These included: (5) the number and
timing of tobramycin TDM blood samples collected; (6) empirical (initial)
dose selection; (7) final maintenance dose prescribed throughout hospital
admission; and (8) the frequency and precision of target concentration
attainment. Given our younger patient demographic with preserved renal
function, the tobramycin target $AUC_{0-24h}$ used at our institution during
the study period was ≥100 mg·h·L$^{-1}$.\textsuperscript{28} Precision dosing was defined as attain-
ing a tobramycin $AUC_{0-24h}$ within the range of 100 to 110 mg·h·L$^{-1}$.

Local practice and procedures

At our centre, clinical pharmacists working in a CF team (consisting of clinici-
ants, physiotherapists, nutritionists etc.) oversee tobramycin dosing and
monitoring. As per local guidelines, tobramycin is administered in the
morning as a once-daily infusion over 30 mins. An empirical dose of
10–12 mg/kg (up to a maximum of 600 mg) is typically prescribed.
The first $AUC_{0-24h}$ is ideally calculated within 48 h of commencing therapy,
which is then used to guide dose adjustment.

With the LLR method, two blood tobramycin concentrations from
each patient are drawn during a dosing interval: the first between
30 min to 2 h and the second between 6 and 10 h after the infusion.
These two ‘paired’ measurements are entered into a Microsoft Excel
spreadsheet embedded with first-order PK equations described by
Hennig et al.\textsuperscript{29} The $AUC_{0-24h}$ is characterized as a mono-exponential
curve and the recommended dose is calculated linearly.

Using BF, only a single blood tobramycin concentration is collected at
any timepoint after the infusion is complete. This measurement, along
with patient’s demographic and clinical data, is entered into DoseMe\textsuperscript{30}
(http://doseme.com.au), an online Bayesian dose individualization
platform. Here, the AUC$_{0-24}$ is estimated based on the integrated population model.

At our hospital, laboratory MIC testing is often not performed or only made available after a delay of several days. Importantly, even when testing is performed, the individual MIC measurements may not be sufficiently accurate. Thus, a target MIC of 1 mg/l is assumed for Gram-negative organisms treated with tobramycin and, in essence, AUC$_{0-24}$ alone is used to guide dosing. This strategy remained consistent during the entirety of the study period and is commonly used amongst other hospitals and across different antibiotics.

Regarding lung function assessment, all spirometry testing is performed by a respiratory scientist and conducted at our on-site respiratory laboratory. In general, only patients older than 4 years of age are considered eligible. A referral from the admitting respiratory physician is required to initiate an assessment. For each referred patient, spirometry is performed ideally twice, once near to time of admission and then once prior to discharge.

**Statistical analysis**

Data analyses were performed using JASP® statistical software (Version 0.16.3 https://jasp-stats.org). Continuous variables are reported as mean ± SD or mean (IQR), for parametric and non-parametric data, and compared using Student's t- or Mann-Whitney U-tests, respectively. Categorical variables are reported as numbers and/or proportions and compared using χ² test. Results were deemed statistically significant when the P value was <0.05. Repeat hospital admissions were noted for a cohort of patients in both the LLR and BF groups and assumed to be independent for the purposes of statistical analysis.

**Ethics**

Ethics approval was sought and granted by the Sydney Children's Hospitals Network Human Research Ethics Committee (2019/ETH11521). Cross-institutional approval was conferred by University of Notre Dame Australia (2021-0735).

**Results**

A total of 376 hospital admissions for CF pulmonary exacerbations were included in the study. Tobramycin therapy was guided by LLR during 66% (n = 248) of the admissions whilst BF was utilized in the remaining 34% (n = 128). Patient demographics were similar between LLR and BF cohorts in terms of gender ratios, age, weight and BMI (Table 1). A homoyzygous p508 del genotype was more prevalent in the BF group (45%; 57/128) compared with the LLR group (32%; 79/248) (P = 0.02). CF transmembrane conductance regulator (CFTR) modulators were more commonly used during BF (29%; 37/128) as opposed to LLR (3%; 8/248) admissions (P < 0.001). Baseline mean FEV₁ was -5% greater amongst those treated with BF (P = 0.02). All patients received twice-daily airway physiotherapy and nutritional support during each admission.

