NOVA

University of Newcastle Research Online

nova.newcastle.edu.au

Donagher, Joni, Martin, Jennifer H. & Barras, Michael A. "Individualised medicine: why we need Bayesian dosing" Published in *Internal Medicine Journal*, (2017).

Available from: <http://dx.doi.org/10.1111/imj.13412>

This is the peer reviewed version of the following article: Donagher, J., Martin, J. H. & Barras, Michael A. (2017). Individualised medicine: why we need Bayesian dosing. Internal Medicine Journal, 47(5), pp. 593-600, which has been published in final form at <http://dx.doi.org/10.1111/imj.13412>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Accessed from: <http://hdl.handle.net/1959.13/1351360>

A Clinicians Guide to Individualised Drug Dosing and an Introduction to Bayesian dosing

Donagher J^{1,2}, Martin JH², Green B³, Barras MA^{1,2}

¹Royal Brisbane and Women's Hospital, ²University of Queensland; ³Model Answers Pty Ltd

Abstract

Patient specific, personalised drug dosing has been shown to improve patient outcomes and reduce adverse drug events. Bayesian methods are being increasingly investigated and used to improve drug dosing however, clinicians are unfamiliar with the science and terminology and it is not well explained in standard textbooks. It is a method that helps determine an individual's response to therapy thereby allowing individualised dose changes. It is more accurate than traditional therapeutic drug monitoring (TDM) as the patient's past clinical responses are taken into account. Studies using Bayesian methods to adjust drug dosing have shown that clinicians are able to achieve a therapeutic range quicker than standard practice. This reduces mortality, side effects of drugs, the length of patient stay in hospital, as well as the number of assays required.

Bayesian methods that use a population pharmacokinetic (PK) model with current patient information allow the determination of a patient specific concentration-time profile. This can be continually optimised allowing for timely and accurate modification of a patients treatment regimen. The aims of this article are to demystify the misconceptions of Bayesian dosing, set the context of the Bayesian approach and discuss its benefits over current dosing TDM methods at practitioner level. There is a practical clinical case to demonstrate how this method can and should be utilised in everyday clinical practice.

Keywords: [Bayesian, Computerised dose prediction, pharmacokinetics, pharmacodynamics, target concentration intervention]

Introduction

Drug dosing in the contemporary patient is complex as no two patients are the same. The same drug at the same dose given to two different people will elucidate two unique responses. This is a dilemma faced by clinicians during a typical day when treating multiple patients with multiple medications, whilst trying to provide optimal care in a health environment.

What if a dosing strategy existed that allowed clinicians to treat patients more effectively than current methods, reduced the length of hospital stay and decreased fiscal burden for the healthcare system? What if this system used current drugs but allowed clinicians to use them more judiciously and efficaciously? This strategy already exists. It is called Bayesian dosing and it was proposed as far back as 1969¹ as a method to accurately predict future drug doses that are patient specific to ensure effective treatment. The FDA already uses Bayesian methods in conducting clinical trials to inform modification of trial design, for example slowing or expanding accrual, removal or addition of treatment arms or changing the trial population to focus on a patient subset that responds better the therapy².

Implementation of Bayesian dosing into modern medical practice has been hindered by the fact that the mathematics underlying this method are difficult to understand, computationally intensive and require specialised software. The outputs then required further interpretation by a trained clinician with pharmacometric knowledge such as an experienced clinical pharmacist or clinical pharmacologist. Only at this point could results be applied to patients. However, there are now software packages with user friendly interfaces, clear graphics and predictive capabilities that allow even the most junior clinician to dose with accuracy and confidence.

This is ideal as junior medical doctors are responsible for most inpatient prescribing in hospitals. In addition, there is always an expectation that clinicians will prescribe the most appropriate medication

at the most effective dose with the smallest chance of an adverse event. However, often dosing is based on an “educated guess”. In many hospitals, clinical pharmacists are available to help doctors with their prescribing, however often these are junior pharmacists who lack the knowledge and experience to confidently and accurately adjust levels in complex patients. Although undergraduate degrees for Medicine and Pharmacy teach students about therapeutic drug monitoring (TDM) it is only covered in very basic detail and the concepts of Bayesian dosing are currently not included in curriculums.

