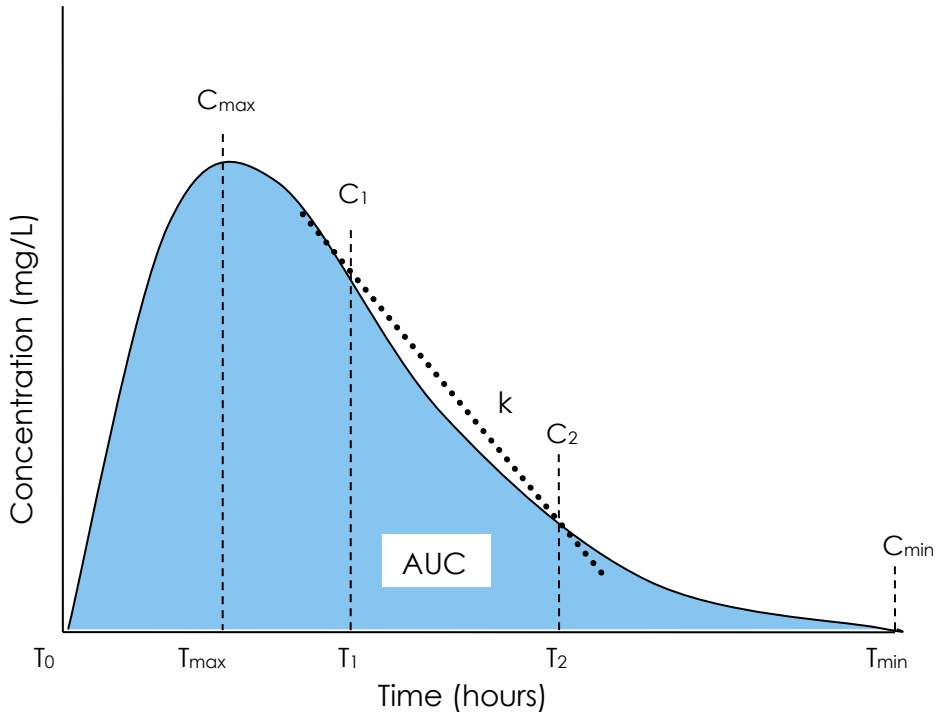
TRAINING WORKBOOK FOR THERAPEUTIC DRUG MONITORING OF AMINOGLYCOSIDES AND VANCOMYCIN

Sixth edition 2022



Produced by the Clinical Pharmacology and Hospital Pharmacy Departments, Canterbury District Health Board, New Zealand

Training Workbook for Therapeutic Drug Monitoring of Aminoglycosides and Vancomycin

The aim of this workbook is to help you to acquire the basic skills and knowledge that are needed to calculate and interpret aminoglycoside and vancomycin serum concentrations, and to estimate further doses based on patient parameters. It is designed as a training aid for new pharmacists and interns, and to update and refresh the knowledge of current pharmacists.

This sixth edition was revised by Marie-Claire Morahan and Dr Paul Chin.

Earlier editions were contributed to by Dr Sharon Gardiner, Pam Buffery, Dr Heather Isenman, Dr Phillip Drennan, Dr Richard McNeill, Louise McDermott, Barbara Robertshawe, Judy Dalrymple, Jane Vella-Brincat and Jessica Dodd.

Contents

1. Introduction

1.1. How to use the workbook

The workbook contains an introductory section and four tutorials:

- Adult aminoglycosides
- Paediatric aminoglycosides
- Neonatal aminoglycosides
- Vancomycin

The tutorials contain brief background information about the specific topic followed by some worked examples and finally some examples for you to work through. For each worked example, use Bayesian monitoring software (see 2.2 and 2.3) where possible to determine your next dose recommendation. Hand calculations are provided for comparison.

After you have worked through these example scenarios you should discuss your calculations and recommendations with a senior pharmacist such as your preceptor, team leader or Medicines Information pharmacist.

1.2. Pharmacokinetic and pharmacodynamic principles of antimicrobial dosing

The minimum inhibitory concentration (MIC; the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism) represents the most elemental pharmacodynamic (PD) measure for antimicrobials. However, this value simply reflects the potency of the given agent, providing no information regarding the time course of antimicrobial effect, nor whether the rate of bacterial killing may be altered by changing drug exposure. It is more informative to consider MIC in conjunction with pharmacokinetics to assess the ability of a given antimicrobial and its dosing regimen to kill the infecting pathogen.

Three major PD parameters link antimicrobial pharmacokinetics to efficacy:

- The percentage of time that free drug remains above the MIC over a 24-hour period (fT>MIC).
- The ratio of free drug area under the concentration-time curve (AUC) to MIC over a 24-hour period (fAUC:MIC). The AUC reflects the actual body exposure to a drug after administration of a dose. It is dependent on the dose administered and the rate of elimination of the drug from the body.
- The ratio of maximum concentration (C_{max}) to MIC (C_{max}:MIC).

An additional factor is the post-antibiotic effect (PAE), which quantifies the persistence of bacterial suppression after short exposure to the drug, thus adding to the overall duration of effect. In general, all antibiotics exhibit some degree of PAE against susceptible Gram-positive organisms, with values ranging from <2 hours for β-lactams to about 5 hours for vancomycin against S. aureus. B-lactams (except for carbapenems) have virtually no PAE against Gram-

negative pathogens. Agents that alter protein or nucleic acid synthesis, such as aminoglycosides and fluoroquinolones, tend to display a prolonged PAE against any susceptible organism, as it takes considerably longer for bacteria to regenerate these elements than components of the cell wall. PAE values derived from animal models for these agents are on average between two and six hours, thus, longer dose intervals are possible without compromising treatment efficacy.

Antimicrobial bacterial killing can be classified as follows:

- **time-dependent antimicrobials** (e.g. β-lactams)

  Substantially increasing drug concentrations has minimal effect on the overall rate and extent of bacterial killing. Instead, maintaining a free drug concentration above the MIC of the organism for a portion of the dosing interval (fT>MIC) best predicts efficacy. A shorter dosing interval will increase the fT>MIC.

- **concentration-dependent antimicrobials** (e.g. aminoglycosides)

  Bacterial kill is maximised by attaining higher peak concentrations (C_{max}:MIC). Here, maintaining concentrations above the organism MIC for an extended period of the dosing interval is unnecessary, and in fact discouraged, due to an increased risk of adverse effects.

- **AUC-dependent antimicrobials** (e.g. glycopeptides such as vancomycin)

  This is sometimes considered by other authors as a subset of time-dependent antimicrobials. The fAUC:MIC metric affords flexibility in the dosing regimen, as simultaneously adjusting both the magnitude and frequency of the dose will result in identical fAUC values. Consequently, this index incorporates components of both time and concentration-dependent bacterial kill.

Antibiotic	**PD index**	**PAE**	**Kill classification**
aminoglycosides	fC_{max}:MIC and fAUC:MIC	prolonged	concentration-dependent
β-lactams	fT>MIC	minimal (except for carbapenems)	time-dependent
fluoroquinolones	fAUC:MIC and fC_{max}:MIC	prolonged	concentration-dependent
glycopeptides	fAUC:MIC	minimal	AUC-dependent
macrolides	fAUC:MIC	moderate to prolonged	time-dependent

2. Aminoglycosides

2.1. What are aminoglycosides and how do they work?

Aminoglycoside antibiotics (e.g. gentamicin, tobramycin and amikacin) are derived from the *Streptomyces* and *Micromonospora* bacteria. They tend to be poorly orally absorbed, are usually given by injection, have a narrow therapeutic index and are potentially toxic.

Mechanism of Action

Aminoglycosides are transported into bacteria where they bind to mRNA and interfere with protein synthesis, leading to eventual cell death.

Aminoglycosides differ from some other antibiotic classes in four main ways:

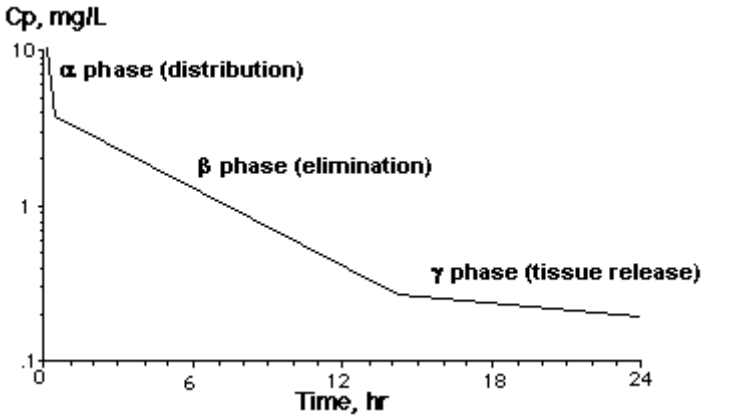
1. Concentration-dependent bacterial kill: the higher the peak concentration, the greater the rate of kill. Aminoglycosides eradicate bacteria best when they achieve a C_{max} at least 10 times the MIC. This contrasts with β-lactams, where time above the MIC determines rate of kill. An MIC of 1 mg/L can be assumed for most organisms; however, higher MICs such as 2 mg/L are more common with Pseudomonas.
2. PAE: residual bactericidal activity persists for one to eight hours after the serum concentration has fallen below the MIC. Higher peak concentrations prolong this phenomenon.
3. Adaptive resistance: bacteria exposed to aminoglycosides develop resistance that resolves when drug exposure declines. Studies have shown that to obtain the highest kill rates there needs to be a six to eight-hour period where little or no aminoglycoside is present. Once-daily dosing helps minimise this adaptive resistance as concentrations at the end of the dosing interval are very low.
4. Toxicity: aminoglycosides are associated with nephrotoxicity (thought to be related to high trough concentrations and/or AUC) and ototoxicity (possibly idiosyncratic). Evidence shows that once-daily dosing causes less nephrotoxicity; data are less clear for ototoxicity.

Pharmacokinetics

The pharmacokinetics of aminoglycosides are different for adults, children and neonates. The figures listed below are based on adult parameters.

- Oral bioavailability: nil
- Protein binding: <0.1
- Volume of distribution (Vd): 0.27 L/kg (0.24-0.33)
- Clearance (CL): 0.06 L/h/kg (0.04-0.12)
- Fraction excreted unchanged by the kidneys (fe): >0.9
- Half-life (t½): 2.5 hours

When given by IV infusion over 30 minutes, aminoglycosides follow a 3-compartment pharmacokinetic model consisting of the alpha (distribution), beta (elimination) and gamma (tissue release) phases. With typical doses, the gamma phase begins approximately sixteen hours post-infusion, when drug that was tissue-bound to various organs is released. This leads to an apparent half-life of about 30 hours.



Third-spacing

The human body is mostly water: approximately 60% of total body mass in adult males and approximately 55% in adult females. Of total body water, about two-thirds is intracellular fluid and one-third is extracellular fluid. Extracellular fluid is distributed between the interstitial compartment (tissue) and intravascular compartment (plasma).

Third-spacing is the physiological concept that body fluids may collect in a 'third' body compartment that is not normally perfused with fluids. Examples include:

- pleural effusions
- ascites
- fluids pooling in the burn site in patients with severe burns

Clinically, it is common that the extent of third-spacing is unknown. It therefore serves more as a theoretical concept for problem-solving rather than as a concrete value. Sometimes the specific site of the third space is not clear (as may occur during sepsis). However, the concept of a third space is useful to explain the shift of fluids from the plasma and tissues and therefore the alteration in pharmacokinetics (i.e. Vd and hence half-life) of drugs that distribute predominately into body water such as the aminoglycosides.

2.2. Monitoring

The aims of monitoring aminoglycoside concentrations are to ensure adequate dosing and avoid excessive drug exposure. Generally, concentrations should be monitored after the first dose, after a dose change and, if the patient is on a stable dose, two or three times a week. However, concentrations may need to be monitored more frequently if the patient is very unwell, has poor renal function, or the pharmacokinetics are likely to change (e.g. after major surgery, losing large volumes of fluid such as via a drainage tube, resolving sepsis). If you are unsure of how frequently your patient should be monitored, then ask a senior pharmacist for help. Renal function (serum creatinine) should be monitored both before and during therapy.

See the CDHB Antimicrobial guidelines for current dosing and concentration monitoring recommendations.

Bayesian therapeutic drug monitoring

Bayesian therapeutic drug monitoring methods formally incorporate information about a drug's population pharmacokinetics, individual patient variables (e.g. age, sex, weight, renal function) and measured drug concentrations. By combining both population and patient-specific information, individual pharmacokinetic parameters can be estimated to optimise dose regimens for a specific target. Advantages of the Bayesian approach include faster achievement of target exposure, reduced toxicity and reduced cost.

The concentration-time outputs from the Bayesian approach can be divided into population-based and individual-based. The population-based output, also called *a priori*, accounts for all covariates used in the drug model (including age, sex etc.) but not measured drug concentrations. The individual-based output, also called *a posteriori*, accounts for all covariates **and** measured drug concentrations.

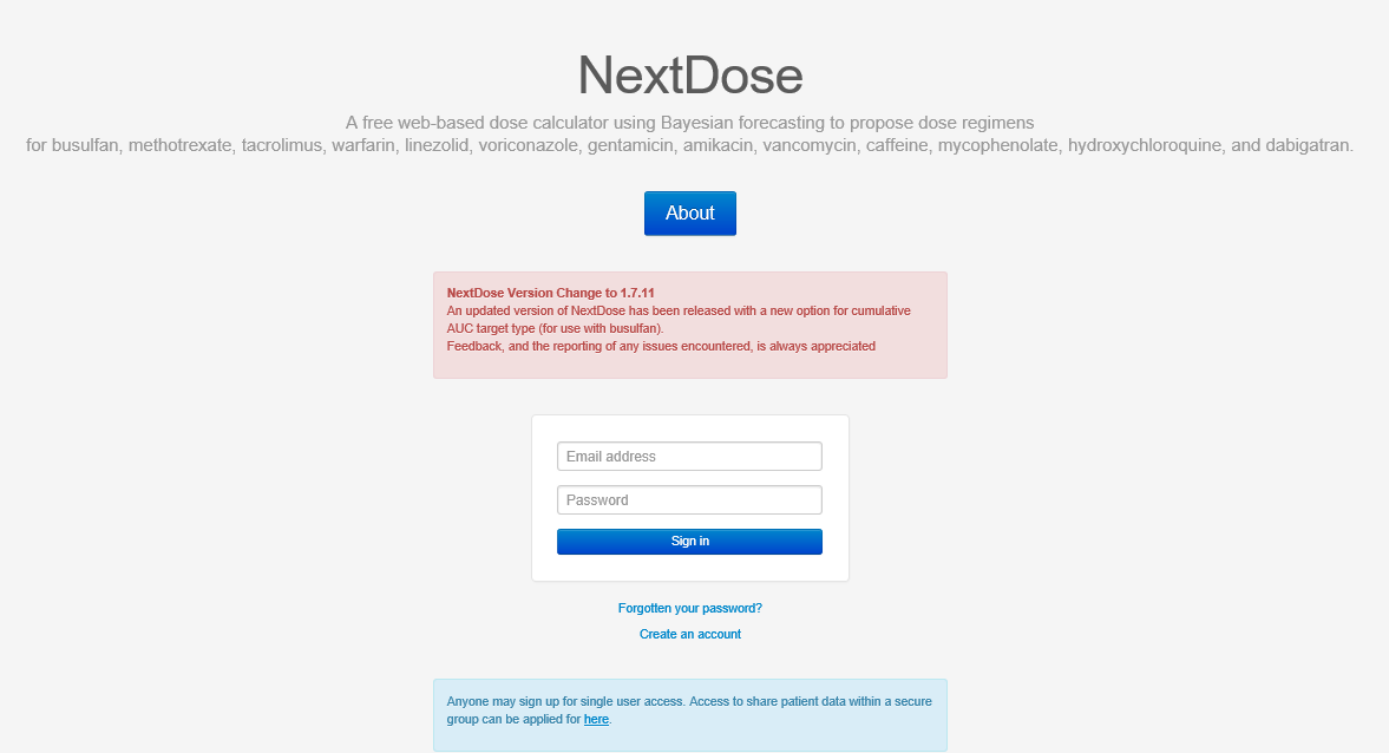
Various Bayesian modelling software products are available. CDHB currently use NextDose: see 2.3.

2.3. NextDose

NextDose is an online Bayesian therapeutic drug monitoring platform developed at the University of Auckland, New Zealand.

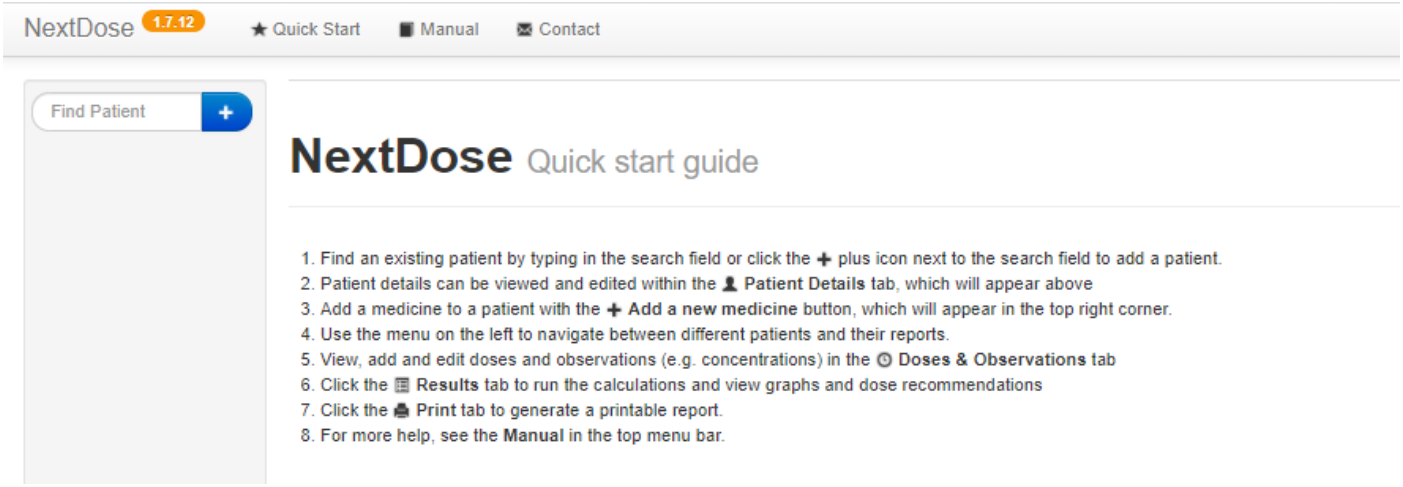
Accessing NextDose for the first time

- Email sharon.gardiner@cdhb.health.nz, paul.chin@cdhb.health.nz or marie-claire.morahan@cdhb.health.nz (who all have administrator rights) to let them know that you need access to NextDose. They will add you to the CDHB user group. This allows patient data to be shared within the secure group, which is necessary for patient care and for auditing.
- You will be sent an email link to create an account. You must use your CDHB email address for this.
- After creating your account, you can use your email address and password to access NextDose at www.nextdose.org.

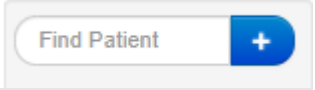


- If NextDose is down (e.g. you get a 'server response empty' error when attempting to log-in), contact either Paul Chin (paul.chin@cdhb.health.nz), Sharon Gardiner (sharon.gardiner@cdhb.health.nz) or Medicines Information (medicines.information@cdhb.health.nz) to check on the problem. If the problem is confirmed, they will contact NextDose (n.holford@auckland.ac.nz and sam@nextdose.org), and also let the pharmacy team (Team-PHM-Pharmacists@cdhb.health.nz) and Medicines Information (medicines.information@cdhb.health.nz) know that NextDose is down. Communications will also be sent out once the problem has been resolved.

NextDose landing page



- The landing page is where you can create a new patient, search for existing or recent patients, or look at demo patients for the various medicine models.
- To add a new patient, select "+".



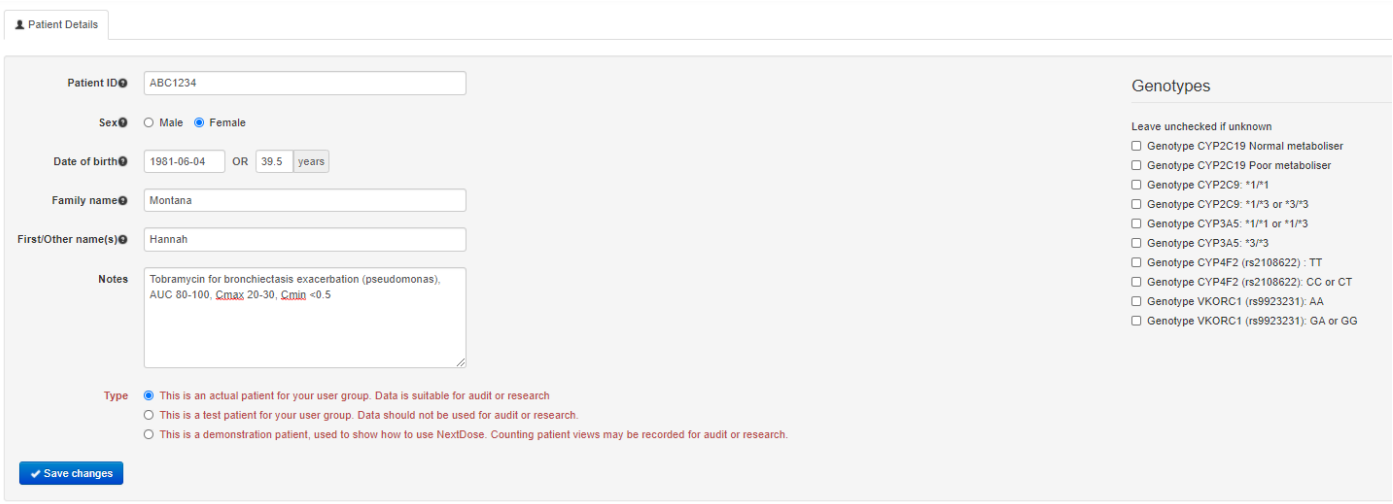
- To find an existing patient type the NHI into the "Find Patient" search bar or click on the relevant recent patient.

- Test patients, which may be used for practice, can be found by entering "ZZZ" and selecting any from the drop-down list, except for those that begin with "ZZZ00". These are read-only and non-editable, created specifically to be used as model answers for the example scenarios that follow in this workbook.

Entering a new patient

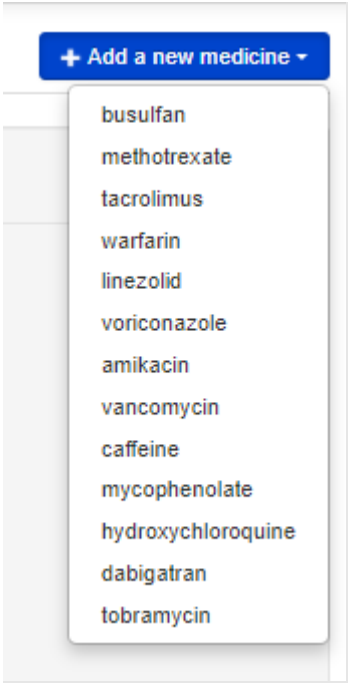
Patient Details

- Enter NHI for patient ID, sex, date of birth, family name and first name. In the notes section you can include additional details as relevant such as infection type, organism and targets e.g. AUC, C_{max}, C_{min} etc.
- Ignore "Genotypes".
- For "Type" click "*This is an actual patient for your user group*" when entering a "real" patient.
- Click "Save changes".