Sputum and/or bronchial lavage samples were collected at the time of hospital presentation (prior to antibiotic therapy) in 45% (58/128) of the BF admissions and 52% (130/248) of the LLR admissions (P = 0.19). In each cohort, ~90% of collected samples yielded positive cultures (P = 0.78) (Table 1). P. aeruginosa was isolated in 19% (11/58) of cultures in the BF group and 38% (50/130) of cultures from LLR group (P = 0.01).

With regard to clinical outcomes (Table 2), there were no significant differences found in overall hospital LOS or rates of admission for CF pulmonary exacerbations. Overall, patients in both groups had improved lung function at the end of tobramycin treatment, with a comparable mean AFEV₁ during hospital admission (LLR = 8.1% versus BF = 7.8%; P = 0.65). Incidence of AKI was rare, with only one diagnosis made in the LLR group.

In terms of performance outcomes (Table 3), patients treated with LLR on average had twice the number of TDM blood samples collected during a single hospital admission (LLR = 3.8 versus BF = 1.9; P < 0.001). The TDM samples for LLR were all collected within 10 h following dose administration, reflecting a bimodal time distribution (Figure 1). With BF, a wider timeframe for TDM sampling was observed, with blood sample collection occurring up to 16 h post tobramycin dosing. Of all blood samples collected, 35% (86/249) were dedicated entirely to tobramycin TDM (i.e., with no other laboratory test ordered concurrently) in the BF group and 74% (650/933) in the LLR group (P < 0.001).

The median tobramycin dose prescribed was higher during admissions where BF was used compared with LLR, both during empiric (initial) (430 versus 390 mg; P = 0.18) and maintenance (400 versus 395 mg; P = 0.89) therapy. A change from the empiric dosage was more frequently observed in the BF group (72% (92/128) compared with the LLR group (63%; 155/248), although this difference was not statistically significant (P = 0.07). Compared with the LLR group (18%; 45/248), fewer patients treated with BF (11%; 14/128) required three or more AUC$_{0-24}$ calculations to be performed.

The mean tobramycin AUC$_{0-24}$ was higher in the BF group both when the first (BF = 106 mg/l/h versus LLR = 94.7 mg/l/h; P < 0.001) and final (BF = 102.6 mg/l/h versus LLR = 95.1 mg/l/h; P < 0.001) calculated AUC$_{0-24}$ in each admission were considered (Figure 2). The tobramycin target AUC$_{0-24}$ of ≥100 mg/l/h was more frequently attained during hospital admissions where BF was used (72%; 92/128) compared with LLR (50%; 124/248) (P < 0.001). A higher proportion of the BF group (39%; 50/128) also achieved an AUC$_{0-24}$ within the precision range of 100–110 mg/l/h, compared with the LLR group (25%; 61/248) (P = 0.004).

A subset of patients (n = 44) contributed data both to LLR and BF phases. A pairwise comparison was performed for this cohort, evaluating outcomes from their last LLR admission against those of their first BF admission. In this analysis, with a small sample size, no meaningful conclusions could be drawn (data not presented).

**Discussion**

The recurrence of pulmonary exacerbations and associated decline in FEV₁ is regarded as the most significant predictor of mortality from CF. Thus, optimizing the treatment of CF pulmonary exacerbations is paramount, particularly antibiotic therapy. Dosing of antibiotics in patients with CF is challenging given the inherent PK variability associated with the condition, poor intrapulmonary penetration of systemic antibiotics, and the potential for antimicrobial resistance and drug toxicity. In this setting, utilizing TDM coupled with a suitable dosing method is now considered the standard of care in enabling individualized, efficacious and safe therapy.

A consensus on the ideal dosing approach for use in daily practice remains elusive. In our literature review, we were unable to identify any published studies equating patient outcomes during
Log-linear and Bayesian dosing methods—a comparative study

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Study cohort</th>
<th>LLR</th>
<th>BF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>105</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>No. of admissions</td>
<td>248</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>No. admissions per patient</td>
<td></td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>1</td>
<td>49</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>30</td>
<td>17</td>
<td></td>
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</table>

Demographics

<table>
<thead>
<tr>
<th>Gender, n (%)</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>112</td>
<td>52</td>
</tr>
<tr>
<td>Female</td>
<td>136</td>
<td>76</td>
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</table>