Current dosing methods can be problematic as patients are intricate “systems” and will respond differently to drugs for multiple reasons. Major organ function on which drug metabolism is highly dependent is dynamic and can fluctuate acutely as well as over a patient’s lifetime. For example, 1.7 million Australians have indicators of CKD ³, which affects renal clearance for hydrophilic drugs. Infants only start to reach adult values for GFR by 8-12 months⁴. Drugs such as cyclosporin show an age-dependent increase in plasma clearance in children less than 10 years of age, necessitating higher weight based doses ⁵. Liver function is reduced in the elderly, as well as gastric motility, and gastric emptying; all of which can affect how a drug is absorbed and metabolised.

This high level of inter patient variability necessitates personalised dosing for many drugs and this is where Bayesian dosing can be a very powerful tool.

Main Text

The current dosing systems

A clinician might ask the question “we already have nomograms & guidelines to help direct our dosing?” The answer is yes and the demand to prescribe quickly in a busy hospital leads to a heavy reliance on dosing guidelines or nomograms. These methods are used for a variety of drugs including but not limited to anticoagulants, antibiotics and chemotherapeutic agents. A recent audit of vancomycin dosing at a local, tertiary hospital found up to 50% of initial doses and dose adjustments were made based on guidelines with clinical experience used the rest of the time⁶.

The major problem with these methods is that they were created from and designed for populations not individuals and indicate how the “average” patient should respond. Classic TDM nomograms recommend dose modifications based on only one drug concentration but this does not eliminate individual variation over a dosing period as one concentration (or result) only reflects one point in time not what will occur in the future. Nomograms are usually created in controlled environments, with reasonably healthy subjects who lack the morbidities associated with hospitalised patients, for example extremes of age, weight and/or renal function. Importantly, they assume individuals will eliminate a drug at a constant rate.

Guideline based dose ranges are often wide to allow the incorporation of large numbers in the dosing population. This makes dose individualisation difficult. For example, “the dose should be reduced when the renal function falls between 30 to 60ml/min”⁷ or “the loading dose is 15 to 25mg per kg of body weight”.⁷ This can lead to variability in patient outcomes due to over and under dosing.⁸ Guidelines and nomograms have been shown be inferior to TDM based on Bayesian forecasting.⁹⁻¹² A study comparing different methods used to monitor gentamicin in patients with febrile neutropenia found that using a nomogram only achieved a therapeutic range 35% of the time while this was increased to greater than 70% using Bayesian methods.¹³ Studies assessing Bayesian methods are summarized in Table 1.

An Introduction to Bayesian methods

The success of Bayesian methods are linked to the ability to integrate a previous “experience” or an individual response such as a drug concentration. The term Bayesian can conjure notions of mathematical complexity, beyond the understanding of the average clinician. Although this may be true in advanced settings the underlying principles are quite straight forward, as the following example will demonstrate.

Humans intuitively think “in Bayesian”, learning from past experiences and using this to inform future decisions. A relevant example is the use of travel guides such as Google maps. You would like to estimate how long it will take to get from point A to point B. When you input the required destination you receive a number of different estimates depending on which route you take. These estimates are derived from the average journey time for a population using models for speed and distance. When you drive from A to B the journey time will most likely be different to the map estimate. However, while en route you learned information about the route and every time you drive that route in the future you “learn” something new, for example the time of the day the traffic is more congested or a shortcut you can take to reduce time. This impacts your future thinking and you will use this information to plan your future trips.

Bayesian forecasting is a branch of statistics that deals with conditional probability and the three important elements can be described using the above example:

1. Prior distribution or probability: all the previous information we know about the route – contained within Google map models.
2. Likelihood function: a mathematical equation used to update the prior distribution (1) with new information obtained - information learned about the journey en route.
3. Posterior distribution or future probability: the output obtained after updating the prior distribution (1) with new information via the likelihood function (2) - predicting a future route from A to B.

For therapeutics, the concept of having prior information and drug data from an individual patient lends itself to calculating drug doses.

Current dosing strategies and when to use Bayesian?

“Fixed dosing”, for example 20mg daily or 1g twice daily is commonly used for drugs such as proton pump inhibitors, statins, antibiotics, and opioids. However, it is inadequate method for many drugs. This “one dose fits all” strategy is often replaced by covariate based dosing. Covariate methods use patient specific variables such as weight (mg/kg) and renal function to explain and reduce variability. Bayesian methods work best when there is inter-patient variability in drug response beyond what we can currently account for with known patient factors or covariates.