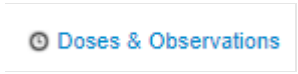
Add a medicine to a patient

- Click "Add a new medicine" at the top right of the screen and choose from the drop-down list of medicines.



Doses and Observations

- Click on the "Doses & Observations" tab



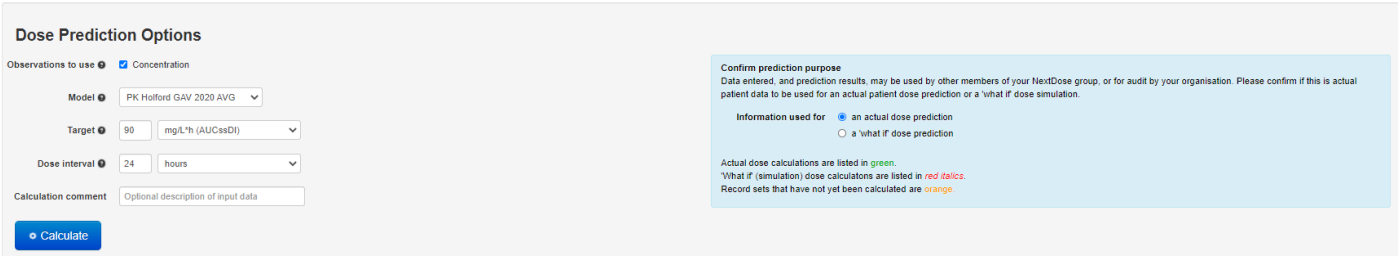
- Click "Add observation" and add each observation type as relevant for the medicine (usually weight, height, creatinine (µmol/L) and concentrations).
- The date entered for the height, weight and creatinine should **precede** the date of the first dose. This is to help the software model "know" patient dimensions and renal function before estimating pharmacokinetics, which should give better predictions.
- "Lab no" and "Sample arrival boxes" can be left blank.
- You can use the button for below the limit of quantification (BLQ), but NextDose will treat this as a missing data point and does not take the result into account when predicting the concentrations. To address this, enter the concentration as $\frac{BLQ\ concentration}{2}$ e.g. if BLQ is <0.5 mg/L, then enter 0.25 mg/L.

Click on "Save changes" for each observation entered.

- Click "Add dose" to enter all doses given to the patient, with corresponding start time, and infusion duration or end time.
    - Infusion duration for intermittent vancomycin may vary between 500 and 1000 mg/hour. It is especially important to enter an accurate duration when the dose is associated with a measured **peak** concentration. If the intermittent infusion time is unknown, enter a duration that relates to a rate of 750 mg/hour. For continuous infusions, enter 24 hours. Note a warning alert will fire if the infusion duration entered is more than 6 hours. This does not impact on the model (e.g. for vancomycin given over 24 hours) and can be ignored.
    - Note that it is possible to enter future doses i.e. that have NOT yet been given. This should primarily be done for the purpose of 'what if' dose predictions (see below for further details).
- Click on "Save changes" for each dose added.

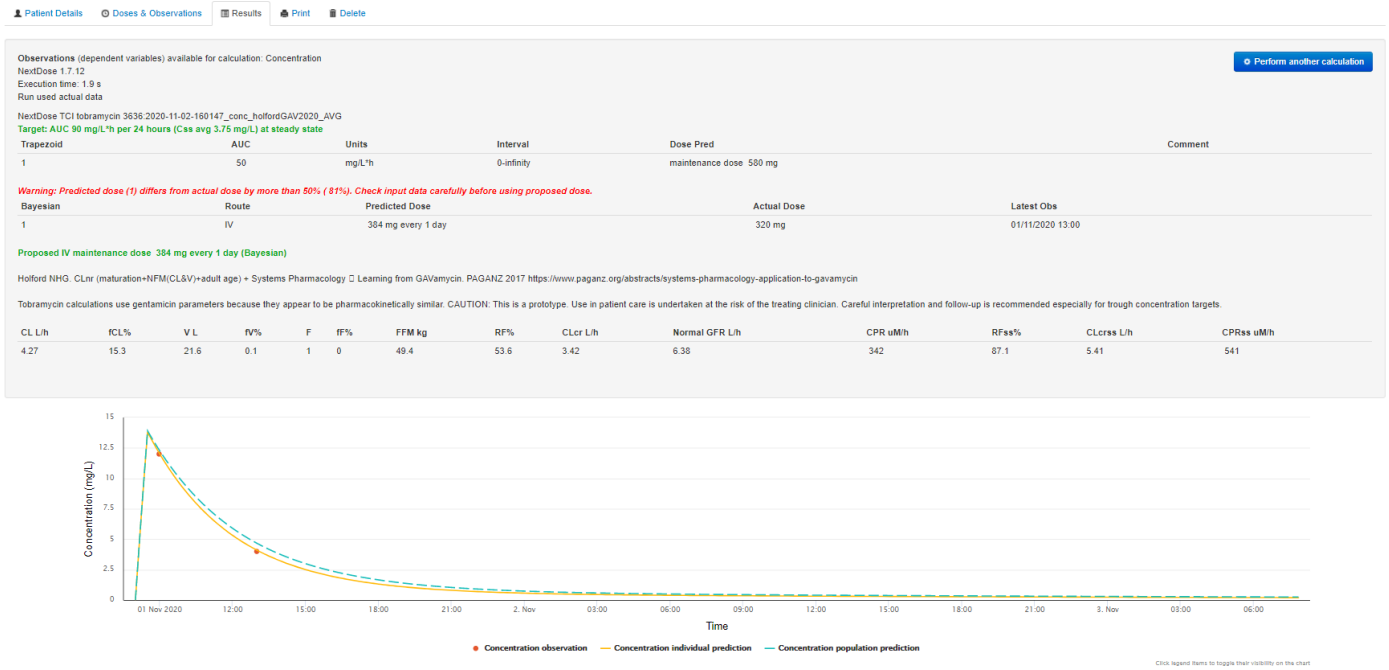
Results

- After all the observations and doses are entered, click on the "Results" tab.



- Enter the "Target" AUC and "Dose interval" and indicate if it is an "an actual dose prediction" or "a 'what if' dose prediction".
    - Note that for most drugs there is a reference range for the AUC rather than a single target. However, a single target is required in NextDose to perform the analysis. In these cases, use the middle of the range as the single target e.g. 500 for vancomycin if aiming for 400-600 mg/L.h, and 90 for gentamicin if aiming for 80-100 mg/L.h.
- Use "actual dose prediction" for "real" predictions based on the doses that have been given to the patient. Doses that have not yet been given should NOT be part of the dataset. This will be recorded in green on the left-hand side of the screen.

- Use a "what if" dose prediction if you want to try out alternative dosing scenarios. These will be recorded in red on the left-hand side of the screen.
- Do not change the "Model". The default model is the most recent.
- The "Calculation comment" field can be left blank, or used to make notes about the prediction e.g. "trying 48 hourly dosing".
- Click "Calculate" and a concentration-time curve will be generated.



- The red dots are the measured concentrations, the dotted blue line is the population prediction (Bayesian) model and the yellow line is the individual prediction model. If the lines are similar, then the patient "fits" the population model well. If the red dots are a long way from the prediction curves, the "fit" is poor. As a rule of thumb, a discrepancy of more than 20% in concentrations may be considered a poor fit. Discrepancies between the individual model and the population model are not necessarily 'incorrect' – unpredictable individual pharmacokinetic variability is why we need to need to measure concentrations in an individual patient:

Possible reasons for discrepancies

- Incorrect data
    - sampling error (see 2.7.)
    - documentation error e.g. times or doses by ward staff on the lab form, or transcription error of times, concentrations, doses or patient demographics into NextDose
        - A time on the lab report of 0000 or 0001 is indicative that no time was written on the sample tube. You will need to clarify the sample time with ward staff in this case.
        - laboratory error in measurement of creatinine or drug concentration
- Patient variables not in the model
    - Extremes of body size: ideal body weight is an imperfect method of accounting for variability in body composition and size. The 1.8 m 120 kg obese patient has less body water than the 1.8 m 120 kg professional rugby prop forward, but both will have the same ideal body weight.
    - Third-spacing (see 2.1.)
    - Presence or removal of a surgical drain changes clearance

- Rapidly changing renal function: creatinine has a half-life of 6 hours with normal renal function, and thus reaches steady state more slowly than aminoglycosides. Hence creatinine may not accurately reflect current renal function.
- Change in disease e.g. sepsis leads to more permeable membranes and larger Vd for polar molecules.

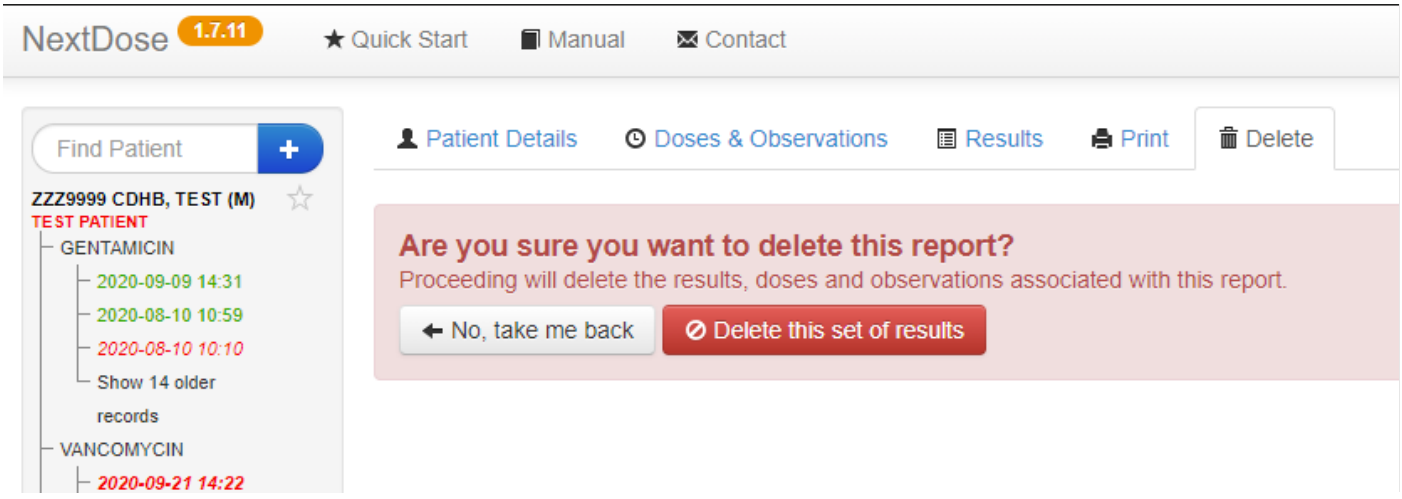
- fCL% and fVd% show the difference in CL and Vd for that patient compared to the general population e.g. if fCL% is 20, then the patient's CL is 20% higher than the population prediction. If fCL% is -20, then the patient's CL is 20% lower than the population prediction. A difference greater than 25% indicates that the patient is significantly different to the population model.

NextDose calculates a recommended dose ("Proposed IV maintenance dose - Bayesian") that should achieve your desired AUC target.

- The AUC achieved off the current dosing schedule is not given. You can calculate it yourself by multiplying the target AUC by the ratio of the proposed dose to the actual dose:

$$AUC\ achieved = (actual\ dose \div proposed\ dose) \times target\ AUC$$

- If the AUC achieved is outside of the reference range, then the dose should be adjusted.
- C_{max} and C_{min} can be found by hovering over the relevant time-points on the curve.
- You can click on the legends for Concentration observation, Concentration individual prediction and Concentration population prediction to toggle their visibility on the chart.
- You can click on "Perform another calculation" to re-run the scenario with a different target or dose interval. Do this as "a what if dose prediction", which will be listed in red on the left-hand side of the patient record.
- For tidiness, limit the number of saved "what if" predictions: e.g. you might try out four different predictions and keep the one or two most useful. Keeping a "what if" prediction can be useful to see the reasoning behind the final dose prediction. Use the "Delete" button to delete unwanted "what if" datasets or if you have made a mistake.



- If a very large dose increase is proposed, then consider whether a more conservative increase may be appropriate.
- Consider the drug vial/ampoule size for ease of administration e.g. gentamicin and tobramycin both come as 80 mg/2 mL, amikacin 500 mg/2 mL and vancomycin 500 mg and 1 g vials.

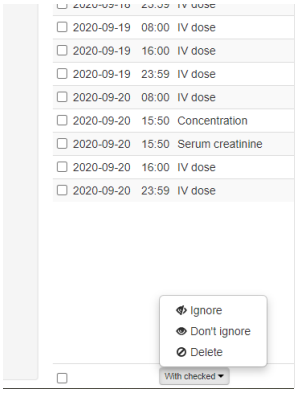
- If you need help with a dose recommendation, contact your Team Leader, Sharon Gardiner, Medicines Information or Paul Chin (in that order).

Finding an existing patient on NextDose to continue a current course

- When you come back to add new data to an existing patient (e.g. 3 days after the last dose prediction), add the data to the most recent green dataset i.e. containing 'real' data. A new data group or date line will be generated incorporating both the old and new data.

Finding an existing patient on NextDose who is starting a new course

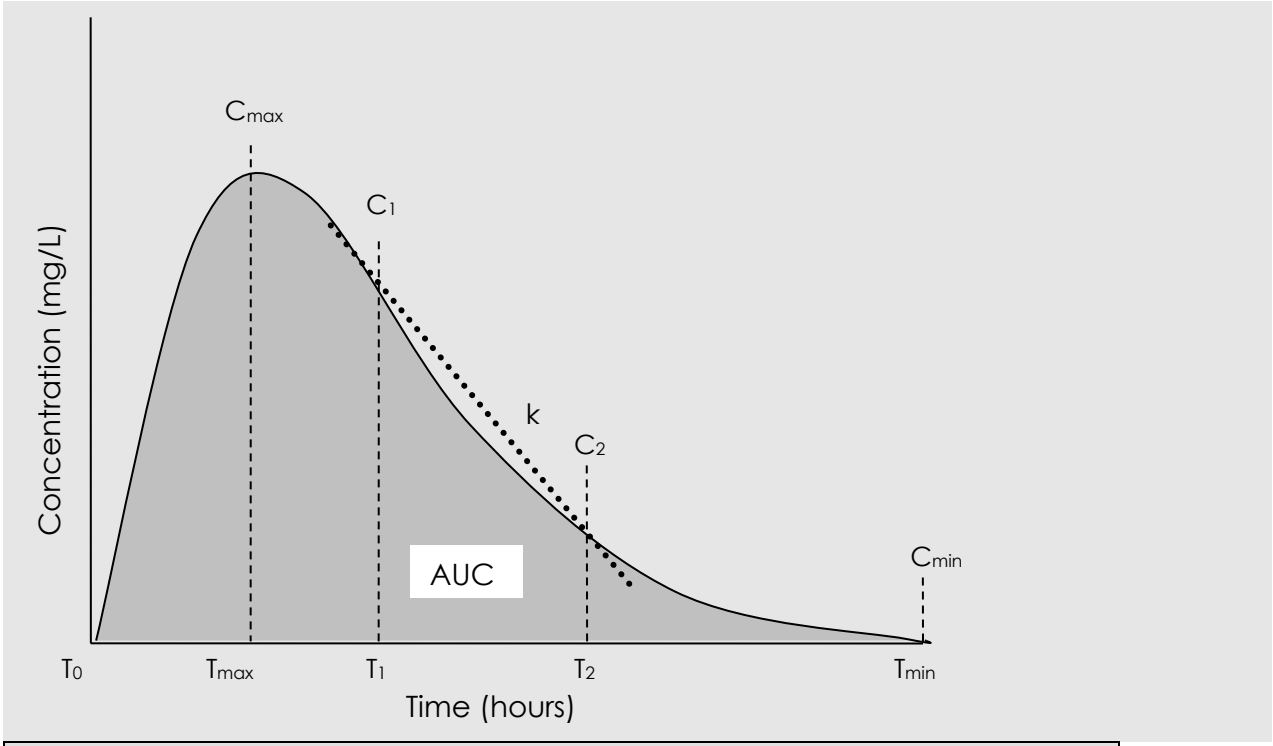
- When you come back to add new data to an existing patient (e.g. a new vancomycin course 6 months after the previous), add the data to the most recent green dataset i.e. containing 'real' data. A new data group or date line will be generated incorporating both the old and new data.
- If you want to predict a dose using only the new data, then you can select the old data and choose to **ignore** it using the tools in the bottom left of the screen. This might be useful if a patient has come back in for a new episode of care some months later.



- NextDose cannot calculate more than ~160 doses. If this is a problem, consider setting earlier doses to "Ignore". If 'ignoring', take this into account when interpreting NextDose results. Clinically, setting earlier doses to "Ignore" is usually ok to do if the doses are a long time ago in relation to the drug's half-life in the patient.

2.4. Hand calculations

Where a Bayesian software programme is unavailable, hand calculations using a log-linear regression method can be undertaken. Two serum concentrations are required if you are using this method.



Key			
Known values		Calculated values	
T_0	infusion start time	C_{max}	maximum concentration
T_{max}	time at the end of the infusion (usually 0.5 hours after T_0)	C_{min}	minimum concentration
T_1	time of first sample	k	elimination rate constant
T_2	time of second sample	AUC	area under the curve
T_{min}	time at the end of dosing interval (usually 24 hours after T_0 unless the dosing interval is extended beyond this)	$t_{1/2}$	half-life
C_1	sample concentration at T_1		
C_2	sample concentration at T_2		
$T_2 - T_1$	time between T_1 and T_2 (hours)		
$T_1 - T_{max}$	time between T_{max} and T_1 (hours)		
$T_{min} - T_2$	time between T_2 and T_{min} (hours)		

To obtain the calculated values you will need two sample concentrations (C_1 and C_2), the infusion start and stop times (T_0 and T_{max}), the times that the two samples were taken (T_1 and T_2) and the dosing frequency. You will also need to determine the time in hours between:

- T_1 and T_2 (depicted as $T_2 - T_1$ in the equations below)
- T_{max} and T_1 (depicted as $T_1 - T_{max}$ in the equations below)
- T_2 and T_{min} (depicted as $T_{min} - T_2$ in the equations below)

Once you have this information follow the equations below. It is important to use enough decimal places when calculating k (the elimination constant) to work out an accurate prediction (consider working to four or more decimal places). You will need a scientific calculator. Alternatively, or as well as, you can also use software (such as the 'Johnny Gent' Excel spreadsheet calculator) to double-check your results. Ask a Medicines Information pharmacist or your preceptor or Team Leader to show you how it works.

Equations

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

$$t_{½} = \frac{0.693}{k}$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

$$AUC = \frac{C_{max} - C_{min}}{k}$$

Once you have calculated the above you can adjust the patient's dose as follows:

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

2.6. What happens in the laboratory?

Once the samples are taken from the patient they are:

- Delivered to the laboratory reception.
- Registered onto the laboratory computer system.
- Taken to the separating room, centrifuged and stored in the fridge.
- Put on the automated analyser and results entered into Health Connect South.

Turn-around time is approximately two hours from receipt of samples at the laboratory.

Analysing of gentamicin, tobramycin and vancomycin is a core laboratory function and is available 24 hours a day and seven days a week in the Biochemistry laboratory. Analysis of amikacin samples is conducted by the Toxicology laboratory and is available Monday to Friday from 8am to 5pm. At the weekends analysing of amikacin requires a laboratory technician to be brought in on-call.

2.7. What can go wrong with the samples?

Problems or errors can arise with the samples and may be generated by the person taking the sample, the laboratory technician or the pharmacist. Generally, most errors related to laboratory tests occur prior to the sample reaching the lab. Some of problems include:

- Samples taken out of the cannula/CVC/PICC lines and the sample has been diluted by a line flush/previous infusion giving a falsely low concentration OR is contaminated by the residual aminoglycoside infusion in the cannula/CVC/PICC line giving a falsely high concentration. In these cases, it is generally better to obtain another sample before advising on the dose.
- The sample tube is not labelled with the time and/or the time is not recorded in the nursing notes.
- If the time is reported as 0000 or 0001, this probably means that there was no time written on the sample tube. You will need to clarify the sample time with ward staff in this case.
- Sample tubes being mixed up.
- The nurse did not give the correct dose.

If you are unsure about the results from the laboratory for any reason, then discuss with either a senior or Medicines Information pharmacist.

3. Equations

3.1. Ideal body weight (IBW)

- Males: 50 kg + 0.9 kg for each cm >150 cm in height

  e.g. For a male with an actual body weight of 99 kg and height of 195 cm the calculated ideal body weight is:

$$IBW = 50\ kg + ((195\ cm - 150\ cm)\ \times\ 0.9) = 90.5\ kg$$

- Females: 45 kg + 0.9kg for each cm >150 cm in height

  e.g. For a female with an actual body weight of 69 kg and height of 165 cm the calculated ideal body weight is:

$$IBW = 45\ kg + ((165\ cm - 150\ cm)\ \times\ 0.9) = 58.5\ kg$$

3.2. Creatinine clearance: Cockcroft and Gault

The Cockcroft and Gault equation is a useful tool to help estimate renal function in patients with stable creatinine. Use actual body weight if this is less than ideal body weight.

Its accuracy is reduced in patients who differ from the 'average' such as in extremes of age (very young or old) and size. Further, its accuracy is reduced if the plasma creatinine concentration is not at steady state e.g. evolving acute kidney injury (normally, creatinine has a half-life of 6 hours).

$$CrCl\ (mL/min)\ = \frac{(140 - age)\ \times\ ideal\ body\ weight\ (kg)}{plasma\ creatinine\ (micromol/L)\ \times\ 0.8}\ \times\ 0.85\ if\ female$$

3.3. Estimated glomerular filtration rate (eGFR)

Glomerular filtration rate or creatinine clearance can be estimated by using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation. Like the Cockcroft and Gault equation it also considers the patient's age and gender; however, it does not consider size, and thus the units are mL/min/1.73m^2, rather than mL/min.

When plasma creatinine is measured in the laboratory an eGFR is generally automatically calculated. Like the Cockcroft and Gault equation it also has several limitations.

CKD-EPI equation (Ann Intern Med 2009; 150: 604-12)

$$eGFR = 141 \times \left(min\frac{[Cr]}{0.0884 \times \alpha}, 1\right)^{\beta} \times \left(max\frac{[Cr]}{0.0884 \times \alpha}, 1\right)^{-1.209} \times 0.993^{age} \times (1.018\ if\ female)$$

α and β are sex and [creatinine] dependent constants.

4. Adult aminoglycosides

4.1. Gentamicin/tobramycin dosing and monitoring in adults

All patients, except those with tetraplegia (see 4.5) and some patients with endocarditis (see 4.4), should receive once-daily dosing. Follow the dosing and monitoring guidelines in the Pink Book.

Gentamicin and tobramycin are available as 80 mg/2 mL ampoules. Take this into consideration when recommending doses and suggest multiples of 40 mg if possible, for ease of administration.

Monitoring targets for gentamicin and tobramycin

- C_{max}: 15-30 mg/L (optimal if ≥ 10 times the MIC; an MIC of 1 mg/L can be assumed for most organisms; however, higher MICs such as 2 mg/L are more common with Pseudomonas)
- C_{min}: as close to zero as possible (< 1 mg/L)
- AUC over 24 hours (AUC_{24}):

Infection	**Target AUC_{24} (mg/L.h)**
Urinary tract infection	70*
Other infections	80-100 (depending on severity)
Sepsis or life-threatening infection	100

* The lower target AUC for urinary tract infections reflects the fact that aminoglycosides concentrate in the urine at higher concentrations than in the plasma.

4.2. Amikacin dosing and monitoring in adults

Amikacin is typically dosed once daily, although often patients with atypical mycobacterium infections are dosed with 15-25 mg/kg three times weekly.