<table>
<thead>
<tr>
<th>Genotype pF508.del homozygous, n (%)</th>
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<th></th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>79</td>
<td>57</td>
</tr>
<tr>
<td>No</td>
<td>169</td>
<td>71</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Age (years), mean (SD)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>No</td>
<td>41</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (kg), mean (SD)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI (kg/m²), mean (SD)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>8</td>
<td>37</td>
</tr>
<tr>
<td>No</td>
<td>240</td>
<td>91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CFTR modulator use, n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>124</td>
<td>58</td>
</tr>
<tr>
<td>No</td>
<td>84</td>
<td>47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-administered antibiotic, n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/tazobactam</td>
<td>47.5</td>
<td>43.7</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>69.7</td>
<td>74</td>
</tr>
<tr>
<td>Meropenem</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Cefepime</td>
<td>114/130</td>
<td>50/98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Creatinine (μmol/L), mean (SD)³</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of positive cultures⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>S. aureus</td>
<td>60</td>
<td>31</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Entrobacteriaceae</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Repeat hospital admissions were assumed to be independent for the purposes of statistical analysis. Demographic variables have been calculated using total number of admissions as the denominator (LLR = 248; BF = 128), unless otherwise specified.

³Baseline creatinine and FEV₁ were not assessed/available for all admissions. Creatinine was available for LLR (n = 207; 83%) and BF (n = 109; 85%). FEV₁ was available for LLR (n = 222; 90%) and BF (n = 107; 84%).

⁴Sputum and/or bronchial lavage samples were not collected/available for all admissions. A microbiology culture was available for LLR (n = 130; 52%) and BF (n = 58; 45%). Not all microbial isolates are reported.

Pharmacotherapy was guided by LLR and BF. This is despite the longstanding use of both these approaches for drug dosing of antimicrobials and in other therapeutic areas including oncology and transplantation. To the best of our knowledge, our study is the first to systematically compare patient clinical outcomes with LLR and BF methodologies during antibiotic therapy. We attempted to mitigate confounding by assessing a relatively homogeneous cohort of paediatric patients with CF pulmonary exacerbations treated with once-daily IV tobramycin.

With regard to homogeneity of the study cohorts, we note that a small difference (~5%) in mean baseline FEV₁ was detected between the LLR and BF groups, yet clinical interpretation of this was difficult. On the one hand, this could imply greater baseline disease severity in the LLR group, in keeping with higher rates of Pseudomonas colonization. On the other hand, the BF group exhibited higher rates of pF508 del homozygosity, which typically indicates poorer lung function. Additionally, the prevalence of CFTR modulator use was greater in the BF group, consistent with recent changes in clinical practice. This represents a further potential confounder given the efficacy of these agents in improving baseline FEV₁ (by ~3% to 7%) and suspected interaction with airway microbiome. Overall, it is likely that the difference in baseline FEV₁ simply reflects the inherent variability of spirometry testing.

In our evaluation of clinical outcomes, we did not find any significant difference in hospital LOS or readmission when LLR or BF
Table 2. Clinical outcomes per admission

<table>
<thead>
<tr>
<th></th>
<th>LLR (n=258)</th>
<th>BF (n=128)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS (days), mean (SD)</td>
<td>15.1 (4)</td>
<td>16.1 (6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospital readmission, n (%)</td>
<td>12 (5)</td>
<td>5 (4)</td>
<td>0.68</td>
</tr>
<tr>
<td>AKI, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Δ FEV&lt;sub&gt;1&lt;/sub&gt;, mean (SD)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.1 (10)</td>
<td>7.8 (8)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

<sup>a</sup>Δ FEV<sub>1</sub>, change in FEV<sub>1</sub> from time of hospital admission to discharge.

<sup>b</sup>Hospital readmission for pulmonary exacerbations of CF within 1 month of discharge.

<sup>c</sup>AKI based on clinical suspicion/diagnosis or second blood test.