Covariate dosing, such as mg/kg, is a sound method for many drugs; however there will always be unknown drug-patient responses that need to be taken into consideration. These are generally categorised into genetic and non-genetic factors. Genetic polymorphisms of proteins involved in physiological functions such as drug metabolism or drug transport can account for some variability. This is seen for drugs for many drugs metabolised by the P450 isoenzymes, such as warfarin, perhexiline and tacrolimus. Environmental chemicals, co-administered drugs, dietary constituents, tobacco smoking, alcohol use, disease states, exercise, pregnancy, starvation and circadian rhythm can all affect how an individual will respond to a drug. These factors account for what is called “between subject variability” (BSV) – the variability seen between patients and/or “between occasion variability” (BOV) - the variability seen within a patient. These factors affect both the pharmacokinetics and pharmacodynamics of a drug to alter a concentration or effect.

Therefore, covariate based dosing works up to a point but for many drugs more information is necessary to dose effectively. For example, a drug such as vancomycin, which has extensive renal elimination can be dose adjusted using a covariate such as creatinine clearance and therefore this dosing metric should be taken into consideration. It is interesting to understand that “covariate

models will only account for 20% or less of the difference in variability in the overall population and the variability seen between patients with the same predicted typical value”¹⁴. In reality most of the variability is unknown (Figure 1)¹⁵ but can be incorporated into Bayesian methods to enable individualised drug dosing.

Figure 1: A bar plot visualising the relative contributions of the covariates and unexplained variability to the total variability in clearance (adapted from Pharmacometrics: the science of quantitative pharmacology 2006)

The following example demonstrates how small changes in a covariate can have a major impact on drug clearance. Take, for example, a 37-year-old male with height 186cm and weight 67.5kg. Figure 2 describes the concentration time curve for vancomycin administered according to a fixed dose regimen of 1g twice a day. Going sequentially from graph a - f, the GFR is decreased by 10ml/min starting with a GFR of 100ml/min. It can be seen that a decrease in renal function causes the drug to accumulate.

Figure 2: Concentration-time curves for a patient with decreasing renal function

a

b

c

d

e

f

If covariate dosing is inadequate, then fixed dosing will certainly not achieve or maintain patients in therapeutic range. This is emphasised by figure 3, which shows a data set collected from a dosing trial for vancomycin¹⁷ and their individual responses to a fixed dose of 1g twice a day. As seen there is marked variation and very few trough concentrations within the therapeutic range (15 to 25 mg/L in this case).

Figure 3: Concentration-time curve for vancomycin in multiple patients

These examples further dismiss any benefits of nomograms as they can't account for all variability. Nomograms assume constant PK parameters and fail to account for the fact that patient's covariates are dynamic along with their disease. If a patient has varying PK parameters nomograms should not be used. This is why the Australian Therapeutic Guidelines no longer recommend the use of nomograms when calculating aminoglycoside doses. Many patients were under-dosed using this method.^{22,23}

A motivating clinical case (Part 1)

Mr AB, a 36-year-old male presents to hospital with a large paraspinal and epidural abscess from T12 to S2, which has cultured methicillin resistant *staphylococcus aureus* (MRSA). He has a 10-year history of intravenous drug use, hepatitis C and four previous *staphylococcus aureus* infections yielding non-multi resistant MRSA. He has an estimated glomerular filtration rate (GFR) of

133ml/min calculated using the Cockcroft and Gault method using a height and weight of 186cm and 68kg respectively.

On admission his relevant biochemical results are:

- C - reactive protein: 260 mg/L (reference range <5 mg/L)
- White Cell Count: 23×10^9 (reference range $4-11 \times 10^9$ /L)
- Neutrophils: 19×10^9 (reference range $1.8 - 7.5 \times 10^9$ /L)
- Serum creatinine: 65 micromol/L (reference range 60-110 micromol/L).