Calculate the first dose following the steps below:

- Calculate the patient's creatinine clearance using the Cockcroft and Gault equation
- Calculate the first dose using the table below:

CrCl (mL/min)	Dose in mg/kg (IBW)	Time of second blood sample (hours)
>66	15-20 depending on infection severity	12-20
55-66	15	14-22
41-54	12	16-24
31-40	10	18-24
20-30	8	18-24
<20	not recommended	N/A

- Amikacin is available as 500 mg/2 mL vials. Take this into consideration when recommending doses and suggest multiples of 125 or 250 mg if possible, for ease of administration.
- Two blood samples should be taken:
    - the first 30 minutes after the end of the infusion
    - the second after six to 22 hours (based on renal function: see table above)
- Depending on the clinical scenario, repeat blood samples every three days or so.

Monitoring targets for amikacin

Targets for once-daily amikacin are generally double that of gentamicin/tobramycin:

- C_{max}: 30-60 mg/L
- C_{min}: as close to zero as possible (< 2 mg/L)
- AUC_{24}: 160-200 mg/L.h

Targets may differ for thrice weekly dosing – seek specialist advice in these cases. The British Thoracic Society suggest a target C_{max} of 65-80 mg/L for thrice weekly dosing.

4.3. Reasons for going outside the 24-hour dosing interval

In adults, aminoglycosides are typically dosed every 24 hours. However, some patients may have poor renal clearance and as a result are not able to clear the drug within 24 hours. In these scenarios an alternative antibiotic is generally recommended for several reasons:

- There are limited data on extended interval (>24-hour) dosing in adult patients.

- Nurses and clinical staff on the adult wards are less familiar with extended interval dosing, leading to a greater risk of administration (multiple doses being given) and blood sampling errors.
- If 36-hour dosing is used this can lead to infusions being given in the middle of the night, which may be unnecessarily disruptive to unwell patients.

Generally, extending the dosing interval of aminoglycosides in adult patients is only undertaken when there are no other suitable alternatives. In these cases, a 48-hour dosing interval is much easier for nursing and clinical staff to manage on the wards and minimises the risk of administration errors. It is important with extended interval dosing to ensure that samples are taken correctly and frequently as the patients already have poor renal function. Remember that the target AUC (AUC_{48}) is double that of AUC_{24} for patients undergoing 48 hourly dosing.

4.4. Gentamicin in bacterial endocarditis

Bacterial endocarditis is usually treated with a combination of antibiotics including gentamicin. In this instance, gentamicin is used synergistically; it is thought to potentiate the effects of concomitant β-lactam antibiotics. Historically doses of approximately 1 mg/kg given 8 to 12-hourly have been used. The CDHB has moved to once daily dosing of gentamicin for the treatment of most types of bacterial endocarditis (some consultants prefer to use 8 to 12-hourly dosing for patients with enterococcal endocarditis) using an initial dose of 3 mg/kg based on ideal body weight. For dosing and monitoring information see the Gentamicin/Tobramycin Dosing Guidelines section of the CDHB Pink Book Antimicrobial Guidelines.

CDHB patients who have been discharged on once daily gentamicin for endocarditis only require one blood sample to be taken about 6 hours after the infusion ends.

The target AUC_{24} is between 30 to 50 mg/L.h and C_{min} <0.5 mg/L. The C_{max} will likely be ~10 mg/L in normal renal function, but may be less in some patients, such as those with poor renal function.

4.5. Patients with spinal injuries

At high plasma concentrations aminoglycosides have been associated with respiratory depression due to neuromuscular blockade. In patients with high spinal lesions (T1 or higher) who have compromised respiratory function, once daily dosing could lead to respiratory failure especially in combination with other respiratory depressant drugs. If patients are paraplegic, they can receive once-daily dosing as they do not have compromised respiratory function as a result of their spinal injury. Refer to the Gentamicin/Tobramycin Dosing in Patients with Spinal Injuries section of the Pink Book for tetraplegic (including those with TI involvement) patients.

Calculate the patient's creatinine clearance using the Cockcroft and Gault equation or use the estimated GFR supplied by the laboratory. This has limited usefulness in patients with long-term spinal injuries as they tend to have a degree of muscle wastage (may be large in some patients) and therefore plasma creatinine may not reflect their true renal function,

The dose for tetraplegic patients given daily divided doses should be adjusted to achieve:

- C_{max}: 6-10 mg/L
- C_{min}: <1 mg/L

- These pharmacokinetic parameters will likely yield an AUC_8 of no more than approximately 30 mg/L.h (i.e. AUC_{24} ~90 mg/L.h).

4.6. Community patients

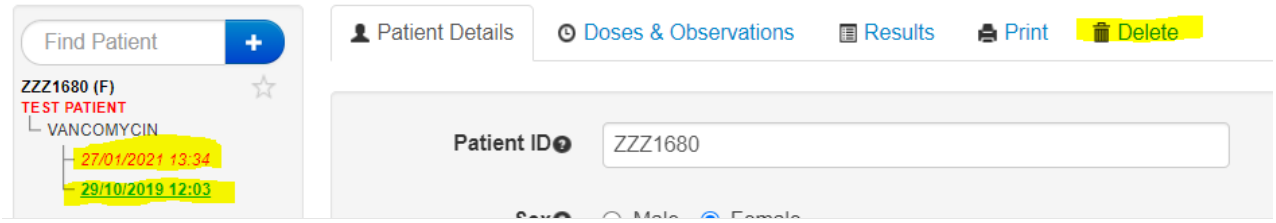
Some patients (e.g. those with cystic fibrosis, bronchiectasis or bacterial endocarditis) may be initiated on home aminoglycoside therapy. Some patients may be educated on the ward to self-administer and take their own blood samples, while others are visited by community nurses (e.g. Nurse Maude). Monitoring is generally undertaken twice weekly, usually after the Thursday and Sunday doses. Either the respiratory pharmacist (cystic fibrosis patients) or the Medicines Information service (all other community patients) is responsible for checking the results, usually on Mondays and Fridays, and advising on further dosing.

4.7. Worked examples

For each worked example, use Bayesian monitoring software (see 2.2 and 2.3) to determine your next dose recommendation. Worked model answers using NextDose and hand calculations are provided for comparison.

How to use NextDose for the practice patient examples:

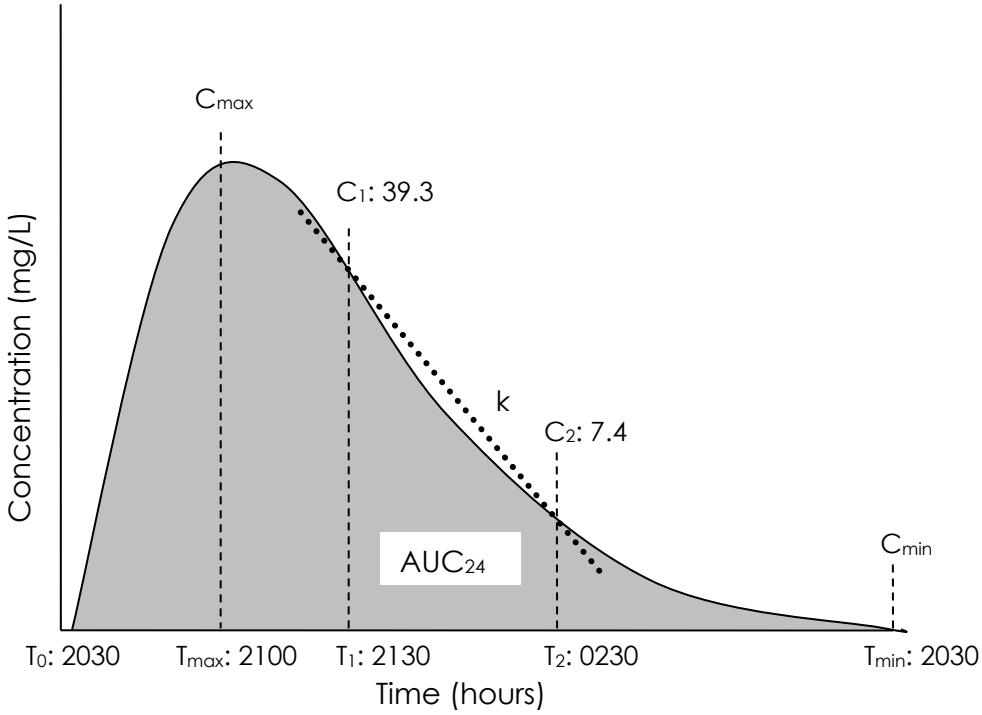
1. Search in NextDose for the NHI assigned to that case (note this NHI is different to that used for the model answer for the case, which are designed to be non-editable).
2. Check Patient Details (sex and date of birth) match the case.
3. Add the medicine and enter the data.
   - If the previous person working on the example did not delete their inputted data once they had finished, then the medicine will already be in the patient's record. If this is the case, you can delete their data before you start by clicking on each dataset and deleting it:



4. Once you have finished, delete your dataset/s so that the next person can start fresh.

Example 1: Outpatient cystic fibrosis patient

Name	GM Test
NHI	ZZZ1000
Sex	Female
Age	24 years
Weight	47 kg
Height	163 cm
Creatinine	78 micromol/L
Drug	tobramycin
Dose	660 mg 24 hourly over 30 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	90-100

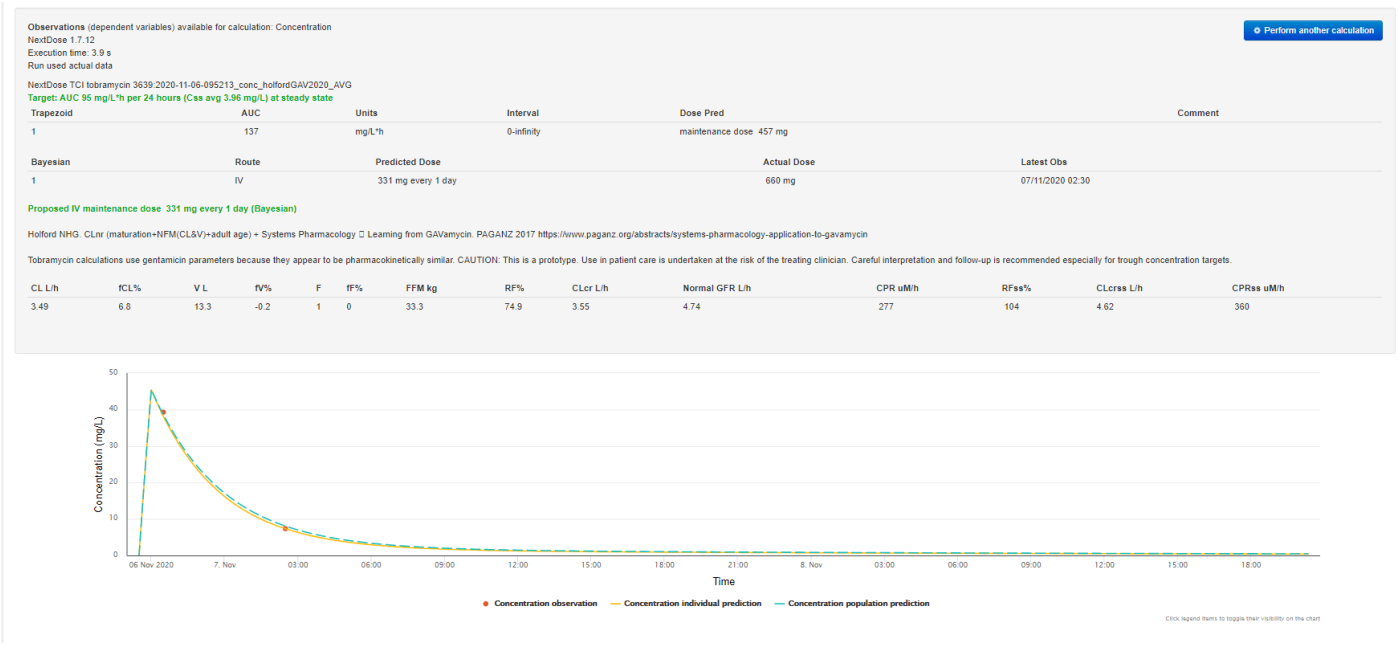


GM is a cystic fibrosis patient who is receiving tobramycin as an outpatient. She is also on meropenem 2 g IV three times a day. GM has had several doses of tobramycin, what would you now recommend?

Answer

Calculated by NextDose:

https://www.nextdose.org/#/6030/34630/results



Observations (dependent variables) available for calculation: Concentration
NextDose 1.7.12
Execution time: 3.9 s
Run used actual data

Perform another calculation

NextDose TCI tobramycin 3639:2020-11-06-095213_conc_holfordGAV2020_AVG
Target: AUC 95 mg/L*h per 24 hours (Css avg 3.96 mg/L) at steady state

Trapezoid	AUC	Units	Interval	Dose Pred	Comment
1	137	mg/L*h	0-infinity	maintenance dose 457 mg	

Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	331 mg every 1 day	660 mg	07/11/2020 02:30

Proposed IV maintenance dose 331 mg every 1 day (Bayesian)

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

Tobramycin calculations use gentamicin parameters because they appear to be pharmacokinetically similar. CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
3.49	6.8	13.3	-0.2	1	0	33.3	74.9	3.55	4.74	277	104	4.62	360

C_{max} (mg/L)	45
C_{min} (mg/L)	1

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times target\ AUC$$

$$AUC\ achieved = \frac{660\ mg}{331\ mg} \times 95 = 189$$

Recommendation:

GM is a good fit to the model i.e. the actual and Bayesian-predicted concentrations are very similar. Given the AUC, C_{max} and C_{min} are all higher than desired, suggest decreasing the dose to 360 mg 24 hourly and repeating samples twice weekly (as normal for outpatient therapy).

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 5 hours

$$k = \frac{ln39.3 \ - ln7.4}{5}$$

$$k = 0.3339$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.3339}$$

$$t_{½} = 2.1 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 0.5 hours

$$C_{max} = 39.3 \times e^{0.3339(0.5)}$$

$$C_{max} = 46.4 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 18 hours

$$C_{min} = 7.4 \times e^{-0.3339(18)}$$

$$C_{min} = 0.018 \ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{46.4 - 0.018}{0.3339}$$

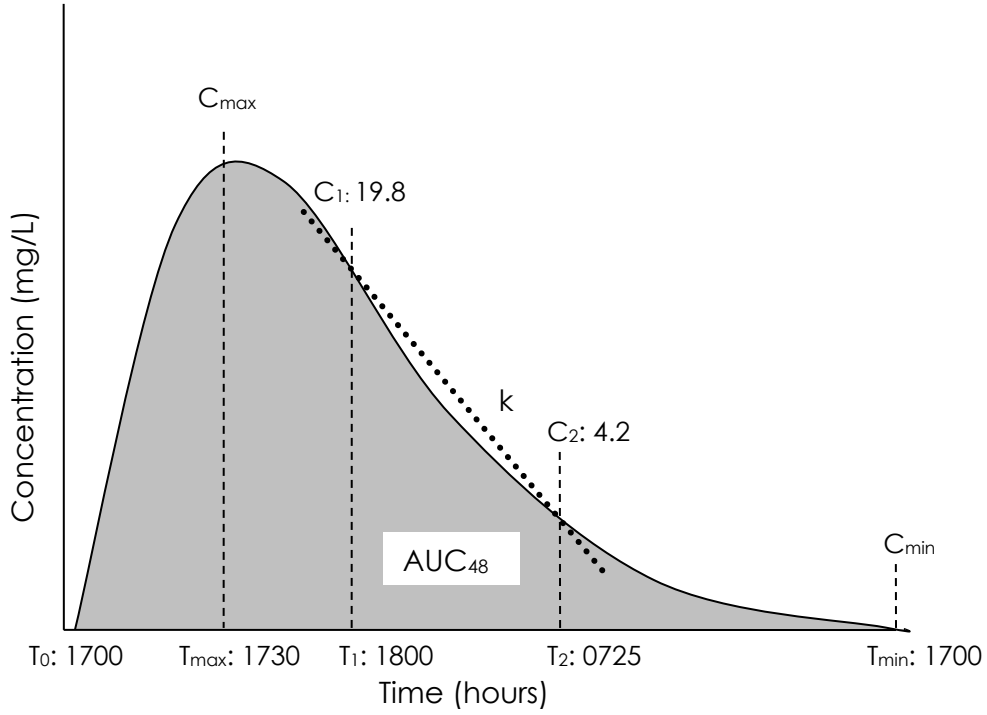
$$AUC_{24} = 139 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{95}{139} \times 660 = 451 \ mg$$

Example 2 – resistant UTI – in hospital

Name	MB Test
NHI	ZZZ1002
Sex	Female
Age	86 years
Weight	47.5 kg
Height	153 cm
Creatinine	110 micromol/L
Drug	gentamicin
Dose	240 mg 48 hourly over 30 minutes
Infection	UTI
Target AUC_{48}	140

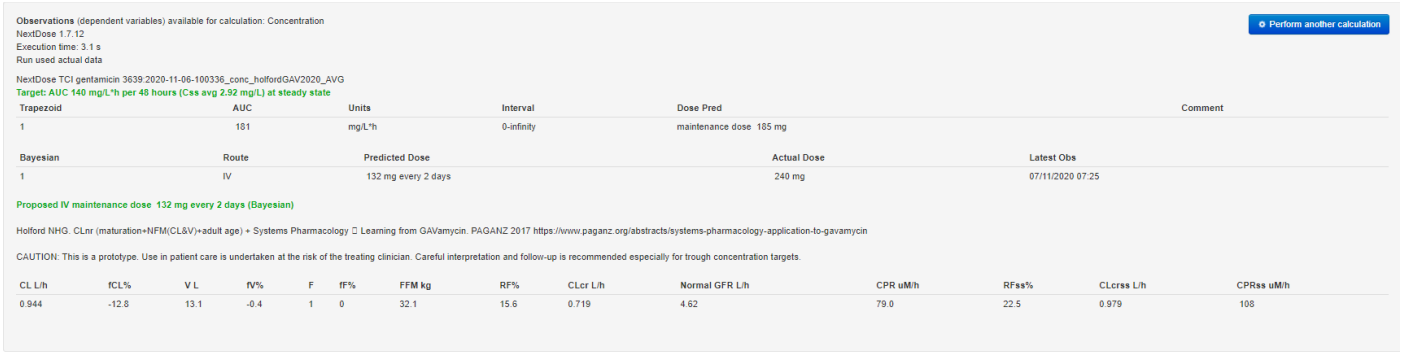


MB is an elderly patient with an UTI that is resistant to all tested antibiotics except gentamicin. MB has had one dose of 48 hourly gentamicin, what would you now recommend?

Answer

Calculated by NextDose:

https://www.nextdose.org/#/6033/34631/results



Observations (dependent variables) available for calculation: Concentration
NextDose 1.7.12
Execution time: 3.1 s
Run used actual data

Perform another calculation

NextDose TCI gentamicin 3639:2020-11-06-100336_conc_holfordGAV2020_AVG
Target: AUC 140 mg/L*h per 48 hours (Css avg 2.92 mg/L) at steady state

Trapezoid	AUC	Units	Interval	Dose Pred	Comment
1	181	mg/L*h	0-infinity	maintenance dose 185 mg	

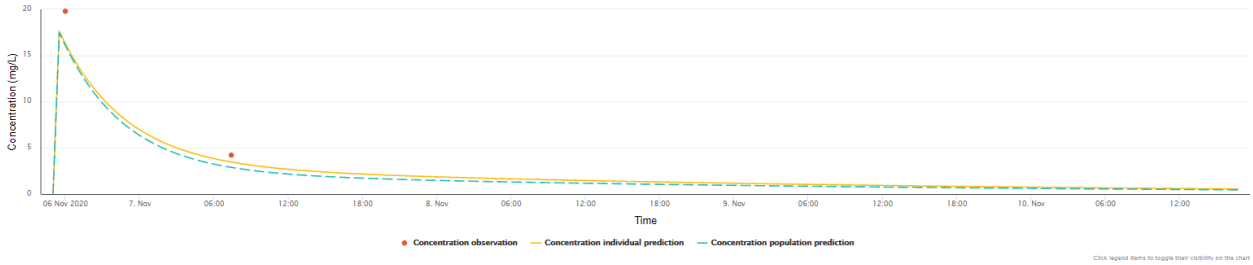
Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	132 mg every 2 days	240 mg	07/11/2020 07:25

Proposed IV maintenance dose 132 mg every 2 days (Bayesian)

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology □ Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
0.944	-12.8	13.1	-0.4	1	0	32.1	15.6	0.719	4.62	79.0	22.5	0.979	108



C_{max} (mg/L)	17.5
C_{min} (mg/L)	1.1

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times target\ AUC$$

$$AUC\ achieved = \frac{240\ mg}{132\ mg} \times 140 = 254$$

Recommendation:

In this example we can see NextDose has regarded the C_1 as being too far from that expected and chosen to 'ignore' it. The C_{min} at 1.1 mg/L is higher than desired so suggest increasing the dose to 280 mg and switching to 72-hourly dosing. This should achieve a reasonable C_{max}, while at the same time allowing the patient more time to clear the gentamicin. Repeat samples after the next dose.