<sup>d</sup>Δ FEV<sub>1</sub> was not available in all patients. Data were available for LLR (n=222; 90%) and BF (n=107; 84%).

were used. Likewise, there was no difference in rates of AKI, which was seldom diagnosed in both cohorts. To account for this, it is likely that the risk of nephrotoxicity for all study patients was mitigated in the first instance by the routine use of TDM (during target concentration attainment) and once-daily tobramycin dosing.<sup>40</sup> The recognized incidence of aminoglycoside-induced AKI is also commonly low in paediatric patients.<sup>41</sup> Thus, our results may have differed if adult populations, exposed to long-term accumulative doses, were considered. Finally, we found that the changes in FEV<sub>1</sub> pre- and post-tobramycin treatment were comparable between the BF and LLR groups. This is particularly important given that FEV<sub>1</sub> has been validated as a surrogate measure of risk of death and quality of life in CF and is regarded as the most meaningful clinical outcome.<sup>12,13</sup>

In terms of performance outcomes, our results demonstrate that BF can halve the number of blood collections required during each admission compared with LLR. A major limitation of LLR is that it requires two blood samples. The sample collections must also be meticulously timed for results to be accurate,<sup>13</sup> which is often difficult to coordinate during a hospital admission. Of note, the repeated venepunctures with LLR can be particularly invasive and a source of psychological distress for paediatric patients.<sup>13</sup> With BF, timing of collections is flexible and can be aligned with daily pathology rounds in most instances. Additionally, the option of opportunistic sampling is easier to facilitate as TDM samples can be coupled with other blood draws, as shown in our study. Moreover, it is reasonable to assume that minimizing the number of collections using BF can also offer significant cost benefits over time.<sup>14</sup>

Considering dosing and PK parameters, several studies have demonstrated that LLR and BF can predict tobramycin AUC<sub>0-24</sub> with similar accuracy.<sup>13,19,24,28,45</sup> In contrast, Avent et al.<sup>46</sup> found that in a cohort of patients with febrile neutropenia, treatment with gentamicin (another aminoglycoside antibiotic) guided by BF resulted in more frequent and precise attainment of target drug concentrations compared with LLR. This, in part, may be attributed to the fact that the majority of the referenced tobramycin studies were conducted in controlled research settings, using small sample sizes (n<15).<sup>13,19,24</sup> Thus, the seemingly comparable predictive performance of LLR and BF could in fact differ once implemented in larger numbers in daily clinical practice.

In view of this, at our institution, we found that patients for whom dosing was guided by BF achieved the desired target tobramycin concentrations more frequently (72%) compared with LLR (50%) during their admission. Accordingly, BF patients also received greater median doses of tobramycin (both empirically and for maintenance) and had higher rates of dose adjustment. Regarding the latter, frequency of dose adjustments with BF were likely assisted by the relatively easier performance of repeat AUC<sub>0-24</sub> calculations. Additionally, BF offered greater precision of target attainment (defined as an AUC<sub>0-24</sub> between 100 and 110 mgL-lh) compared with LLR at rates of 39% and 25%, respectively.

The limitations of this study are that it was conducted at a single site using a pre-post intervention study design and was not a formal randomized controlled trial. Theoretically, this renders the study susceptible to bias (namely performance bias) such as differences in laboratory services and clinicians overseeing TDM decisions.<sup>47</sup> Reassuringly, there were no official changes to hospital guidelines during the study period and the differences in median tobramycin dose prescribed for initial and maintenance therapy were not statistically significant. A maturation effect is also conceivable, where the outcomes of interest were naturally impacted over time by the improvements in CF targeted therapies, likely accelerated gain in clinician experience or, conversely, the progression of disease. For instance, the use of CFTR modulators increased during the study period. Additionally, the CF clinic at our hospital was gradually restructured to facilitate single room visits as a means of strengthening infection control. Such evolving practices could plausibly explain the decrease in rates of Pseudomonas colonization noted over time.<sup>18,48</sup> Nonetheless, our study reflects real-world clinical care at a large paediatric hospital and so its findings can be relevant to other specialized institutions caring for children with CF.

Regarding assessment of clinical outcomes, in particular hospital LOS, it is valuable to note that treatment of CF pulmonary exacerbations is protocolized in many hospitals, including ours. Although this may influence the minimum hospital LOS, we assume that if significant differences in clinical efficacy did in fact exist between LLR and BF, then admission lengths would have been prolonged accordingly. Furthermore, we were unable to compare other potentially relevant clinical outcomes such as occurrence of ototoxicity. Diagnosing ototoxicity is largely reliant on audiometric evaluation, which is not routinely performed at our institution.