He is admitted to a medical ward where the Infectious Diseases team has recommended six weeks of intravenous vancomycin therapy with a pre-dose serum concentration target of 15 to 20mg/L⁷. The junior doctor prescribes 1g of vancomycin twice daily (BD) as this is the most common starting dose used at the hospital. After five doses the patient has a pre-dose vancomycin level of 6mg/L. The doctor decides to double the dose to 2g BD and a further six doses are administered with a resultant pre-dose vancomycin of 12mg/L. The dose is increased to 2.5g BD after clinical review. Another 6 doses are administered which results in a vancomycin pre-dose level of 21mg/L. After almost a week of therapy the patient has achieved a therapeutic target (15-20mg/L). This means that until this point the patient was being sub optimally treated, which may have led to complications such as drug resistance. This is unfortunately not an uncommon situation²³ however using Bayesian methods to estimate drug doses may have allowed us to avoid this and achieve therapeutic range much faster.

How to apply “Bayesian” methods to this patient

Breaking down the Bayesian elements as before:¹⁶

Stage 1 - The prior distribution: the knowledge we already have.

To calculate a future probability for patient AB, prior information is required. Figure 3 shows a data set collected from a dosing trial for vancomycin,¹⁷ which contains our prior information. Using

population PK modelling, the data was used to develop a “population” model,¹⁷ which is considered the “prior” information. This population model is used to estimate a concentration-time curve as shown in figure 4 and is represented by the red line. This represents what would occur in a patients given the specified vancomycin doses and covariates over time.

Stage 2: The likelihood function: A mathematical equation to describe new information

To improve our model a serum vancomycin concentration is taken from the patient. A likelihood function is created which is a mathematical representation of the relationship between the observed outcome (drug concentration) and an individual’s PK parameter (e.g. Clearance). The likelihood function can be used to update the prior distribution (stage 1) with this new information. As more concentrations are obtained the prior distribution can be further optimised. Dose predictions can be made based on this updated prior distribution.

Stage 3 -The Posterior Distribution: outputs and predictions

This is the final objective. The Bayesian graph represented by the blue line in Figure 4 shows the greatest probability of what we are likely to see in our patient given the new information. The “x”s are the actual drug concentrations entered into the software for the individual patient. Note that the x furthest to the right falls on the population model but not on the individual model even though this data point was taken from the individual patient.

The fundamental principle of the Bayesian approach is to learn about the “weighted average” of some prior beliefs and observations.¹⁶ The main difference between the Bayesian approach and the frequentist approach (used in nomograms) is that the priors (parameter values) have random variability representing a distribution whereas the frequentist approach assumes that there is only one

set of true parameter values, usually the mode (most frequent value), rather than use the entire posterior distribution.

The beauty of using Bayesian to calculate doses is that we can account for measurement errors by knowing real probabilities (priors). In this way uncertainty is measured by probability distributions and this is calculated on parameters, which are conditional or known.

Figure 4. Bayesian concentration-time curve showing a Bayesian patient in “blue” and the population model in “red”.

Clinical Case Part 2

What could have been done differently with patient AB to obtain a therapeutic range within 7 days? A loading dose could have been administered, however, unless an appropriate maintenance dose is given concentrations will quickly drop and the dose will need to be adjusted. Alternatively a loading dose could have been administered and Bayesian methods implemented. In this case a dose of 2.5g twice daily would have been recommended¹⁹ based on a population model and the individual patient covariates. We estimate the patient would likely have been in therapeutic range in less than 48 hours.

How can clinicians use Bayesian methods?

To be able to use Bayesian statistics in a clinical setting, computer software is required. There are a number available including MM-USC*PACK[®], MwPharm[®], TCIWorks, JPKD[®], TDM for R, Antibiotic Kinetics[®], APK[®], Kinetics[®], Kinetidex[®], T.D.M.S 2000 [™], DataKinetics [™], RADKinetics and DoseMe^{®18,24}

Presently, most softwares are not as refined and user friendly for a busy clinician and interpreting outputs can be a tedious task. A 2013 review assessing TDM software found the number of drugs each could handle ranged from 2 to 180 and most but not all were able to predict an accurate regimen from patient covariates such as age, sex & weight.¹⁸ Softwares vary in their ability to accept models for special populations of patients such as those with cystic fibrosis or paediatrics. Most software allow for a printable patient report to accompany the medical chart but it may still need the skills of a clinical pharmacist or clinical pharmacologist to interpret results as programs vary in complexity and their ability to deal with drugs which are 1,2 or 3 compartmental in nature.