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 13.42 hours

$$k = \frac{ln19.8 \ - ln4.2}{13.42}$$

$$k = 0.1155$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.1155}$$

$$t_{½} = 6 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and $T_{1)}$ = 0.5 hours

$$C_{max} = 19.8 \ x \ e^{0.1155(0.5)}$$

$$C_{max} = 21 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 33.58 hours

$$C_{min} = 4.2 \ e^{-0.1155(33.58)}$$

$$C_{min} = 0.09 \ mg/L$$

$$AUC_{48} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{48} = \frac{21 - 0.09}{0.1155}$$

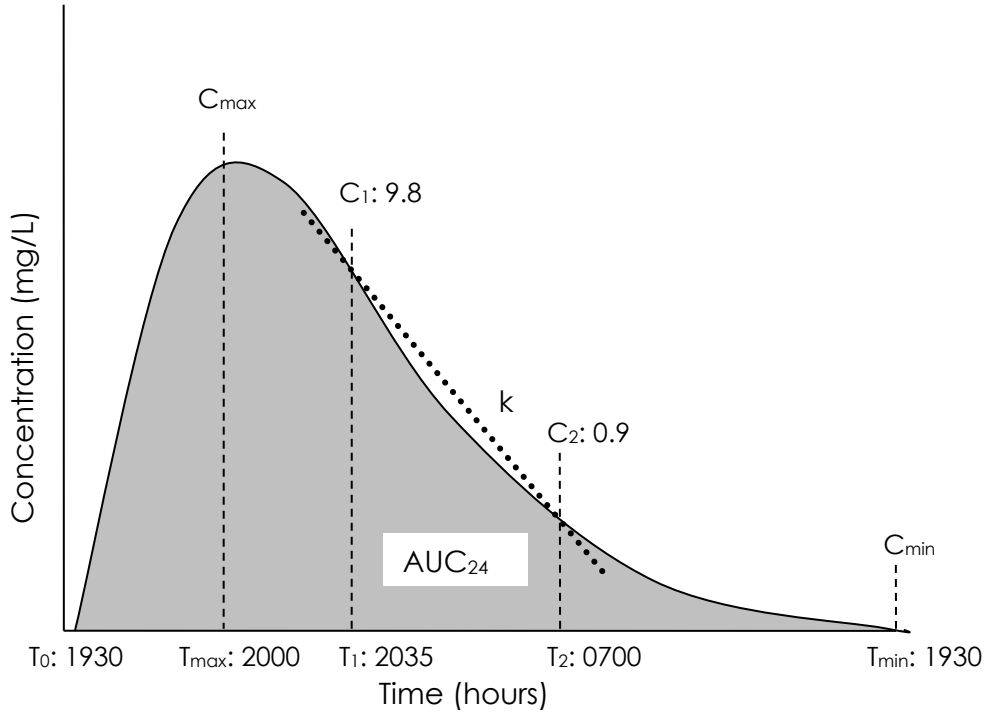
$$AUC_{48} = 181 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{140}{181} \ x \ 240 \ = 186 \ mg$$

Example 3 – UTI in a paraplegic patient – in hospital

Name	OA Test
NHI	ZZZ1003
Sex	Male
Age	60 years
Weight	94 kg
Height	169 cm
Creatinine	78 micromol/L
Drug	gentamicin
Dose	290 mg 24 hourly over 30 minutes
Infection	UTI
Target AUC_{24}	70

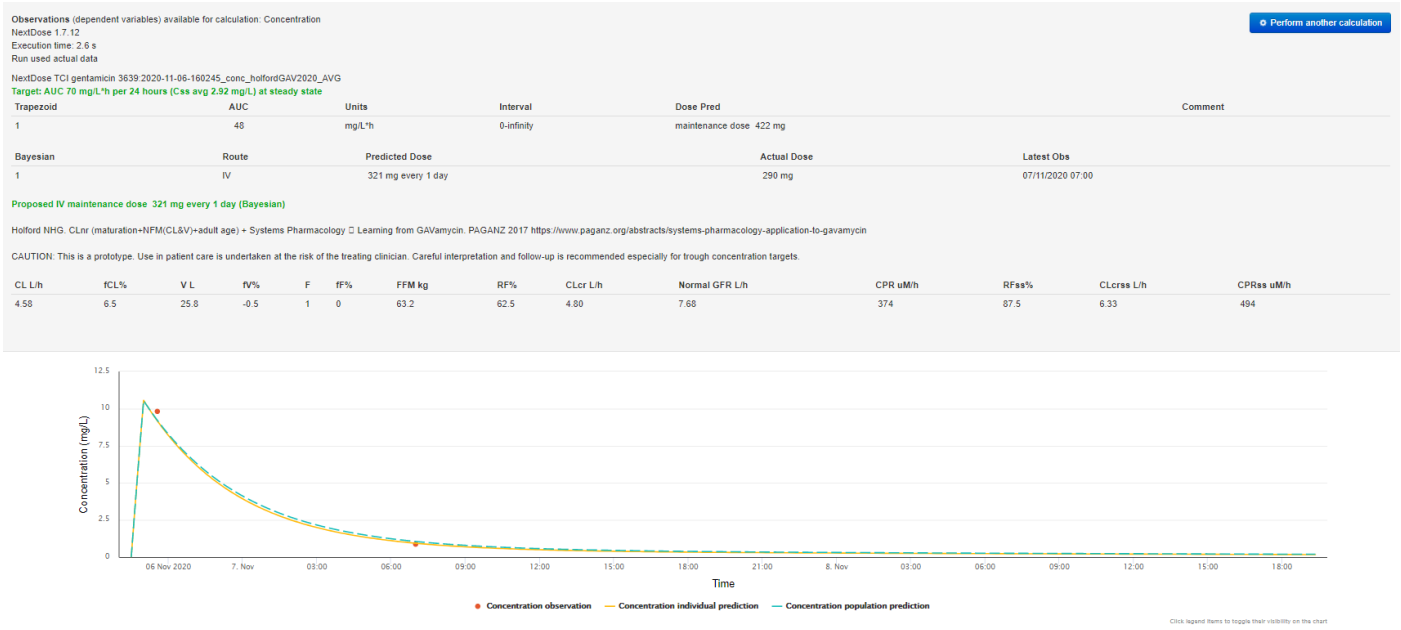


OA is a paraplegic patient with an indwelling catheter who is receiving IV gentamicin on the spinal unit. This is OA's first dose of gentamicin, what would you now recommend?

Answer

Calculated by NextDose:

https://www.nextdose.org/#/6035/34632/results



C_{max} (mg/L)	10.4
C_{min} (mg/L)	0.4

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times target\ AUC$$

$$AUC\ achieved = \frac{290\ mg}{321\ mg} \times 70 = 63$$

Recommendation:

Increase dose to 320 mg 24 hourly. This patient has a urinary tract infection and the C_{max} in the urine will be higher than in the plasma, given that aminoglycosides concentrate there. The lower target AUC_{24} of 70 for urinary tract infections reflects this phenomenon.

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 10.42 hours

$$k = \frac{ln9.8 \ - ln0.9}{10.42}$$

$$k = 0.2292$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.2292}$$

$$t_{½} = 3 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and $T_{1)}$ = 0.58 hours

$$C_{max} = 9.8 \times e^{0.2292(0.58)}$$

$$C_{max} = 11.2 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 12.5 hours

$$C_{min} = 0.9 \ x \ e^{-0.2292(12.5)}$$

$$C_{min} = 0.05 \ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{11.2 - 0.05}{0.2292}$$

$$AUC_{24} = 49 \ mg/L.h$$

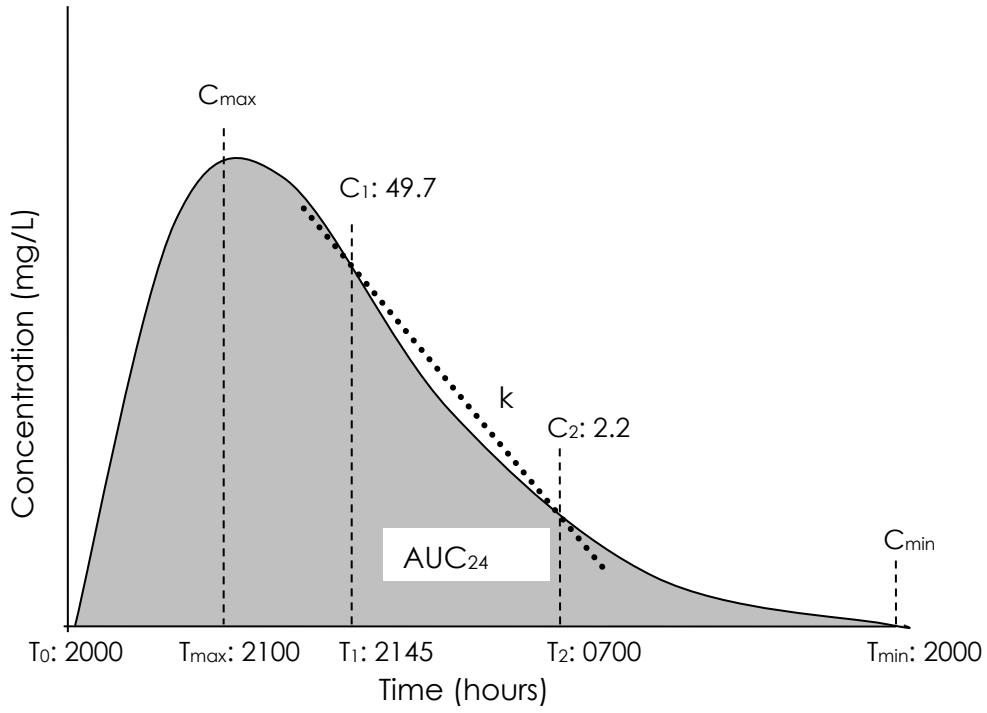
$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{70}{49} \times 290$$

$$New \ dose = 414 \ mg$$

Example 4 – Outpatient amikacin for cystic fibrosis

Name	CL Test
NHI	ZZZ1004
Sex	Male
Age	36 years
Weight	70 kg
Height	183 cm
Creatinine	98 micromol/L
Drug	amikacin
Dose	1100 mg 24 hourly over 60 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	180



CL is a patient with cystic fibrosis who is receiving IV amikacin. What would you now recommend?

Answer

Calculated by NextDose:
https://www.nextdose.org/#/6037/34633/results

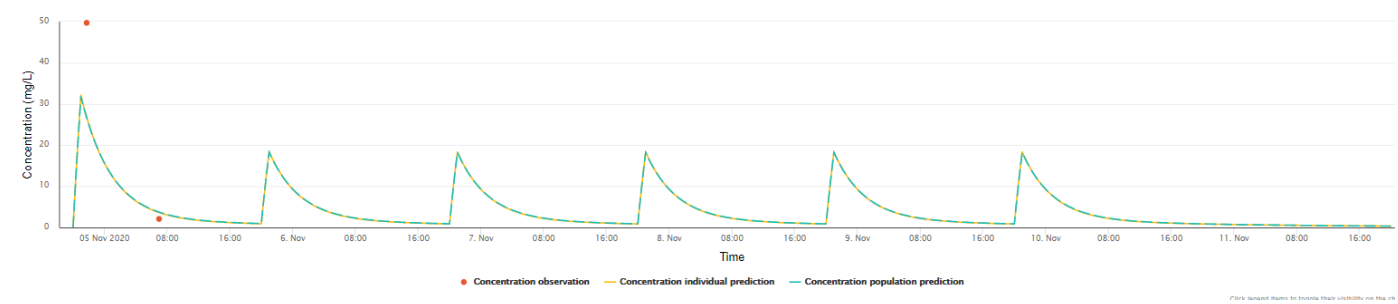
C_{max} (mg/L)	32.1
C_{min} (mg/L)	1

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times target\ AUC$$

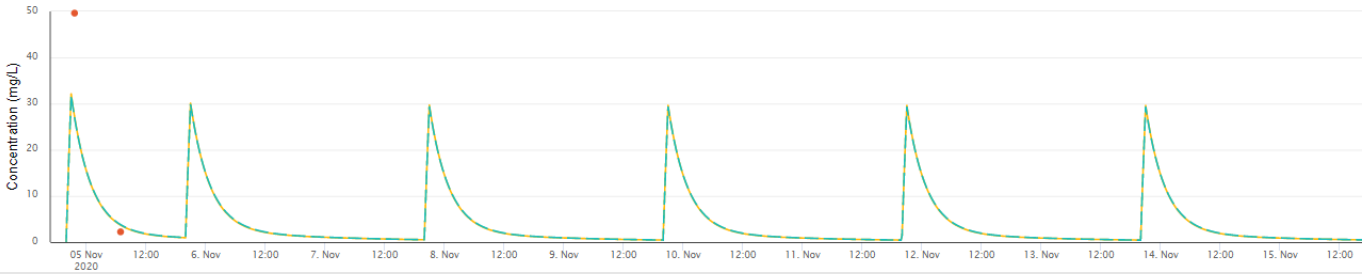
$$AUC\ achieved = \frac{1100\ mg}{1047\ mg} \times 180 = 189$$

Recommendation:

In this case, NextDose has 'ignored' the C_1 of 49.7 as it has found the result to be too 'extreme' to use to fit the individual prediction. To achieve a C_{min} less than 1 mg/L with 24 hourly dosing, a dose of around 600 mg is required, but this only achieves a C_{max} of ~18 mg/L (see the 'what-if' dose prediction: https://www.nextdose.org/#/6037/34634/results



To obtain a more effective C_{max} and lower C_{min}, suggest changing to 1000 mg 48 hourly (see the what-if' dose prediction https://www.nextdose.org/#/6037/34636/results). A 1000 mg dose is also easier to administer than 1100 mg, given the available vial size of amikacin (500 mg/2 mL).


Concentration (mg/L)
50
40
30
20
10
0
05 Nov 2020
12:00
6. Nov
12:00
7. Nov
12:00
8. Nov
12:00
9. Nov
12:00
10. Nov
12:00
11. Nov
12:00
12. Nov
12:00
13. Nov
12:00
14. Nov
12:00
15. Nov
12:00

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 9.25 hours

$$k = \frac{ln49.7 \ - ln2.2}{9.25}$$

$$k = 0.3370$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.3370}$$

$$t_{½} = 2.1 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and $T_{1)}$ = 0.75 hours

$$C_{max} = 49.7 \times e^{0.3370(0.75)}$$

$$C_{max} = 64 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 13 hours

$$C_{min} = 2.2 \times e^{-0.3370(13)}$$

$$C_{min} = 0.03 \ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{64 - 0.03}{0.3370}$$

$$AUC_{24} = 190 \ mg/L.h$$

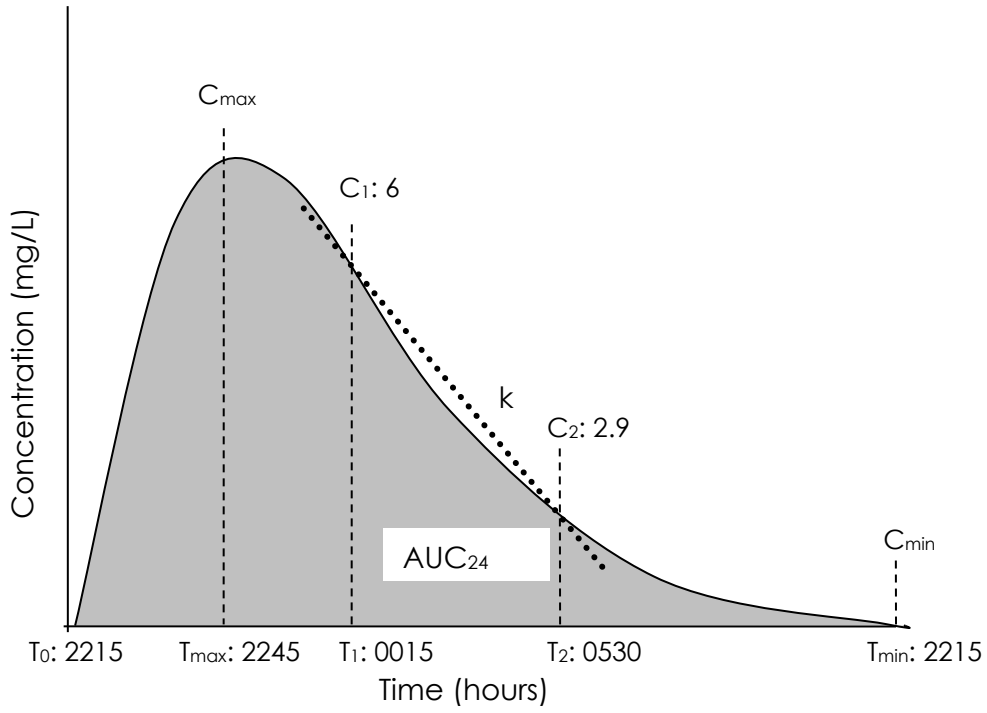
$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{180}{190} \times 1100$$

$$New \ dose = 1042 \ mg$$

Example 5 – Endocarditis

Name	MW Test
NHI	ZZZ1005
Sex	Female
Age	26 years
Weight	85 kg
Height	181 cm
Creatinine	86 micromol/L
Drug	gentamicin
Dose	200 mg 24 hourly over 30 minutes
Infection	Endocarditis
Target AUC_{24}	30-50

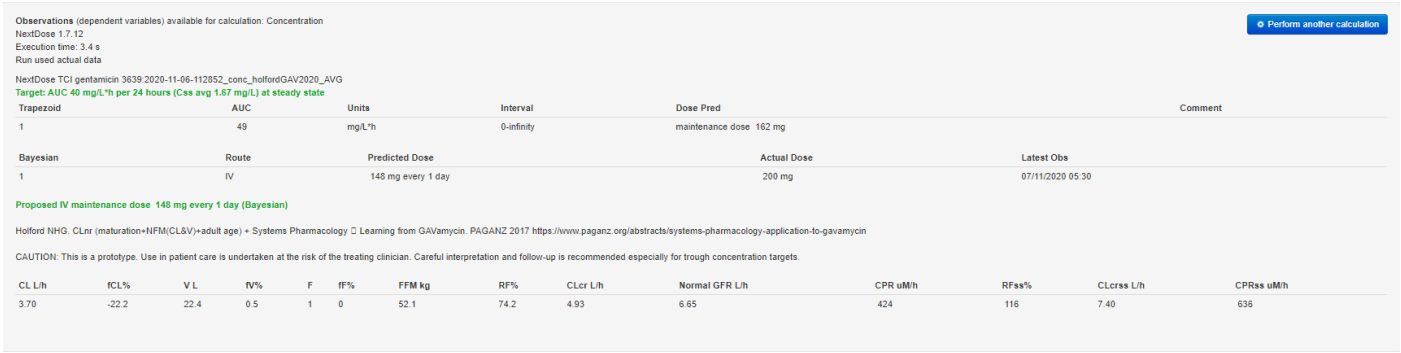


MW is receiving synergistic gentamicin along with benzylpenicillin for treatment of endocarditis. What would you recommend for her next dose?

Answer

Calculated by NextDose:

https://www.nextdose.org/#/6039/34637/results



Observations (dependent variables) available for calculation: Concentration
NextDose 1.7.12
Execution time: 3.4 s
Run used actual data

Perform another calculation

NextDose TCI gentamicin 3639:2020-11-06-112852_conc_holfordGAV2020_AVG
Target: AUC 40 mg/L*h per 24 hours (Css avg 1.67 mg/L) at steady state

Trapezoid	AUC	Units	Interval	Dose Pred	Comment
1	49	mg/L*h	0-infinity	maintenance dose 162 mg	

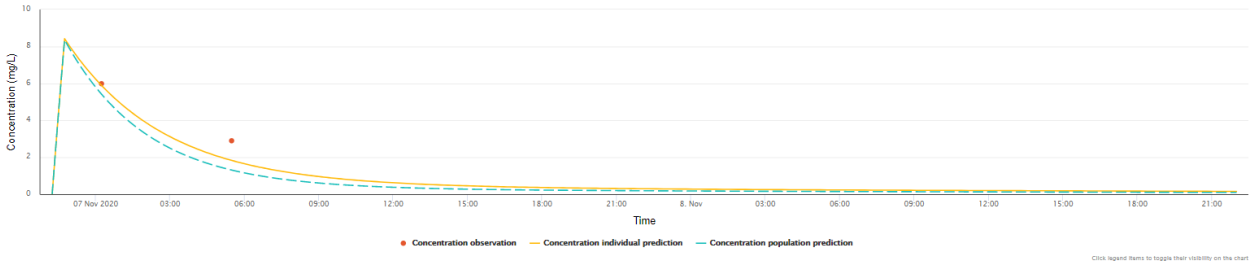
Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	148 mg every 1 day	200 mg	07/11/2020 05:30

Proposed IV maintenance dose 148 mg every 1 day (Bayesian)

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology □ Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
3.70	-22.2	22.4	0.5	1	0	52.1	74.2	4.93	6.65	424	116	7.40	636



C_{max} (mg/L)	8.4
C_{min} (mg/L)	0.9

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times target\ AUC$$

$$AUC\ achieved = \frac{200\ mg}{148\ mg} \times 40 = 54$$

Recommendation:

MW has achieved an AUC_{24} slightly over the maximum target of 50 mg/L.h and is a reasonably close fit to the model. Suggest reducing the dose to 160 mg 24 hourly and repeat concentrations in three days or so.

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 5.25 hours

$$k = \frac{ln6 - ln2.9}{5.25}$$

$$k = 0.1385$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.1385}$$

$$t_{½} = 5\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.5 hours

$$C_{max} = 6 \times e^{0.1385(1.5)}$$

$$C_{max} = 7.4\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 16.75 hours

$$C_{min} = 2.9 \times e^{-0.1385(16.75)}$$

$$C_{min} = 0.29\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{7.4 - 0.29}{0.1385}$$

$$AUC_{24} = 51\ mg/L.h$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{40}{51} \times 200$$

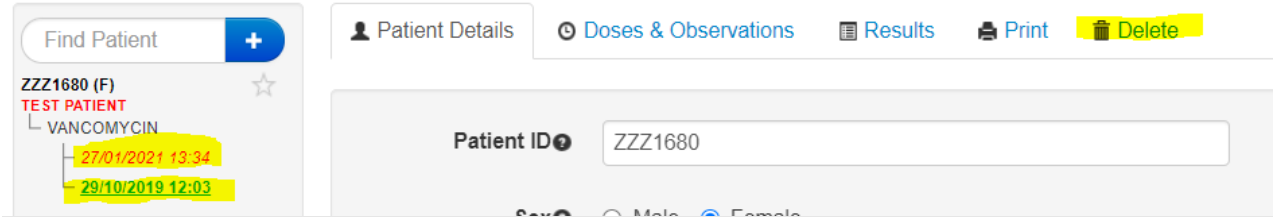
$$New\ dose = 157\ mg$$

4.8. Examples to work through

For each example, use Bayesian monitoring software (see 2.2 and 2.3) to determine your next dose recommendation. Worked model answers using NextDose and hand calculations are provided in section 7.

How to use NextDose for the practice patient examples:

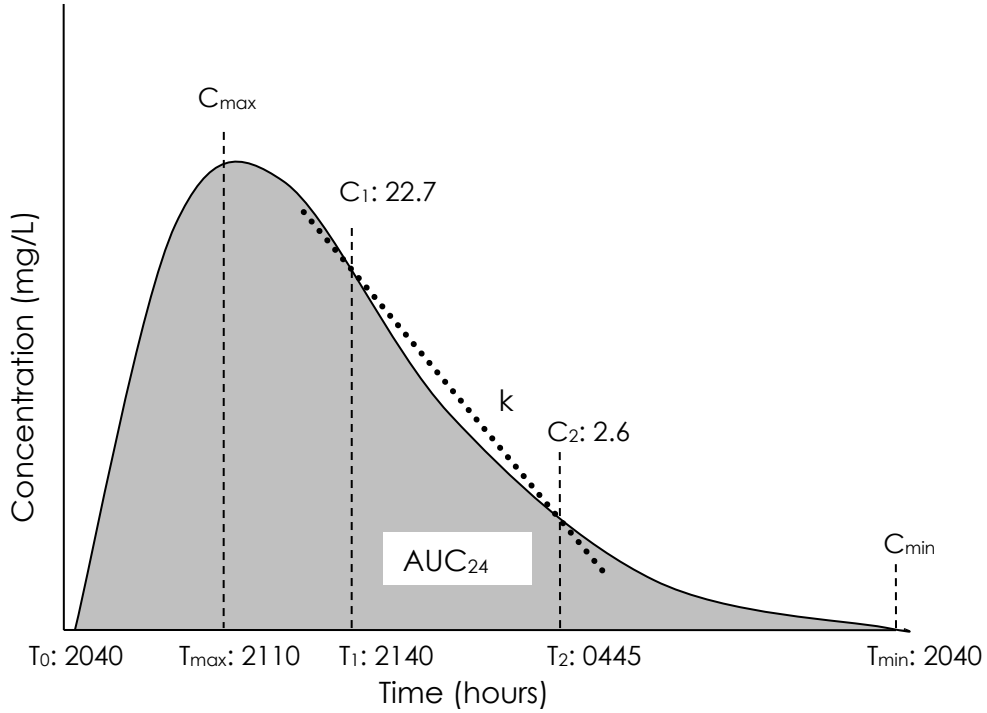
1. Search in NextDose for the NHI assigned to that case (note this NHI is different to that used for the model answer for the case, which are designed to be non-editable).
2. Check Patient Details (sex and date of birth) are correct.
3. Add the medicine and enter the data.
   - If the previous person working on the example did not delete their inputted data once they had finished, then the medicine will already be in the patient's record. If this is the case, you can delete their data before you start by clicking on each dataset and deleting it:



4. Once you have finished, delete your dataset/s so that the next person can start fresh.

Example 1 – cystic fibrosis – in hospital

Name	Test Test
NHI	ZZZ1006
Sex	Male
Age	28 years
Weight	61 kg
Height	185 cm
Creatinine	48 micromol/L
Drug	tobramycin
Dose	680 mg 24 hourly over 30 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	80-100



Test is a cystic fibrosis patient who is receiving IV tobramycin on the respiratory ward. He is also on ceftazidime 2 g IV three times a day. Test has had several doses of tobramycin, what would you now recommend?