Additionally, the apparent PK and dosing advantages of BF found in the study did not impact overall clinical outcomes. Optimizing antibiotic therapy is a continuum, and it is likely that the peaks of clinical benefit are achieved once routine TDM is...
Table 3. Performance outcomes per admission

<table>
<thead>
<tr>
<th>Tobramycin TDM sampling</th>
<th>LLR (n=248)</th>
<th>BF (n=128)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of samples collected, total</td>
<td>933</td>
<td>249</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of samples per admission, mean (SD)</td>
<td>3.8 (2)</td>
<td>1.9 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of dedicated samples, (n/total) (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>690/933 (74)</td>
<td>86/249 (35)</td>
<td></td>
</tr>
<tr>
<td>Tobramycin dosing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage (mg), median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial dose</td>
<td>390 (200)</td>
<td>430 (220)</td>
<td>0.18</td>
</tr>
<tr>
<td>Maintenance dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>395 (188)</td>
<td>400 (200)</td>
<td>0.89</td>
</tr>
<tr>
<td>Initial versus maintenance dose unchanged, n (%)</td>
<td>93 (38)</td>
<td>36 (28)</td>
<td>0.07</td>
</tr>
<tr>
<td>Tobramycin PK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of AUC&lt;sub&gt;D-24&lt;/sub&gt; during admission, n (%)</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>1</td>
<td>131 (53)</td>
<td>56 (44)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>72 (29)</td>
<td>58 (45)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>45 (18)</td>
<td>14 (11)</td>
<td></td>
</tr>
<tr>
<td>First AUC&lt;sub&gt;D-24&lt;/sub&gt; measured (mg/L-h), mean (SD)</td>
<td>94.7 (26)</td>
<td>106.0 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Final AUC&lt;sub&gt;D-24&lt;/sub&gt; measured (mg/L-h), mean (SD)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>95.1 (16)</td>
<td>102.6 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Target attainment during admission, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;D-24&lt;/sub&gt; ≥ 100 mg/L-h</td>
<td>124 (50)</td>
<td>92 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;D-24&lt;/sub&gt; = 100-110 mg/L-h</td>
<td>61 (25)</td>
<td>50 (39)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

<sup>a</sup>A dedicated sample is one that is collected for the purposes of TDM only, with no other laboratory test ordered concurrently.

<sup>b</sup>Maintenance dose is defined as the final dose of tobramycin prescribed during the admission, after any dose adjustments occurred.

<sup>c</sup>Includes patients with at least two AUC<sub>D-24</sub> estimates during a hospital admission, LLR (n=117; 47%) and BF (n=72; 56%).

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**Figure 1.** Post-dose collection time (h) of all tobramycin blood samples (levels) from patients in the LLR (n=933) and BF (n=249) groups.
coupled with LLR guided dosing, particularly at a specialized centre where services are regularly appraised. Importantly, BF did result in better target AUC<sub>0-24</sub> attainment. Hence, on theoretical grounds, there would be at least a marginal gain in clinical benefit using BF, but one that may only become apparent in a larger and better powered study. Nevertheless, the clear practical advantages, convenience and potential cost-savings derived provide sufficient support for BF to be advocated as a preferred method for precision drug dosing.

**Conclusions**

The use of LLR and BF for the dosing of IV tobramycin during CF pulmonary exacerbations results in comparable (non-inferior) clinical outcomes amongst paediatric populations. However, BF can significantly reduce the number of blood collections required during each admission, improve dosing accuracy, and provide more reliable target concentration attainment. Based on the study findings, BF can be considered as superior to LLR in terms of performance and practicality. Future prospective studies can validate our findings, aim to assess patient/parent satisfaction, and attempt to formally analyse the potential cost-benefits associated with implementing a BF approach.

**Acknowledgements**

We are grateful to Dr Craig Smith (from the University of Notre Dame Australia) for his invaluable support with this study. We would also like to thank Ms. Elizabeth Barnes (from the Sydney Children’s Hospital Network) for her guidance during statistical analysis.

**Funding**

This study was carried out as part of our routine work.
Log-linear and Bayesian dosing methods—a comparative study

Transparency declarations
None to declare.

Author contributions
S.I. performed the literature search, collected and analysed data, and prepared the manuscript. I.S. and T.L. conceived and designed the study, collected data and prepared the manuscript. D.F., P.R. and H.S. assisted with study design, data interpretation and review of the manuscript.

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34. vander Meer AF, Marcus MA, Touw DJ et al. Optimal sampling strategy development methodology using maximum a posteriori Bayesian estimation. Ther Drug Monit 2011; 33: 133–46. https://doi.org/10.1097/FDM.0b013e31820f40f8