A practical advantage of these systems is the ability to use drug concentrations when the drug is not at steady state, as well as samples taken at random times. This means that sampling times do not need to be perfectly coordinated with the phlebotomist. Bayesian methods also consider a patients dynamic physiological and disease states to help reduce variability. The advantage with many of these softwares is that they are not significantly more time consuming than alternative nomogram methods and can be easily integrated into everyday practice.

Conclusion

Fixed and covariate based dosing fail to account for patient variability and inevitably dose adjustments are required. Nomograms can rarely be used with certainty in all populations and traditional TDM does not account for all variability. Bayesian methods have been shown to help clinicians achieve a therapeutic range more quickly and improve patient outcomes.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Sheiner LB. Computer-aided long-term anticoagulation therapy. *Computers and Biomedical Research*. 1969;2(6):507-18.
2. Berry DA. Bayesian clinical trials. *Nature Reviews Drug Discovery*. 2006;5(1):27-36
3. Fast facts on CKD in Australia. Kidney health Australia.
<http://www.kidney.org.au/KidneyDisease/FastFactsonCKD/tabid/589/Default.aspx>
4. Sinha Y, Cranswick NE. How to use medicines in children: Principles of paediatric clinical pharmacology. *Journal of Paediatrics and Child Health* 2007;43:107-11.
5. Kearns G, Reed M. Clinical Pharmacokinetics in Infants and Children. Appraisal. *Clin. Pharmacokinet*. 1989; 17(Suppl. 1): 29–67.
6. Donagher J. Evaluation of Therapeutic Drug Monitoring at the Royal Brisbane and Women's Hospital (RBWH) [MPharm thesis] St Lucia, Qld: University of Queensland; 2015. Unpublished
7. Principles of vancomycin use: adults [revised 2014 Oct]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2014 Nov
8. Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic Drug Monitoring of Antimicrobials. *Br J Clin Pharmacol* 2001;73(1):27–36
9. Pryka RD, Rodvold KA, Erdman SM. An updated comparison of drug dosing methods: Part I. *Clin Pharmacokinet*. 1991;20(3):209-17.
10. Erdman SM, Rodvold KA, Pryka RD. An updated comparison of drug dosing methods: Part II. *Clin Pharmacokinet*. 1991;20(4):280-92
11. Erdman SM, Rodvold KA, Pryka RD. An updated comparison of drug dosing methods: Part III. *Clin Pharmacokinet*. 1991;20(5):374-88.
12. Pryka RD, Rodvold KA, Erdman SM. An updated comparison of drug dosing methods: Part IV. *Clin Pharmacokinet*. 1991;20(6):463-76

13. Avent ML, Teoh J, Lees J, Eckert KA, Kirkpatrick CM. Comparing 3 methods of monitoring gentamicin concentrations in patients with febrile neutropenia. *Therapeutic drug monitoring*. 2011;33:592
14. Holford NHG, Holford NHG. *British journal of clinical pharmacology*: Target concentration intervention: beyond Y2K. 01/07/1999;48(1):9
15. Williams PJ, Ette EI. *Pharmacometrics : the science of quantitative pharmacology*. 01/12/2006
16. United States Food and Drug Administration. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials [internet] 2014 [updated 2010 Feb 5; cited 2014 Nov 10]. Available from:<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm>
17. Thomson AH, Staatz CE, Tobin CM, Gall M, Lovering AM. Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations. *J Antimicrob Chemother* 2009;63(5):1050-7
18. Fuchs A, Csajka C, Thoma Y, Buclin T, Widmer N. Benchmarking Therapeutic Drug Monitoring Software: A Review of Available Computer Tools. *Clin Pharmacokinet* 2013; 52:9-22
19. DoseMe®
20. Martin JH, Ah Yui N, Norris R, Kubler P, Barras M, Kirkpatrick CMJ. Optimising gentamicin use in a tertiary hospital setting. *Australasian Society for Clinical and Experimental Pharmacology and Toxicology*; 2010; Melbourne; 2010
21. Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic drug monitoring of antimicrobials. *Br J Clin Pharmacol*. 2012;73(1):27-36
22. Razi Zaidi ST, Dang N, Cheah M. Does one dose fit all? Determinants of therapeutic vancomycin concentrations in adult patients *Int J Clin Pharm* 2013 35:5 SUPPL. 2 (875)
23. Vinks A, Derendorf H, Mouton J. Fundamentals of antimicrobial pharmacokinetics and