Answer

Calculated by NextDose:

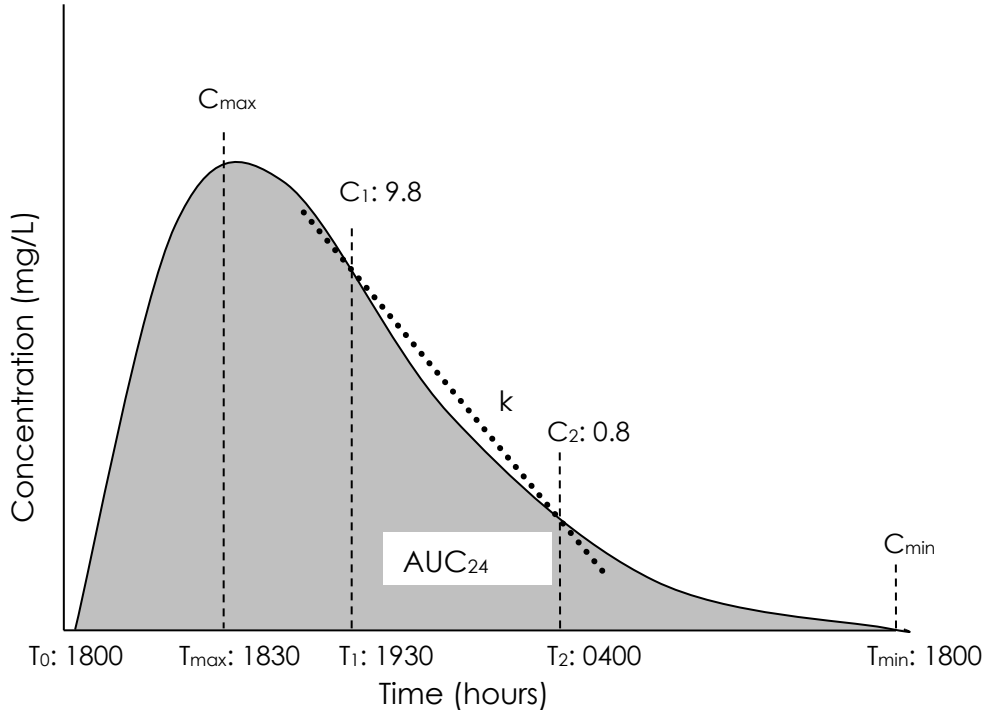
C_{max} (mg/L)	
C_{min} (mg/L)	
AUC_{24} (mg/L.h)	

Calculated by hand:

Recommendation:

Example 2 – suspected perforated appendix – in hospital

Name	Test Test
NHI	ZZZ1007
Sex	Male
Age	37 years
Weight	83.3 kg
Height	187 cm
Creatinine	77 micromol/L
Drug	gentamicin
Dose	400 mg 24 hourly over 30 minutes
Infection	Perforated appendix
Target AUC_{24}	85



Test is a patient with a suspected perforated appendix who is receiving IV gentamicin. This is Test's first dose of gentamicin, what would you now recommend?

Answer

Calculated by NextDose:

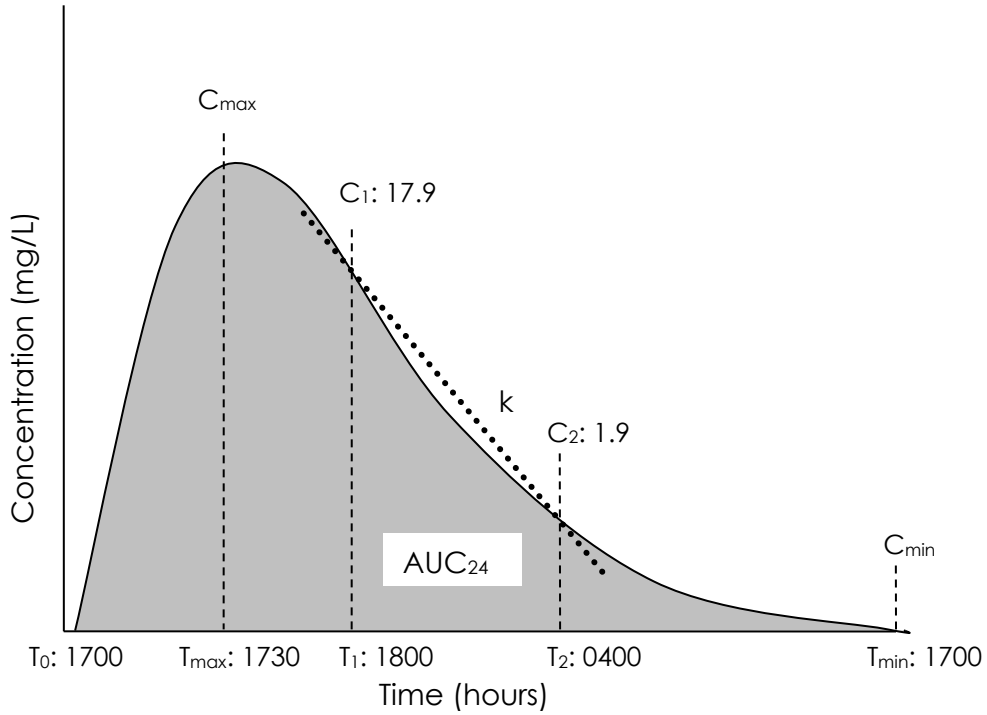
C_{max} (mg/L)	
C_{min} (mg/L)	
AUC_{24} (mg/L.h)	

Calculated by hand:

Recommendation:

Example 3 – urosepsis – in hospital

Name	Test Test
NHI	ZZZ1008
Sex	Male
Age	57 years
Weight	89.9 kg
Height	183 cm
Creatinine	109 micromol/L
Drug	gentamicin
Dose	420 mg 24 hourly over 30 minutes
Infection	Urosepsis
Target AUC_{24}	85-95



Test is a patient with urosepsis who is receiving IV gentamicin. This is Test's third dose of gentamicin, what would you now recommend?

Answer

Calculated by NextDose:

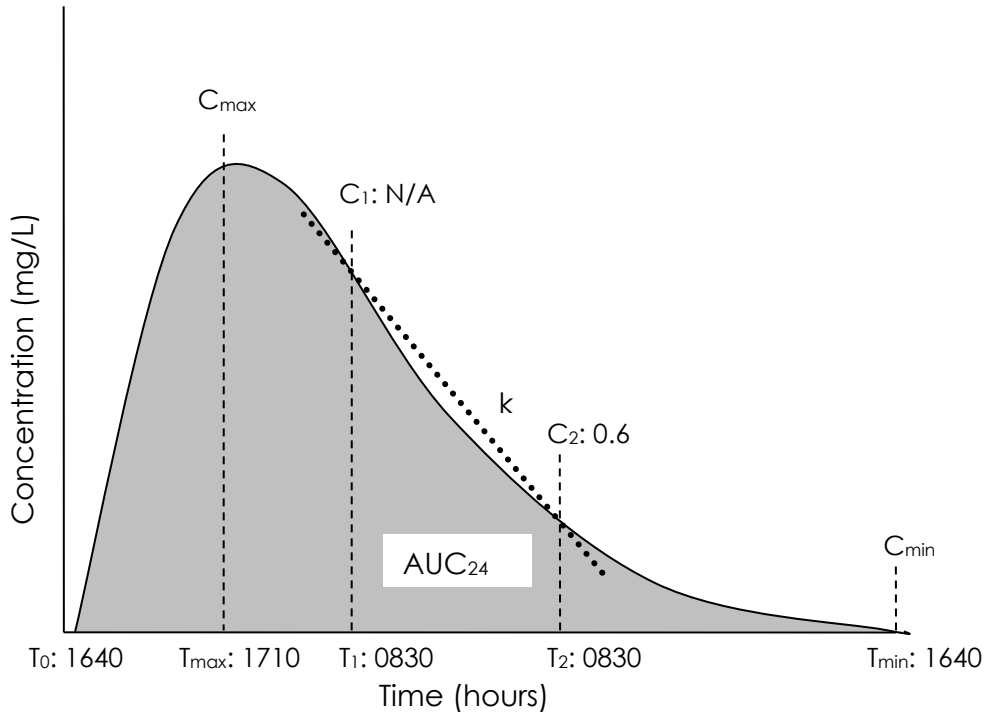
C_{max} (mg/L)	
C_{min} (mg/L)	
AUC_{24} (mg/L.h)	

Calculated by hand:

Recommendation:

Example 4 – suspected peritonitis – in hospital

Name	Test Test
NHI	ZZZ1009
Sex	Male
Age	64 years
Weight	91 kg
Height	180 cm
Creatinine	80 micromol/L
Drug	gentamicin
Dose	240 mg 24 hourly over 30 minutes
Infection	Peritonitis
Target AUC_{24}	85-95



Test is a patient with suspected peritonitis who is receiving IV gentamicin. Only one blood sample has been taken, what would you now recommend?

Answer

Calculated by NextDose:

C_{max} (mg/L)	
C_{min} (mg/L)	
AUC_{24} (mg/L.h)	

Calculated by hand:

Recommendation:

5. Paediatric aminoglycosides

5.1. Gentamicin/tobramycin dosing and monitoring in paediatrics

Refer to the Child Health e-Guidelines on the CDHB Intranet (Gentamicin / Tobramycin in Children) for dosing and monitoring recommendations.

Dosing

As with adults, the usual dosing for aminoglycosides in paediatric patients is once daily.

- Calculate the first dose using ideal body weight.

Gentamicin

- Term babies aged younger than one week: 5 mg/kg 24 hourly
- Children aged one week to 18 years: 7.5 mg/kg 24 hourly
- With very young infants, it is important to ask what their corrected age is. For example, a child who is 8 weeks old but born at 30 weeks gestation will have a corrected age of 38 weeks and should be dosed as a term baby aged younger than one week, instead of aged 8 weeks.

Tobramycin

- 10-12 mg/kg 24 hourly for children with cystic fibrosis (or dose from last treatment course if recent).

Subsequent doses are adjusted according to serum concentrations.

'Maximum' dose

Generally, the usual maximum dose for aminoglycosides is 10 mg/kg/dose. However, in some infections higher doses may be used. If your prediction indicates higher doses than this and you are unfamiliar with paediatric dosing, then check with a paediatric pharmacist. In some instances, twice or three times a day dosing may be more appropriate (see examples for more details).

Monitoring

- For a duration of therapy lasting less than 48 hours (e.g. UTI or febrile infants), concentrations are not necessary unless there is concern regarding renal impairment or the child is on concurrent nephrotoxic or ototoxic medications.
- For therapy likely to continue over 48 hours (e.g. sepsis), concentrations can be taken after the second dose. Two samples should be taken at 30 minutes after the end of the infusion and between six and 10 hours after the infusion. Check plasma creatinine at the same time. Children usually clear aminoglycosides faster than adults. Concentrations should be checked every three days or more frequently if clinically necessary. Note some children have blood samples taken by finger pricks only, which can make frequent monitoring challenging.
- Ototoxicity risk is difficult to predict and can occur despite acceptable concentrations and clearance, especially in infants with other risk factors. Audiology testing should be considered for all infants and children treated with aminoglycosides for longer than 72 hours, or any children thought to be at risk of hearing impairment.

- Children with cystic fibrosis have high clearance of aminoglycosides that rarely changes. Because of this they are generally monitored twice weekly, on Thursdays and Sundays.

CDHB Paediatrics do not currently use Bayesian software for monitoring and calculations must be either done by hand or using the 'Johnny Gent' Excel spreadsheet calculator. In practice, it is good to use both methods as a check to ensure that your calculations are correct.

AUC

As with adult aminoglycoside dosing, the AUC target range, and thus dose, depends on the type of infection:

Infection	**Target AUC_{24} (mg/L.h)**
Urinary tract infection	70
Other infections	80-100 (depending on severity)
Sepsis or life-threatening infection	100

5.2. Amikacin dosing and monitoring in paediatrics

Amikacin is occasionally used to treat paediatric patients, usually those with cystic fibrosis.

Dosing

- First dose 20-30 mg/kg 24 hourly (usual maximum 1.5 g)

Monitoring

- Two blood samples should then be taken:
    - the first 30 minutes after the end of the infusion
    - the second after six to 10 hours

Calculate the patient's AUC and other parameters to determine the next dose and frequency of blood sampling for amikacin concentrations. The AUC_{24} range for amikacin is 160 to 200 mg/L. For severe infections aim for an AUC_{24} of up to 200 mg/L.h. C_{max} should be approximately double that of gentamicin/tobramycin i.e. 30 to 40 mg/L or more and C_{min} should be as low as possible and <2 mg/L. Depending on the clinical scenario samples should be repeated every three days.

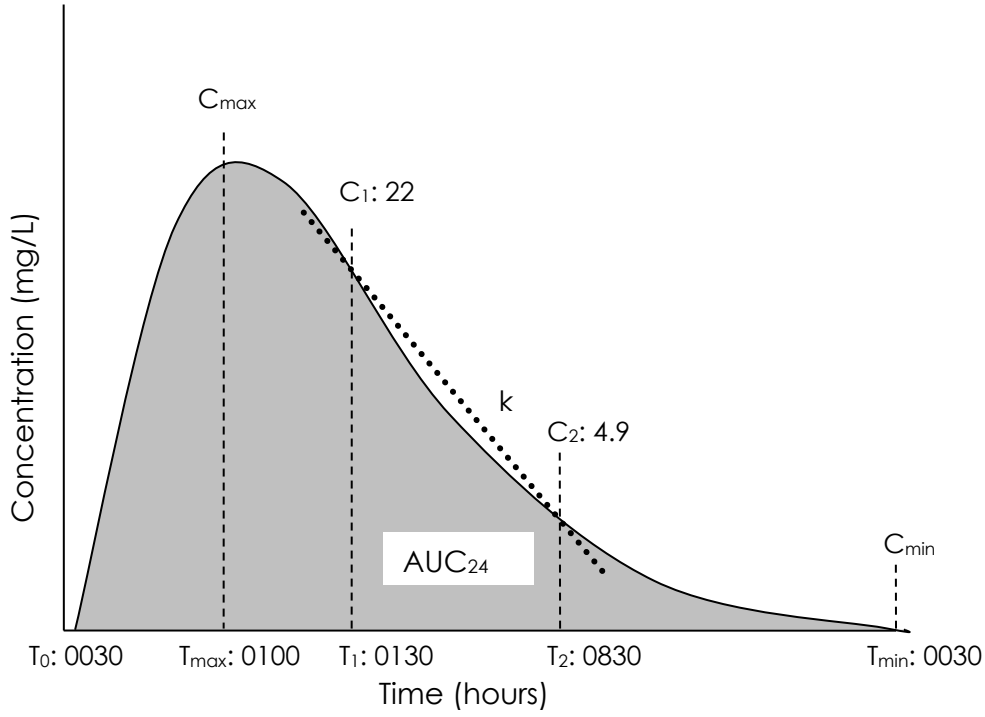
5.3. Patients with cystic fibrosis in the community

Children with cystic fibrosis may be treated as an outpatient. These patients are usually monitored twice weekly on Sunday and Thursday nights and the usual processes apply to calculating their initial dose. However, the parents have a greater role in managing the patient's care. Parents fill in all infusion and blood sampling time columns on the aminoglycoside prescribing sheet. The pharmacist calculates the AUC and contacts the doctor, who will ring the parent with the information regarding any dose adjustment.

5.4. Worked examples

Example 1 – UTI in a young infant

Name	LK Test
Sex	Male
Age	8 weeks
Weight	5.25 kg
Creatinine	normal
Drug	gentamicin
Dose	60 mg 24 hourly over 30 minutes
Infection	UTI
Target AUC_{24}	70



LK is a young infant with an UTI who is receiving IV gentamicin. This is LK's first dose of gentamicin, what would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 7 hours

$$k = \frac{ln22 \ - ln4.9}{7}$$

$$k = 0.2145$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.2145}$$

$$t_{½} = 3.2 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 0.5 hours

$$C_{max} = 22 \times e^{0.2145(0.5)}$$

$$C_{max} = 24.5 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 16 hours

$$C_{min} = 2.2 \times e^{-0.2145(16)}$$

$$C_{min} = 0.16 \ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{24.5 - 0.16}{0.2145}$$

$$AUC_{24} = 113 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{70}{113} \times 60$$

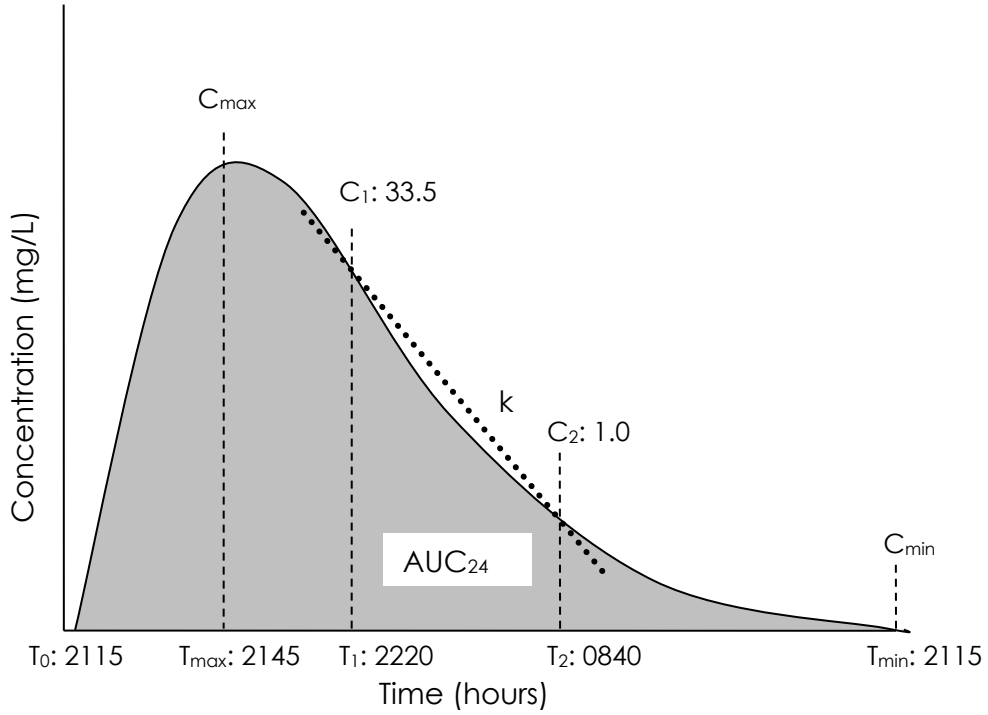
$$New \ dose = 37 \ mg$$

Recommendation:

Reduce dose to 40 mg (rounded for ease of administration). The AUC_{24} is not only over the target for a UTI but above the usual maximum (100), putting the patient at increased risk of toxicity. Repeat samples if gentamicin continues. It is important to check LK's corrected age; he may have been born at 30 weeks gestation or be full-term. If he was born at 30 weeks gestation, his corrected age would be 38 weeks.

Example 2 – cystic fibrosis patient with pseudomonas

Name	GI Test
Sex	Female
Age	15 years
Weight	55.9 kg
Height	156 cm
Creatinine	57 micromol/L
Drug	tobramycin
Dose	440 mg 24 hourly over 30 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	90-100



GI is a cystic fibrosis patient receiving IV tobramycin (plus meropenem, ceftazidime) for pseudomonas. This is GI's first dose of tobramycin, what would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 10.33 hours

$$k = \frac{ln33.5 \ - ln1}{10.33}$$

$$k = 0.3399$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.3399}$$

$$t_{½} = 2\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 0.5 hours

$$C_{max} = 33.5 \times e^{0.3399(0.58)}$$

$$C_{max} = 40.8\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 12.58 hours

$$C_{min} = 1\ x\ e^{-0.3399(12.58)}$$

$$C_{min} = 0.014\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{40.8 - 0.014}{0.3399}$$

$$AUC_{24} = 120\ mg/L.h$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{90}{120} \times 440 = 330\ mg \quad \text{or}$$

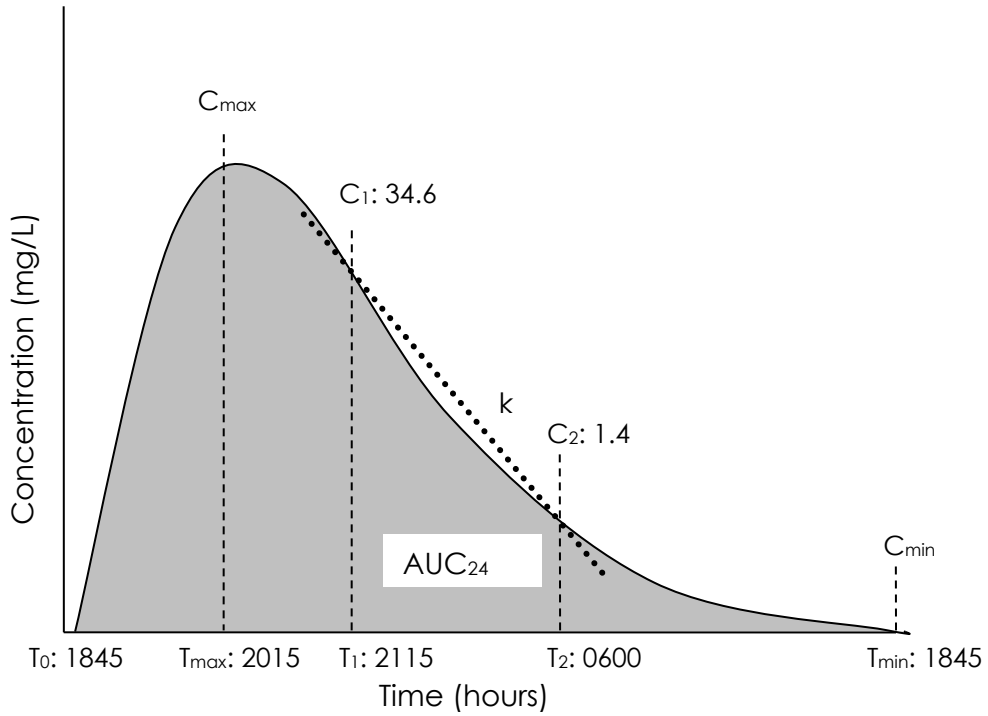
$$New\ dose = \frac{100}{120} \times 440 = 367\ mg$$

Recommendation:

A dose reduction to 360 mg will produce an AUC_{24} of 100. Repeat levels in three days, preferably on Thursday or Sunday (whichever is closer).