pharmacodynamics. New York: Springer; 2014

24. Tobler A, Mühlebach S. Intravenous phenytoin: A retrospective analysis of bayesian forecasting versus conventional dosing in patients. *International Journal of Clinical Pharmacy*. 2013;35(5):790-7
25. Relling MV, Fairclough D, Ayers D, Crom WR, Rodman JH, Pui C, et al. Patient characteristics associated with high-risk methotrexate concentrations and toxicity. *Journal of Clinical Oncology*. 1994;12(8):1667-72
26. Le Meur, Y, Büchler, M, Thierry, A, Caillard, S, Villemain, F, Lavaud, S, Marquet P Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation." *American Journal of Transplantation* 2007; 7(11): 2496-2503.
27. Bleyzac N, Souillet G, Magron P, Janoly A, Martin P, Bertrand Y, et al. Improved clinical outcome of paediatric bone marrow recipients using a test dose and bayesian pharmacokinetic individualization of busulfan dosage regimens. *Bone Marrow Transplant*. 2001;28(8):743-51
28. Barras M, Airaman H, Kirkpatrick CMJ, Harris M, Dakin C, Jess K, Pilbeam M, Norris R. Bayesian optimisation of tobramycin dosing in paediatric patients with cystic fibrosis. *J Pharm Pract Res* 2011; 41: 183-7.
29. Evans WE, PharmD., Relling MV, PharmD., Rodman JH, PharmD., Crom WR, PharmD., Boyett JM, PhD., Pui C, M.D. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *N Engl J Med* 1998 Feb 19;338(8):499-505
30. van Lent-Evers NA, Mathôt RA, Geus WP, van Hout BA, Vinks AA. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: A cost-effectiveness analysis. *Ther Drug Monit*. 1999;21(1):63-73

Table 1: Studies using TDM and Bayesian analysis

Author	Outcome
Tobler A, et al ²⁴	A Bayesian forecasting (BF) regimen was compared to conventional dosing for IV phenytoin. 869 patients were dosed using BF and 1,720 conventionally dosed. BF showed better performance in reaching a therapeutic target faster and for longer duration than conventional dosing.
Avent ML et al ¹³	A retrospective study of 75 patients who received once-daily gentamicin and had 2 sets of paired gentamicin serum concentrations. PK parameters and ensuing doses were compared using a Bayesian method, linear regression and a nomogram. The Bayesian method showed greatest precision and more patients attained a target gentamicin concentration than other methods.
Relling MV et al ²⁵	Outcomes associated with methotrexate concentrations and toxicities were assessed in 134 children treated with high dose methotrexate. Using Bayesian methods, clinical variables can be modified to reduce high-risk concentrations and toxicities.
Le Meur et al ²⁶	137 renal transplant patients were randomised to receive either a fixed dosed regimen of mycophenolate mofetil or a concentration-controlled regimen where Bayesian forecasting was used to adjust mycophenolate mofetil doses. At month 12 patients in the concentration controlled regimen had less treatment failures and less acute rejection episodes.
Bleyzac N et al ²⁷	29 children who underwent allogenic bone marrow transplantation had individual PK parameters obtained following a test dose of busulfan. The performance of the test dose to predict AUC during the busulfan regimen for BMT was evaluated. Individualised busulfan dosages improved early post-transplantation outcome, as shown by the lower probability of developing veno-occlusive disease and the 90-day survival.
Barras M et al ²⁸	2 blood samples were collected from paediatric CF patients prescribed once daily IV tobramycin. It was found that the number of plasma concentrations required for tobramycin can be reduced from 2 to 1 when estimating and AUC using Bayesian methods.
Evans WE et al ²⁹	188 children with acute lymphoblastic leukaemia were randomly assigned to receive treatment based on body surface area or on the clearance of drug in the patient. Patients who received individualised doses had significantly fewer courses of treatment with systemic exposures below the target range than did patients who received conventional doses (P<0.001 for each medication).
van Lent-Evers NA et al ³⁰	Active therapeutic drug monitoring was examined in a prospective study in 4 hospitals. Model-based dosing of aminoglycosides using Bayesian methods resulted in higher antibiotic efficacy, shorter hospitalisation, and reduced incidence of nephrotoxicity.

PK = pharmacokinetics