Example 3 – Six weeks of amikacin therapy for a patient with cystic fibrosis

Name	FF Test
Sex	Female
Age	12 years
Weight	40.2 kg
Height	
Creatinine	53 micromol/L
Drug	amikacin
Dose	600 mg 24 hourly over 60 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	170



FF is a patient with cystic fibrosis who is receiving IV amikacin for six weeks in addition to tigecycline, clarithromycin and ciprofloxacin. What would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 8.75 hours

$$k = \frac{ln34.6 \ - ln1.4}{8.75}$$

$$k = 0.3666$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.3666}$$

$$t_{½} = 1.89 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1 hour

$$C_{max} = 34.6 \times e^{0.3666(1)}$$

$$C_{max} = 49.9 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 12.75 hours

$$C_{min} = 1.4 \times e^{-0.3666(12.75)}$$

$$C_{min} = 0.013 \ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{49.9 - 0.013}{0.3666}$$

$$AUC_{24} = 136 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{170}{136} \times 600$$

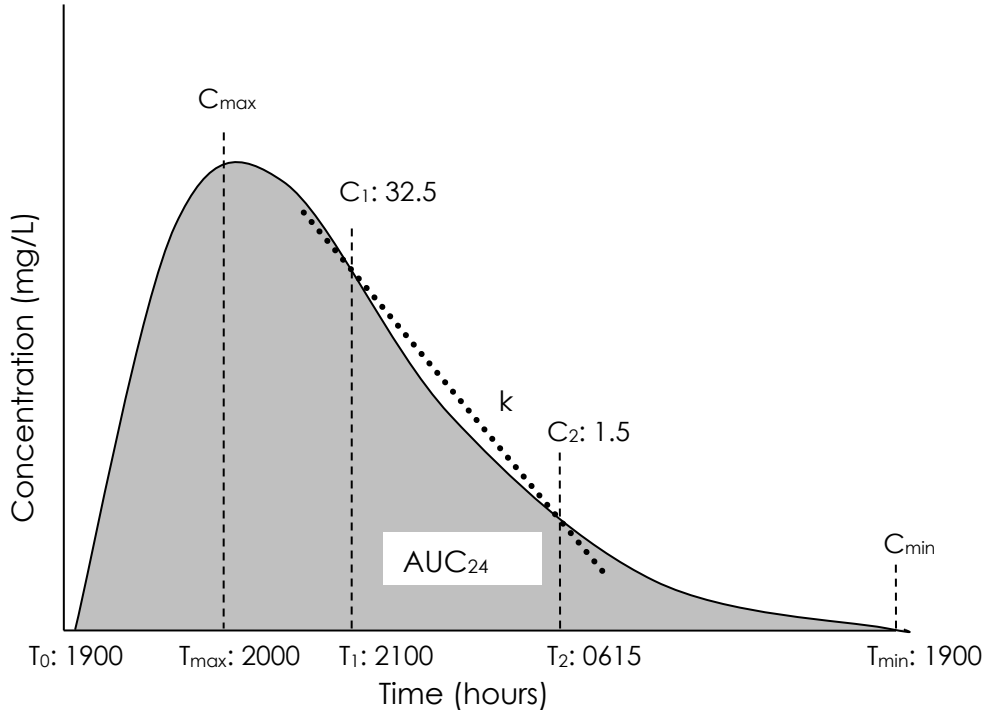
$$New \ dose = 750 \ mg$$

Recommendation:

Increase dose to 750 mg. The AUC_{24} is below target; a dose increase (and resultant C_{max} increase) will increase efficacy.

Example 3 continued – Six weeks of amikacin therapy for a patient with cystic fibrosis

Name	FF Test
Sex	Female
Age	12 years
Weight	40.2 kg
Height	
Creatinine	53 micromol/L
Drug	amikacin
Dose	750 mg 24 hourly over 60 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	170



Three days later after FF's amikacin dose change, what would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 9.25 hours

$$k = \frac{ln32.5\ - ln1.5}{9.25}$$

$$k = 0.3325$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.3325}$$

$$t_{½} = 2.08\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1 hour

$$C_{max} = 32.5 \times e^{0.3325(1)}$$

$$C_{max} = 45.3\ mg/L$$

$$C_{min} = C_2\ x\ e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 12.75 hours

$$C_{min} = 1.5\ x\ e^{-0.3325(12.75)}$$

$$C_{min} = 0.022\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{45.3 - 0.022}{0.3325}$$

$$AUC_{24} = 136\ mg/L.h$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{170}{136} \times 750$$

$$New\ dose = 938\ mg$$

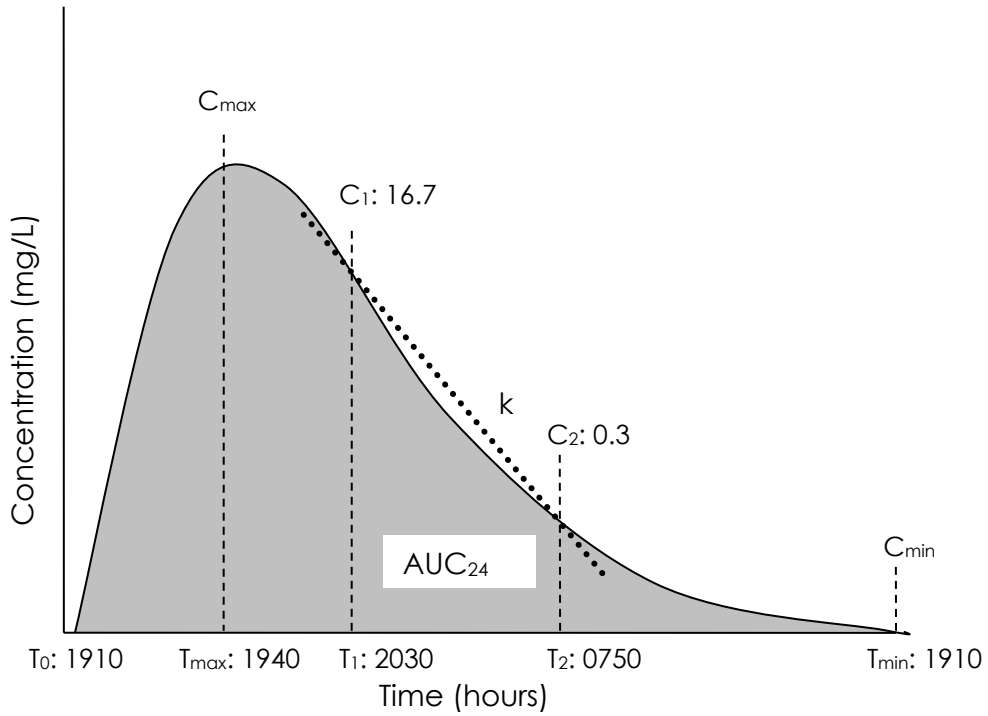
Recommendation:

Increase dose to 900 mg, given the AUC_{24} is still under target. Resample off the next dose.

5.5. Examples to work through

Example 1 – gentamicin for an abdominal abscess

Name	Test Test
Sex	Female
Age	5 years
Weight	30 kg
Height	
Creatinine	34 micromol/L
Drug	gentamicin
Dose	240 mg 24 hourly over 30 minutes
Infection	abdominal abscess
Target AUC_{24}	90



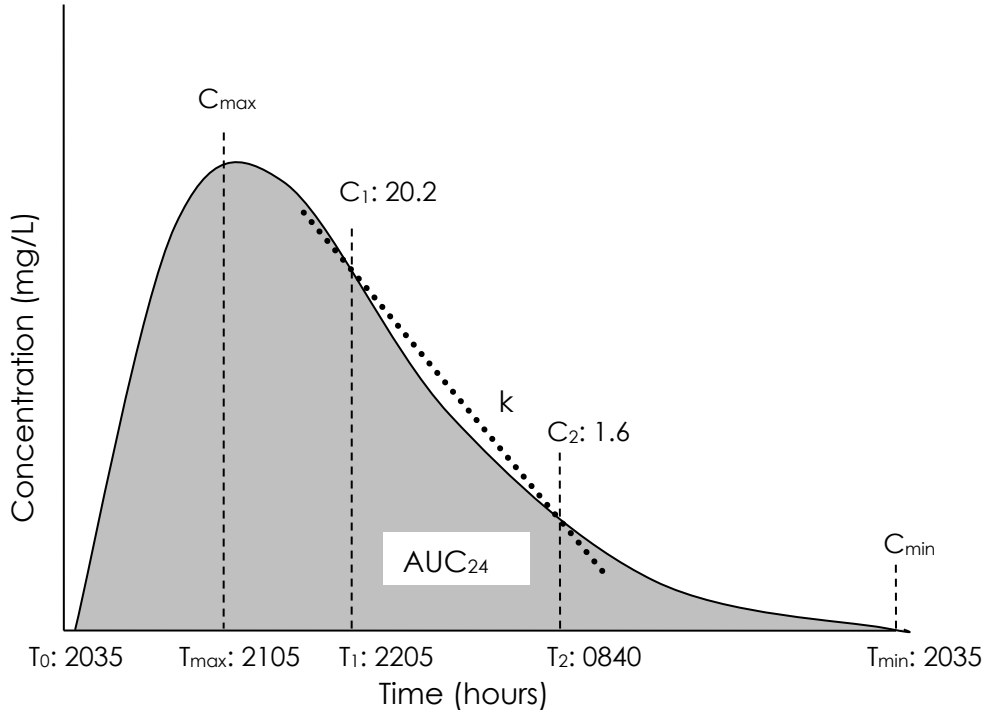
Test presented with an abdominal abscess that is being treated with IV gentamicin and IV clindamycin. This is her second dose of gentamicin, what would you now recommend?

Answer
Calculated by hand:

Recommendation:

Example 2 – cystic fibrosis patient with pseudomonas

Name	Test Test
Sex	Female
Age	9 years
Weight	35 kg
Height	140 cm
Creatinine	72 micromol/L
Drug	tobramycin
Dose	220 mg 24 hourly over 30 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	90-100



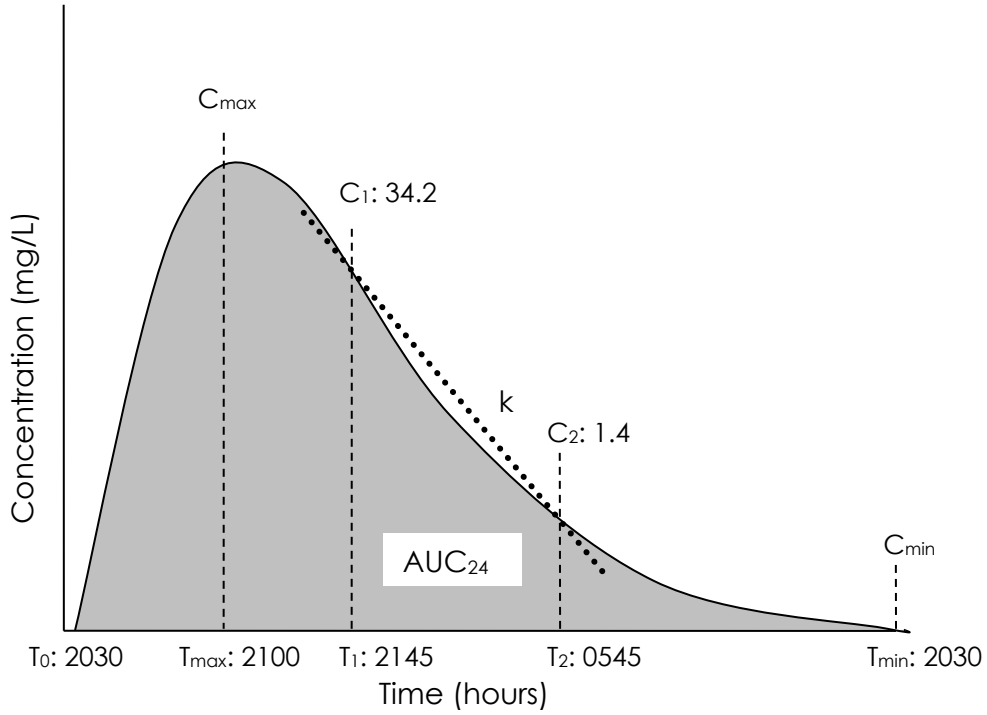
Test has cystic fibrosis and is receiving tobramycin, ceftazidime and clindamycin for pseudomonas via home IV. This is the end of the second week of therapy, what would you recommend?

Answer
Calculated by hand:

Recommendation:

Example 3 – gentamicin for cholangitis

Name	Test Test
Sex	Male
Age	2 years
Weight	15.5 kg
Height	
Creatinine	30 micromol/L
Drug	gentamicin
Dose	220 mg 24 hourly over 30 minutes
Infection	Cholangitis
Target AUC_{24}	85-95



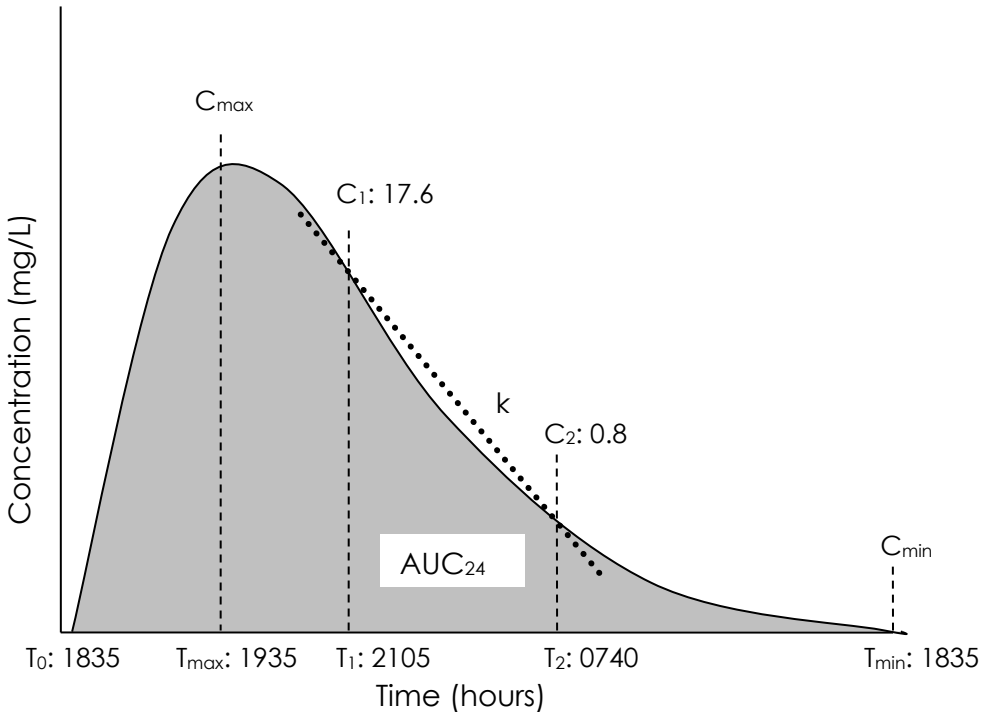
PB has cholangitis that is being treated with gentamicin. This is his third dose (previous doses were 150 mg and 190 mg). What would you now recommend?

Answer
Calculated by hand:

Recommendation:

Example 4 – cystic fibrosis with pseudomonas

Name	Test Test
Sex	Female
Age	15 years
Weight	53.8 kg
Height	
Creatinine	61 micromol/L
Drug	tobramycin
Dose	380 mg 24 hourly over 30 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	90-100



Test is a patient with cystic fibrosis who is on home IV therapy with tobramycin. What would you now recommend?

Answer
Calculated by hand:

Recommendation:

6. Neonatal aminoglycosides

6.1. Aminoglycosides in neonates

In neonates the early diagnosis of sepsis is vital. Initial therapy (including aminoglycosides) is often commenced based on clinical suspicion, as life-threatening infections can become established extremely quickly.

Gentamicin (in combination with amoxicillin) is commonly prescribed for treatment of:

- "At risk" neonates - those with suspected pulmonary infection following inhalation of amniotic and vaginal fluids during birth.
- Neonates with respiratory distress for longer than four hours (or earlier if the infant has major risk factors or other signs of sepsis).

In general, the more risk factors for sepsis that a neonate has the lower the threshold should be to treat and investigate for sepsis. Risk factors include:

- prolonged rupture of membranes (increasing risk after 12 hours)
- maternal illness, especially pyrexia >38°C
- maternal WBC >15 x10E9/L, or elevated maternal CRP
- pathogens (e.g. GBS, E. coli) present in maternal urine or high vaginal swab
- prematurity <37 weeks
- foetal distress or neonatal depression
- foetal tachycardia >160 bpm
- twin gestation

Who calculates neonatal gentamicin/tobramycin dose predictions?

During usual working hours neonatal aminoglycoside dose predictions are calculated by the Neonatal ward pharmacist. After hours and at weekends the on-call pharmacist covers this service.

How are neonatal gentamicin/tobramycin dose predictions calculated?

Dose predictions are calculated from two serum aminoglycoside concentrations (see details in monitoring section). There are two ways in which predictions can be calculated, either by hand using a scientific calculator or by using the Neonatal Gentamicin programme (Access-based and available in Medicines Information and on the on-call laptop). In general, it is good practice to do both as this is a good way to check for calculation errors.

6.2. Aminoglycoside dosing in neonates

The same principles that support the use of extended dosing intervals in adults and paediatrics also apply to neonates. However, there are some important differences:

- Ratio of lean vs. adipose body mass (neonates have very little muscle mass).
- Immaturity of renal function – after birth, the kidneys take a few days to mature meaning that clearance of renally cleared drugs will increase as the neonate (and its kidneys) mature (this can be rapid in term babies).
- Extra-intracellular fluid shifts during the first few days of life: remember aminoglycosides are hydrophilic drugs and will partition into water, which means that fluid shifts can dramatically alter AUC, C_{max}, C_{min} and ultimately the dose of aminoglycosides. Fluid shifts can occur particularly if the infant requires early surgical intervention. In these neonates it is imperative to monitor and dose-adjust with each dose.

Initial dosing of gentamicin/tobramycin in neonates follows the "Vd-based model". This protocol was developed following collaborative research between the Neonatal, Clinical Pharmacology and Pharmacy departments at Christchurch Hospital. The guidelines can be found in the Neonatal Drug Reference for gentamicin on the CDHB Intranet:

Vd-based model protocol

<table>
<tr><td>Dosage/Interval

First dose to be given as shown in table. Subsequent doses to be advised by Pharmacy</td><td>
<table>
<tr><th>Weight (kg)</th><th>First Dose</th><th>Interval</th></tr>
<tr><td>> 1500g</td><td>10mg/kg</td><td>60hrs</td></tr>
<tr><td>750 - 1500g</td><td>7.5mg/kg</td><td>60hrs</td></tr>
<tr><td><750g</td><td colspan="2">Use cefotaxime unless treating pseudomonas or an organism sensitive only to gentamicin.
If need to use gentamicin give 6mg/kg/dose</td></tr>
</table>
</td></tr>
<tr><td>Administration</td><td>IV by infusion pump over 30 minutes
Do not give IM (see Neonatal Handbook)</td></tr>
</table>

- Gentamicin is the first-line Gram negative cover for babies weighing ≥750 g in the Neonatal ward.
- Babies <750 g do not clear gentamicin well and so cefotaxime is preferred in most situations.
- The Neonatal ward has researched gentamicin dosing in neonates for many years and uses extended dosing interval treatment with gentamicin given 60 hourly.
- The Neonatal ward uses 10 mg/mL ampoules.

6.3. Aminoglycoside monitoring in neonates

Monitoring targets for gentamicin

- C_{max}: ≥12 mg/L
- C_{min}: <0.5 mg/L
- AUC_{60}: 250 mg/L.h
- Aminoglycoside monitoring is important to ensure that babies receive adequate doses for bacterial kill as well as adequate clearance of the drug to minimise the risks of toxicity. As most babies are receiving short courses of empirical antibiotics, a pragmatic approach to this has been taken to avoid unnecessary blood tests. Seventy-five percent of babies receiving gentamicin in the Neonatal ward have a single dose only, and so concentrations are **usually** not required.
- As with adult and paediatric patients, renal function (plasma creatinine) should be monitored both before and during therapy. Unlike adults and paediatrics, creatinine concentrations in neonates (particularly during the first few days of life where they reflect maternal creatinine concentrations) are not a reliable predictor for renal function. However, the routine monitoring of neonatal creatinine is important as trends in creatinine concentrations over time may provide an indication of altered renal status.
- Hearing screening is a routine intervention in the Neonatal unit and is an especially important monitoring tool for those infants who are treated with potentially ototoxic antibiotics such as the aminoglycosides.
- See the Neonatal Drug Reference for gentamicin available via the CDHB Intranet:

Monitoring and Further Doses....		**Levels required – Gentamicin week 1 of life**
	≤ 48hrs ie: 1 dose	No levels in most instances but see below for exceptions*
	≥ 5 days	**Dose 1** **1st Level** – When decision is made to give >1 dose: ▪ Call lab to retrospectively analyse a level on the CRP blood test taken after gentamicin was given ▪ If there is no blood in the lab to do this then take a level immediately **2nd Level** - At 24-36hrs **Further Doses** ▪ No levels required if it is a **5 day** course ▪ Pharmacist advises if more levels are required if **≥7 day** course and if they are take: **1st Level** – At 1hr after completion of the dose **2nd Level** – At 24-36hrs

….Monitoring and Further Doses	See Neonatal Handbook for more info	*** Closer monitoring required with levels taken from Dose 1 wherever possible:** ▪ Decision for 5-7 days Ab made before starting gentamicin ▪ Gentamicin after week 1 of life ▪ HIE / renal impairment / oliguria ▪ Significant oedema / hydrops ▪ Gram negative positive blood cultures ▪ Concomittant nephrotoxic drugs ▪ Concern about clinical response **Dose 1** **1st Level** – At 1hr after completion of the dose **2nd Level** – At 24-36 hrs **Further Doses** Pharmacist advises if more levels are required

Standard process for empirical gentamicin given soon after birth:

- Baby is admitted to NICU after birth and gentamicin is given. At this stage, the length of the course is usually unknown.
- The blood taken for the CRP at around six hours of age can be used to retrospectively run a gentamicin level if the decision is made to continue for five or more days (this decision is usually made around 24 hours of age). If no blood sample was taken after administration of gentamicin, then a level should be taken immediately.
- A second level will need to be taken at 24-36 hours.

Exceptional situations where gentamicin concentrations are required after the first dose:

- The decision has been made at birth to continue gentamicin for at least five days.
- Gentamicin given after one week of life – clearance is much higher so the dose may need to be bigger and more frequent. In this instance we are usually treating a true sepsis situation rather than empirical antibiotics after birth.
- Renal impairment (e.g. congenital renal anomaly, hypoxic ischaemic encephalopathy, oliguria).
- Hydrops foetalis or severe oedema: true body weight and volume of distribution will be affected.
- Concomitant use of other nephrotoxic drugs e.g. indometacin, furosemide and vancomycin.
- Suspected or confirmed Gram negative sepsis.
- Concern about clinical response to antibiotics.

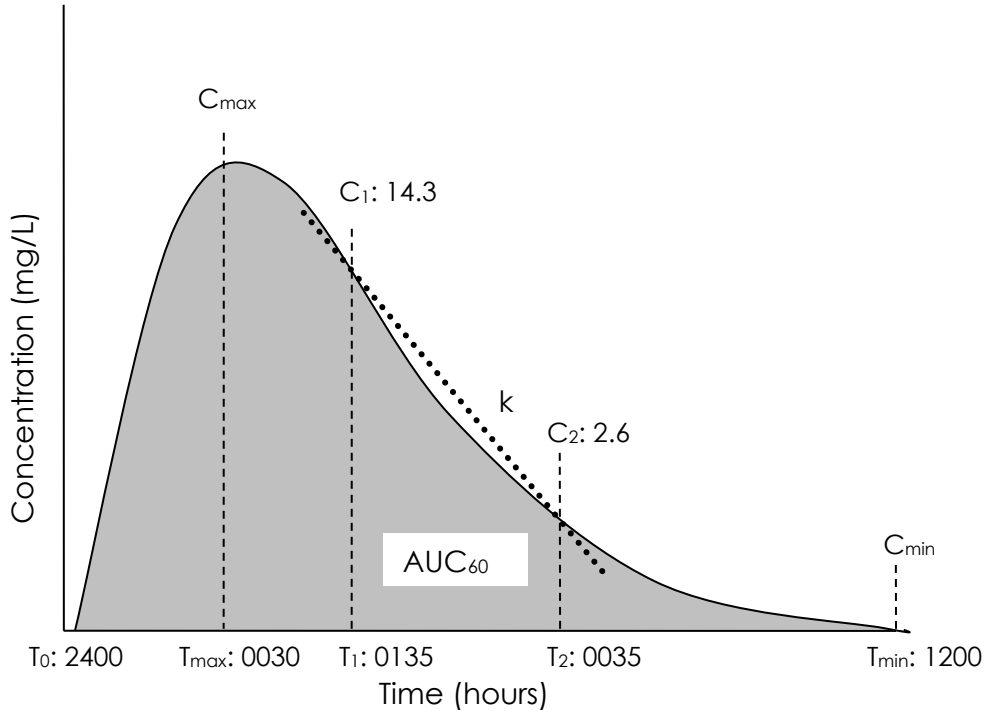
Top tips

- Treatment is often given empirically until sepsis is proven. If no infection is found empiric antibiotic treatment will be stopped.
- If the half-life is >12 hours, then an alternative antibiotic may need to be used.
- Recommend doses that can be easily measured (the Neonatal Unit uses 10 mg/mL gentamicin).
- When rounding doses, round down and not up.
- If you are unsure about a dose recommendation check with a senior pharmacist.

6.4. Worked examples

Example 1 – 60-hour empirical treatment for respiratory distress immediately after birth

Name	LC
Sex	Male
Age	27 weeks
Weight	1.3 kg
Drug	gentamicin
Dose	9.65 mg 60 hourly over 30 minutes
Infection	empirical for respiratory distress
Target AUC_{60}	250



LC is a premature infant who is suffering from respiratory distress immediately after birth; what would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 23 hours

$$k = \frac{ln14.3 \ - ln2.6}{23}$$

$$k = 0.0741$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.0741}$$

$$t_{½} = 9.35 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.08 hours

$$C_{max} = 14.3 \times e^{0.0741(1.08)}$$

$$C_{max} = 15.5 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 35.42 hours

$$C_{min} = 2.6 \times e^{-0.0741(35.42)}$$

$$C_{min} = 0.19 \ mg/L$$

$$AUC_{60} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{60} = \frac{15.5 - 0.19}{0.0741}$$

$$AUC_{60} = 207 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

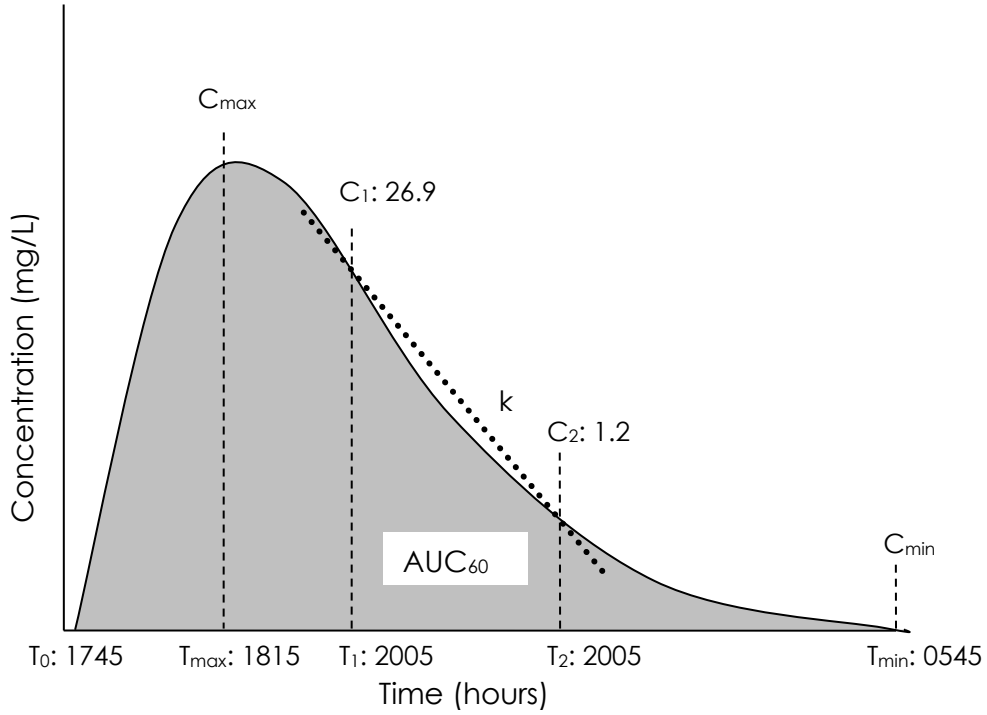
$$New \ dose = \frac{250}{207} \times 9.65 \ mg = 11.6 \ mg$$

Recommendation:

LC has received sufficient gentamicin (i.e. a C_{max} >12 mg/L) and is clearing it adequately (C_{min} <0.5 mg/L). As LC did not develop signs of sepsis a decision was made that no further gentamicin is required.

Example 2 – suspected sepsis, five-day treatment course

Name	BW
Sex	Male
Age	41 weeks
Weight	4.05 kg
Drug	gentamicin
Dose	40.5 mg 60 hourly over 30 minutes
Infection	suspected sepsis
Target AUC_{60}	250



BW is a term neonate with suspected sepsis who has had two doses of gentamicin. What would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 24 hours

$$k = \frac{ln26.9 \ - ln1.2}{24}$$

$$k = 0.1296$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.1296}$$

$$t_{½} = 5.35 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.83 hours

$$C_{max} = 26.9 \times e^{0.1296(1.83)}$$

$$C_{max} = 34.1 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 33.67 hours

$$C_{min} = 1.2 \ x \ e^{-0.1296(33.67)}$$

$$C_{min} = 0.015 \ mg/L$$

$$AUC_{60} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{60} = \frac{33.67 - 0.015}{0.1296}$$

$$AUC_{60} = 260 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{250}{260} \times 40.5$$

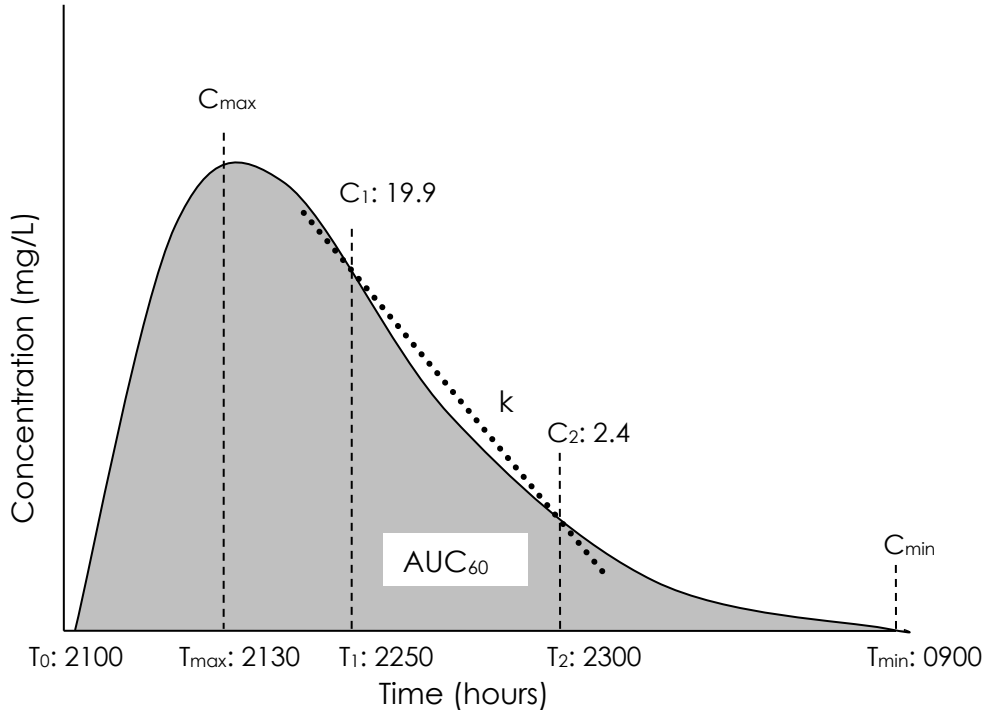
$$New \ dose = 38 \ mg$$

Recommendation:

BW has a very good peak and trough but the AUC_{60} is higher than the maximum of 250. Suggest dose reduction to 38 mg 60 hourly.

Example 3 – 60-hour empirical treatment for respiratory distress immediately after birth

Name	BS
Sex	Female
Age	38 weeks
Weight	2.98 kg
Drug	gentamicin
Dose	29.8 mg 60 hourly over 30 minutes
Infection	empirical respiratory distress
Target AUC_{60}	250



BS is a near-term infant who is suffering from respiratory distress immediately after birth. What would you recommend now?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 24.17 hours

$$k = \frac{ln19.9 \ - ln2.4}{24.17}$$

$$k = 0.0875$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.0875}$$

$$t_{½} = 7.92 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.33 hours

$$C_{max} = 19.9 \times e^{0.0875(1.33)}$$

$$C_{max} = 22.4 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 34 hours

$$C_{min} = 2.4 \times e^{-0.0875(34)}$$

$$C_{min} = 0.13 \ mg/L$$

$$AUC_{60} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{60} = \frac{22.4 - 0.13}{0.0875}$$

$$AUC_{60} = 255 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{250}{255} \times 29.8$$

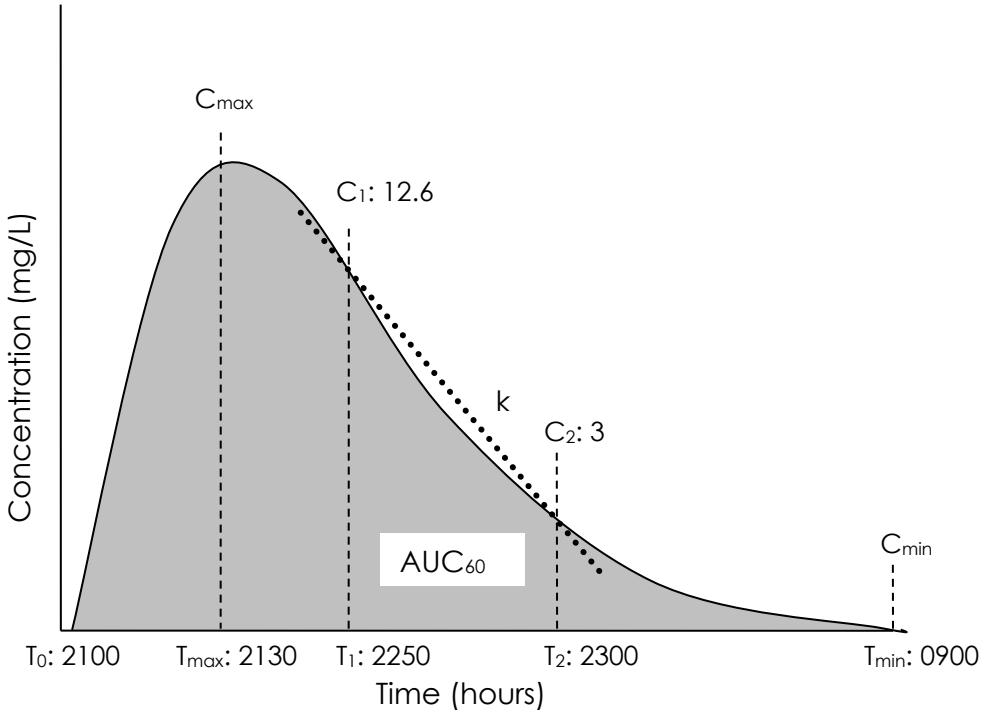
$$New \ dose = 29 \ mg$$

Recommendation:

BS has achieved a good peak and a low C_{min}. However, their AUC_{60} is slightly over the maximum of 250. If BS was continuing on treatment it would be reasonable to reduce the dose slightly to 29 mg 60 hourly.

Example 4 – suspected sepsis, five-day treatment course

Name	FG
Sex	Female
Age	29 weeks
Weight	0.77 kg
Drug	gentamicin
Dose	5.7 mg 60 hourly over 30 minutes
Infection	suspected sepsis
Target AUC_{60}	250



FG is a premature infant who is suffering from respiratory distress immediately after birth. What would you recommend now?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 24.17 hours

$$k = \frac{ln12.6 \ - ln3}{24.17}$$

$$k = 0.0593$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.0593}$$

$$t_{½} = 11.7 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.33 hours

$$C_{max} = 12.6 \ x \times e^{0.0593(1.33)}$$

$$C_{max} = 13.8 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 34 hours

$$C_{min} = 3 \times e^{-0.0593(34)}$$

$$C_{min} = 0.4 \ mg/L$$

$$AUC_{60} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{60} = \frac{13.8 - 0.4}{0.0593}$$

$$AUC_{60} = 226 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{250}{226} \times 5.7$$

$$New \ dose = 6.3 \ mg$$

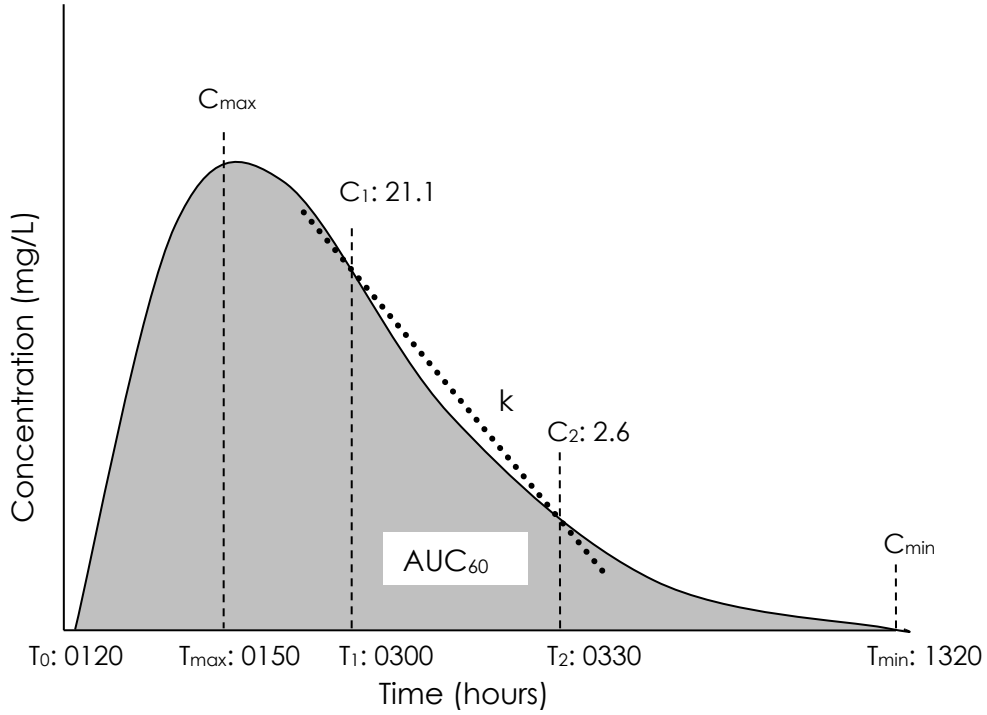
Recommendation:

FG has achieved a C_{max} >12 mg/L, a C_{min} <0.5 mg/L, but an AUC_{60} less than the maximum. It would be possible to slightly increase the dose to 6 mg 60 hourly.

6.5. Examples to work through

Example 1 – suspected sepsis, five-day treatment course

Name	JB
Sex	Male
Age	31 weeks
Weight	1.55 kg
Drug	gentamicin
Dose	15.5 mg 60 hourly over 30 minutes
Infection	suspected sepsis
Target AUC_{60}	250



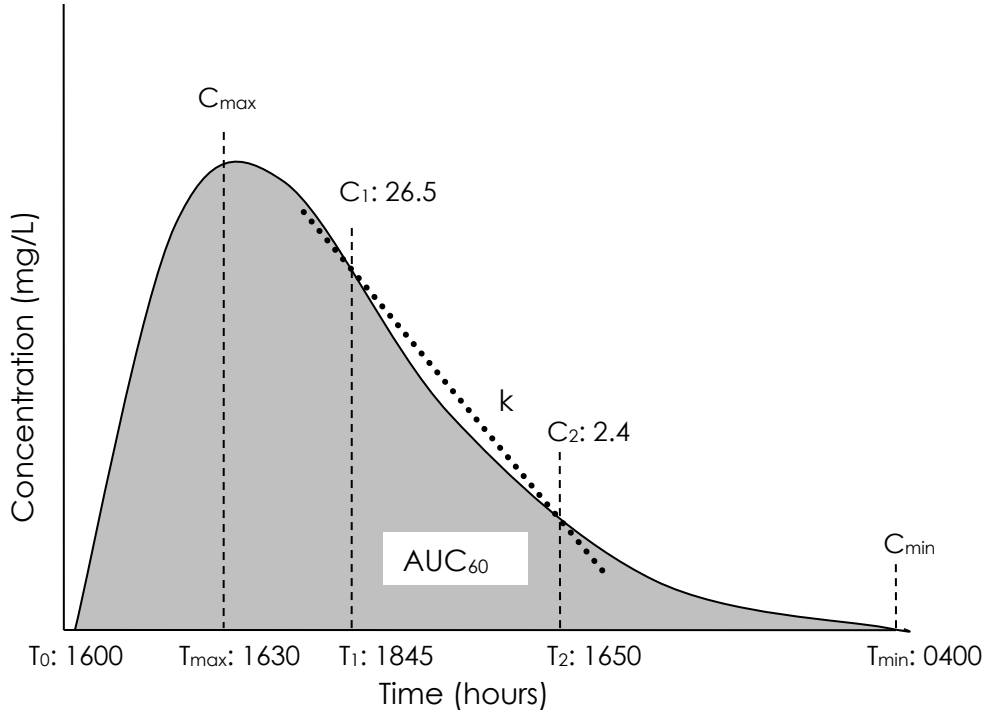
JB is being treated with gentamicin for suspected sepsis and has had two doses. What would you now recommend?

Answer

Recommendation:

Example 2 – meconium aspiration and ventilated neonate

Name	JC
Sex	Male
Age	39 weeks
Weight	3.6 kg
Drug	gentamicin
Dose	36 mg 60 hourly over 30 minutes
Infection	meconium aspiration
Target AUC_{60}	250



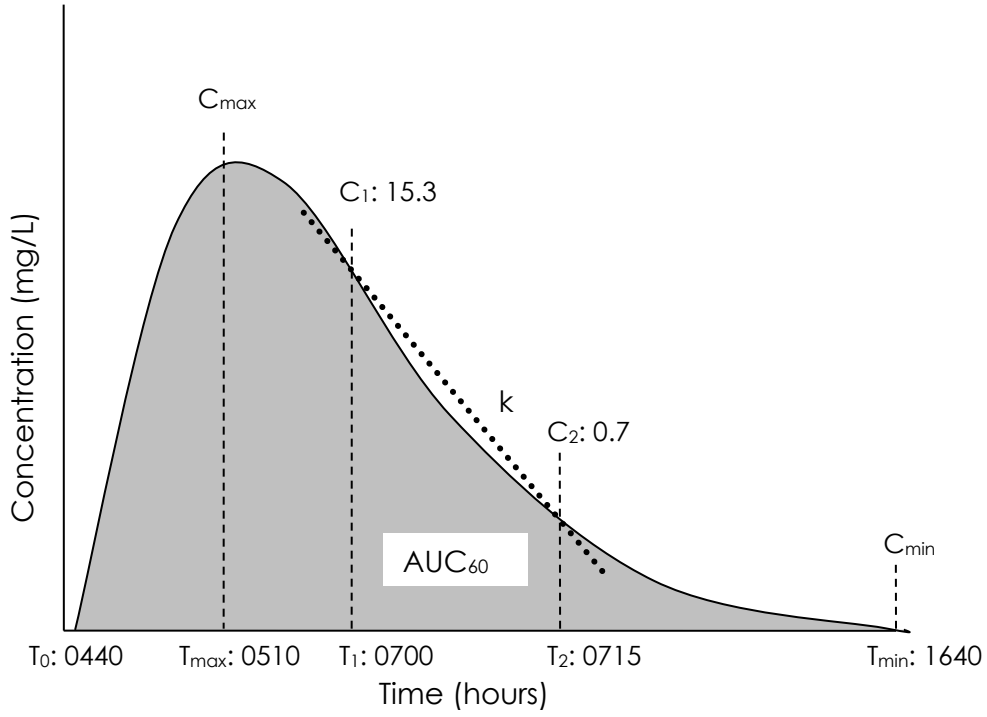
JC aspirated meconium during labour and is now requiring ventilation. As a precaution he is being treated with gentamicin. The doctors do not want to use an alternative antibiotic. What would you now recommend?

Answer

Recommendation:

Example 3 – 60-hour empirical treatment for respiratory distress immediately after birth

Name	BM
Sex	Female
Age	33 weeks
Weight	1.48 kg
Drug	gentamicin
Dose	11.1 mg 60 hourly over 30 minutes
Infection	empirical respiratory distress
Target AUC_{60}	250



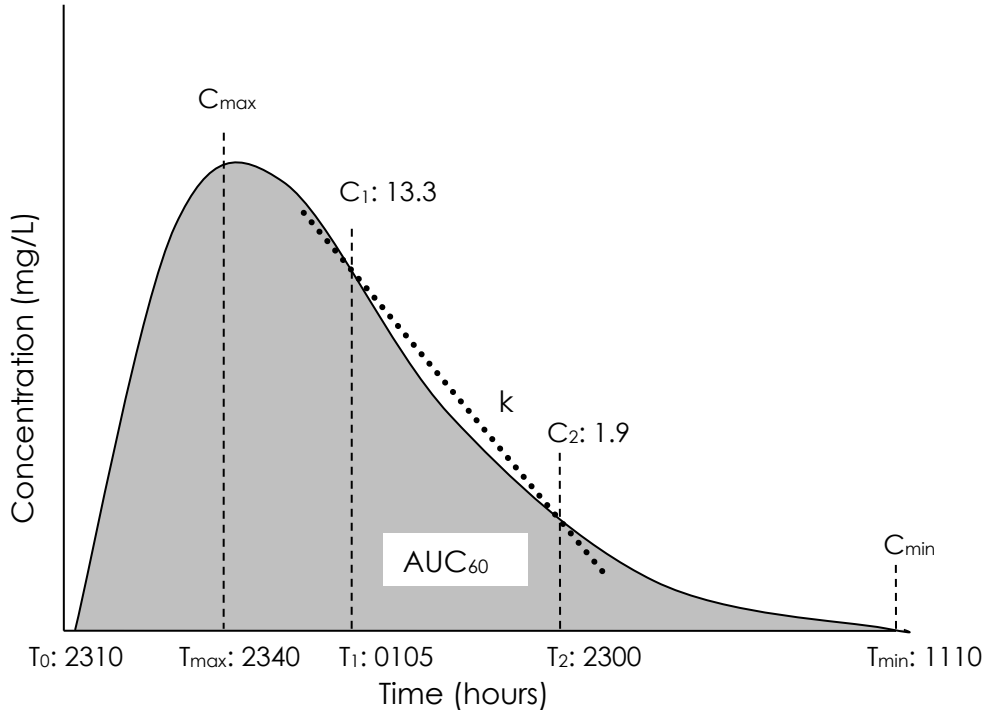
BM is a premature neonate with respiratory distress at birth. As a precaution she has been started on 60-hour empirical treatment. What would you now recommend?

Answer

Recommendation:

Example 4 – five-day treatment for suspected sepsis

Name	BF
Sex	Female
Age	36 weeks
Weight	2.78 kg
Drug	gentamicin
Dose	27.8 mg 60 hourly over 30 minutes
Infection	suspected sepsis
Target AUC_{60}	250



BF had respiratory distress at birth and was showing signs of suspected sepsis. A five-day treatment course including gentamicin was started. What would you now recommend?

Answer

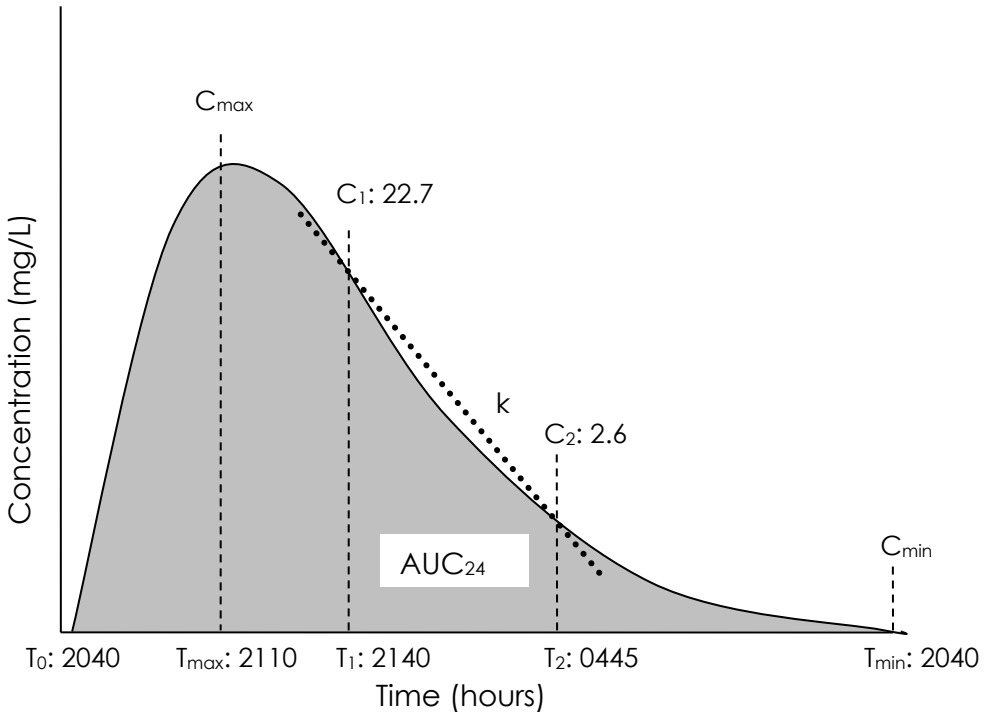
Recommendation:

7. Answers to aminoglycoside examples

7.1. Adults

Example 1 – cystic fibrosis – in hospital

Name	Test Test
NHI	ZZZ1006
Sex	Male
Age	28 years
Weight	61 kg
Height	185 cm
Creatinine	48 micromol/L
Drug	tobramycin
Dose	680 mg 24 hourly over 30 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	80-100

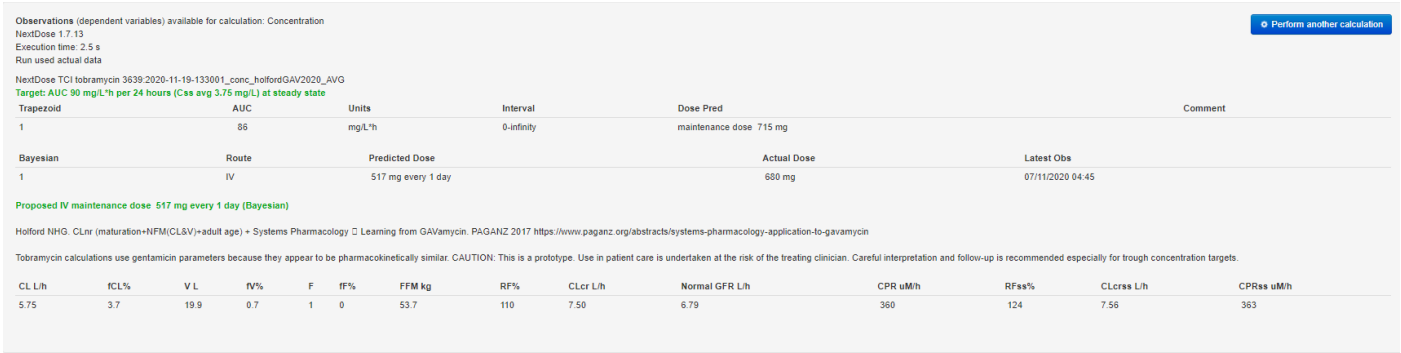


Test is a cystic fibrosis patient who is receiving IV tobramycin on the respiratory ward. He is also on ceftazidime 2 g IV three times a day. Test has had several doses of tobramycin; what would you now recommend?

Answer

Calculated by NextDose:

https://www.nextdose.org/#/6040/34638/results



Observations (dependent variables) available for calculation: Concentration
NextDose 1.7.13
Execution time: 2.5 s
Run used actual data

Perform another calculation

NextDose TCI tobramycin 3639:2020-11-19-133001_conc_holfordGAV2020_AVG
Target: AUC 90 mg/L*h per 24 hours (Css avg 3.75 mg/L) at steady state

Trapezoid	AUC	Units	Interval	Dose Pred	Comment
1	86	mg/L*h	0-infinity	maintenance dose 715 mg	

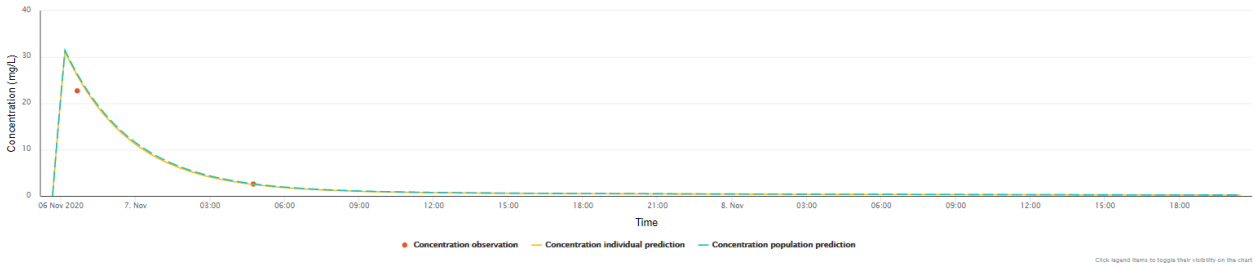
Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	517 mg every 1 day	680 mg	07/11/2020 04:45

Proposed IV maintenance dose 517 mg every 1 day (Bayesian)

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology □ Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

Tobramycin calculations use gentamicin parameters because they appear to be pharmacokinetically similar. CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
5.75	3.7	19.9	0.7	1	0	53.7	110	7.50	6.79	360	124	7.56	363



C_{max} (mg/L)	31.4
C_{min} (mg/L)	0.5

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times target\ AUC$$

$$AUC\ achieved = \frac{680\ mg}{517\ mg} \times 90 = 118$$

Recommendation:

The patient is a good fit for the population model. Given the high AUC, suggest reducing the dose to 520 mg every 24 hours. Recheck concentrations after the next dose.

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 7.08 hours

$$k = \frac{ln22.7 \ - ln2.6}{7.08}$$

$$k = 0.3061$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.3061}$$

$$t_{½} = 2.3 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and $T_{1)}$ = 0.5 hours

$$C_{max} = 22.7 \times e^{0.3061(0.5)}$$

$$C_{max} = 26.5 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 15.92 hours

$$C_{min} = 2.6 \times e^{-0.3061(15.92)}$$

$$C_{min} = 0.02 \ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{26.5 - 0.02}{0.3061}$$

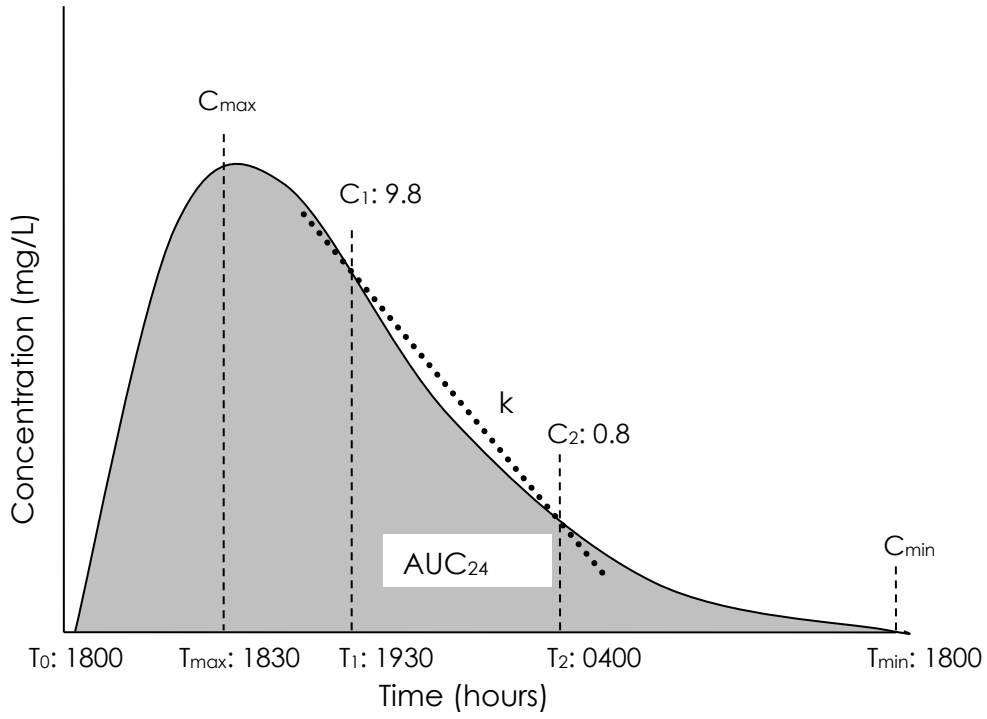
$$AUC_{24} = 87 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

$$New \ dose = \frac{90}{87} \times 680 = 703 \ mg$$

Example 2 – suspected perforated appendix – in hospital

Name	Test Test
NHI	ZZZ1007
Sex	Male
Age	37 years
Weight	83.3 kg
Height	187 cm
Creatinine	77 micromol/L
Drug	gentamicin
Dose	400 mg 24 hourly over 30 minutes
Infection	Perforated appendix
Target AUC_{24}	85

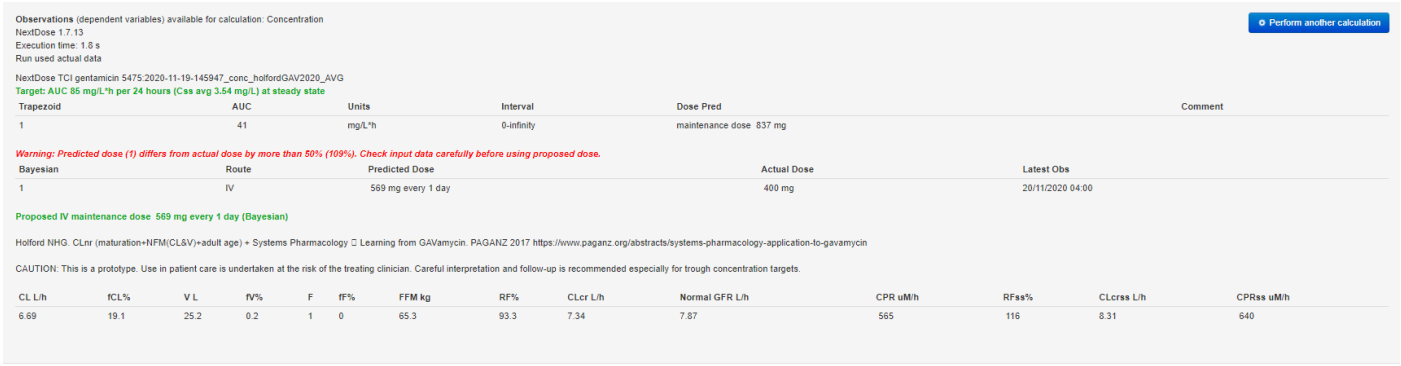


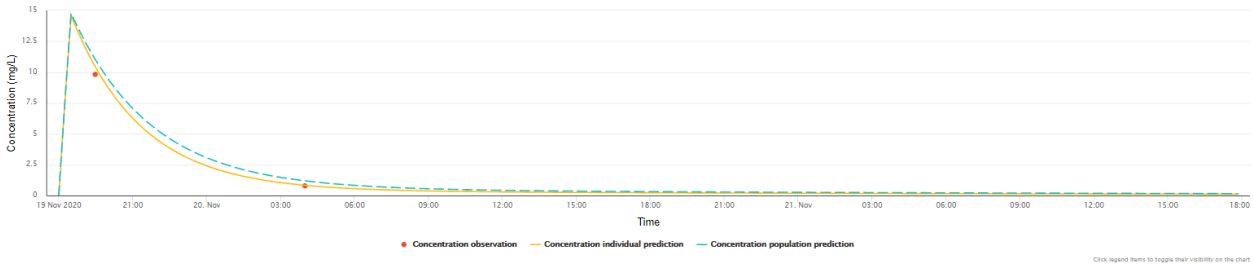
Test is a patient with a suspected perforated appendix who is receiving IV gentamicin. This is his first dose of gentamicin, what would you now recommend?

Answer

Calculated by NextDose:

https://www.nextdose.org/#/5475/30804/results



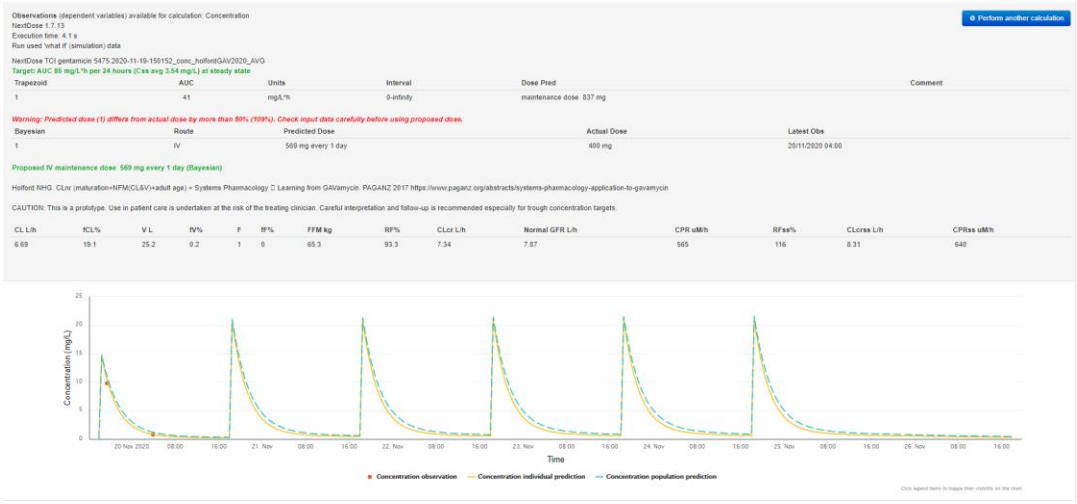


C_{max} (mg/L)	14.8
C_{min} (mg/L)	0.3

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times target\ AUC$$

$$AUC\ achieved = \frac{400\ mg}{569\ mg} \times 85 = 60$$

'What if' calculation for 560 mg: https://www.nextdose.org/#/5475/30806/results



Recommendation:

Increase dose to 560 mg. The patient is a good fit to the model, but the AUC_{24} at 60 is below the target of 85. This allows us to increase the dose and therefore C_{max}, which increases bacterial kill, without overly increasing the risk of toxicity. Repeat concentrations after the next dose.

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 8.5 hours

$$k = \frac{ln9.8 - ln0.8}{8.5}$$

$$k = 0.2948$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.2948}$$

$$t_{½} = 2.4\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1 hour

$$C_{max} = 9.8 \times e^{0.2958(1)}$$

$$C_{max} = 13.2\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 14 hours

$$C_{min} = 0.8 \times e^{-0.2958(14)}$$

$$C_{min} = 0.013\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{13.2 - 0.013}{0.2958}$$

$$AUC_{24} = 45\ mg/L.h$$

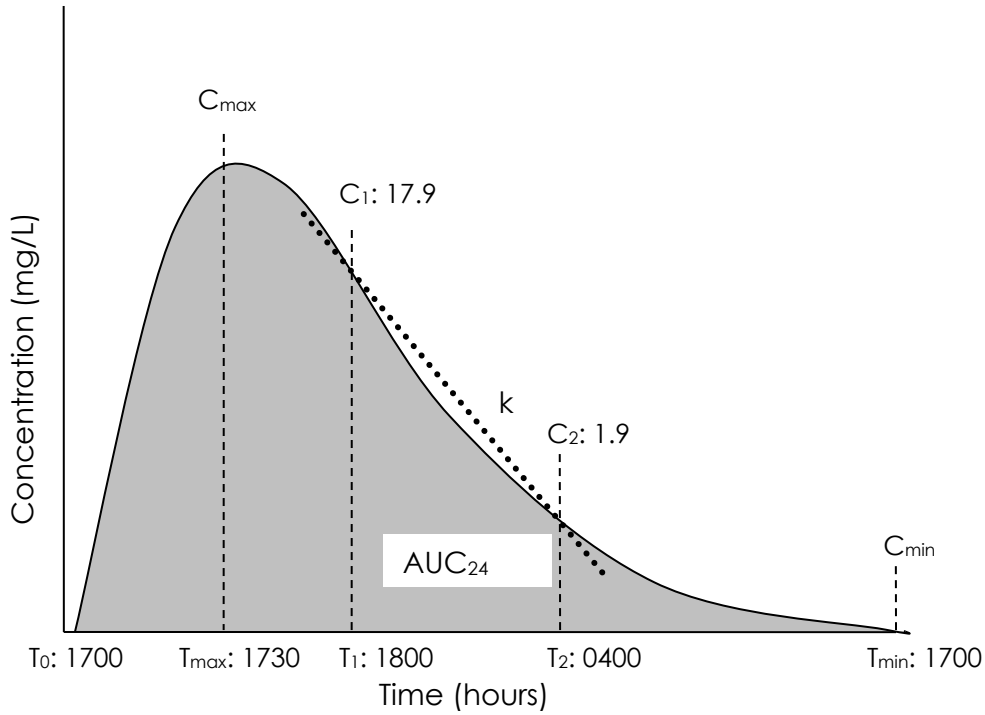
$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{85}{45} \times 400$$

$$New\ dose = 756\ mg$$

Example 3 – urosepsis – in hospital

Name	Test Test
NHI	ZZZ1008
Sex	Male
Age	57 years
Weight	88.9 kg
Height	183 cm
Creatinine	109 micromol/L
Drug	gentamicin
Dose	420 mg 24 hourly over 30 minutes
Infection	Urosepsis
Target AUC_{24}	85-95

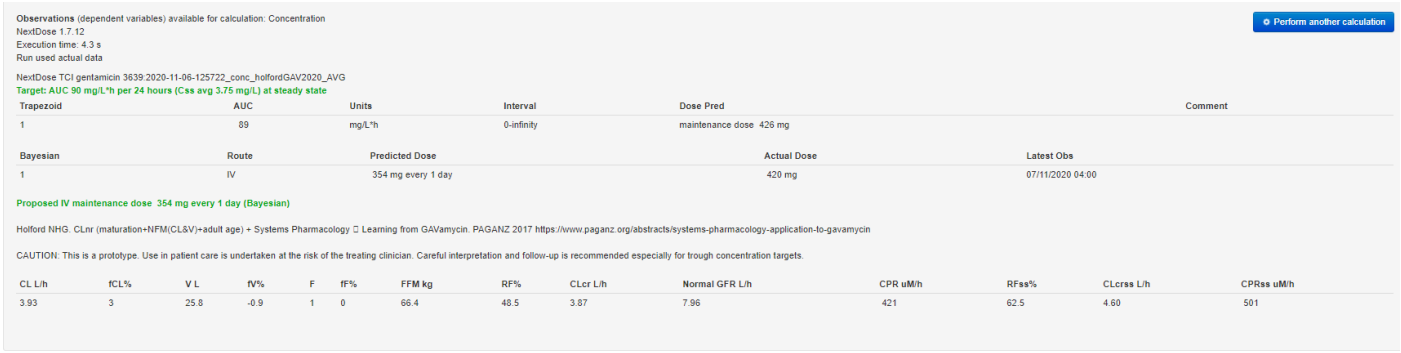


Test is a patient with urosepsis who is receiving IV gentamicin. This is his third dose of gentamicin, what would you now recommend?

Answer

Calculated by NextDose:

https://www.nextdose.org/#/6042/34641/results



Observations (dependent variables) available for calculation: Concentration
NextDose 1.7.12
Execution time: 4.3 s
Run used actual data

Perform another calculation

NextDose TCI gentamicin 3639:2020-11-06-125722_conc_holfordGAV2020_AVG
Target: AUC 90 mg/L*h per 24 hours (Css avg 3.75 mg/L) at steady state

Trapezoid	AUC	Units	Interval	Dose Pred	Comment
1	89	mg/L*h	0-infinity	maintenance dose 426 mg	

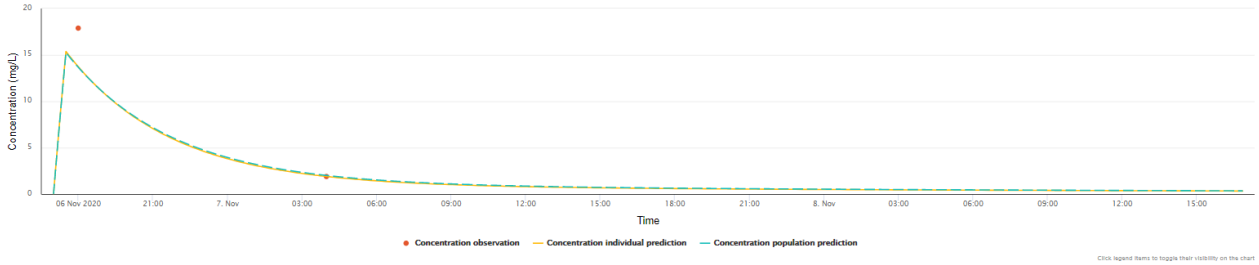
Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	354 mg every 1 day	420 mg	07/11/2020 04:00

Proposed IV maintenance dose 354 mg every 1 day (Bayesian)

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology □ Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
3.93	3	25.8	-0.9	1	0	66.4	48.5	3.87	7.96	421	62.5	4.60	501



C_{max} (mg/L)	15.4
C_{min} (mg/L)	0.7

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times target\ AUC$$

$$AUC\ achieved = \frac{420\ mg}{354\ mg} \times 90 = 107$$

Recommendation:

NextDose has ignored the measured C_1, which has led to a lower predicted C_{max}. The reason for this should be considered clinically e.g. has the patient disproportionately more fat weight than the average individual with the same height and weight. In the absence of further information, two approaches can be taken with the safety-netting of rechecking concentrations after the next dose

1. Use the NextDose C_{max} prediction: this patient would be a reasonable candidate for 48 hourly gentamicin, given that the C_{max} is not particularly high, and the C_{min} is approaching 1 mg/L. Suggest increasing the dose to 560 mg to achieve a higher C_{max} and reducing the frequency to 48 hourly.
2. Use measured C_{max}: continue with 24 hourly dosing but 360 mg to bring AUC and Cmin closer to target, and recheck concentrations after this dose.

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 10 hours

$$k = \frac{ln17.9 - ln1.9}{10}$$

$$k = 0.2243$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.2243}$$

$$t_{½} = 3.1\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 0.5 hours

$$C_{max} = 17.9 \times e^{0.2243(0.5)}$$

$$C_{max} = 20\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 13 hours

$$C_{min} = 1.9 \times e^{-0.2243(13)}$$

$$C_{min} = 0.1\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{20 - 0.1}{0.2243}$$

$$AUC_{24} = 89\ mg/L.h$$

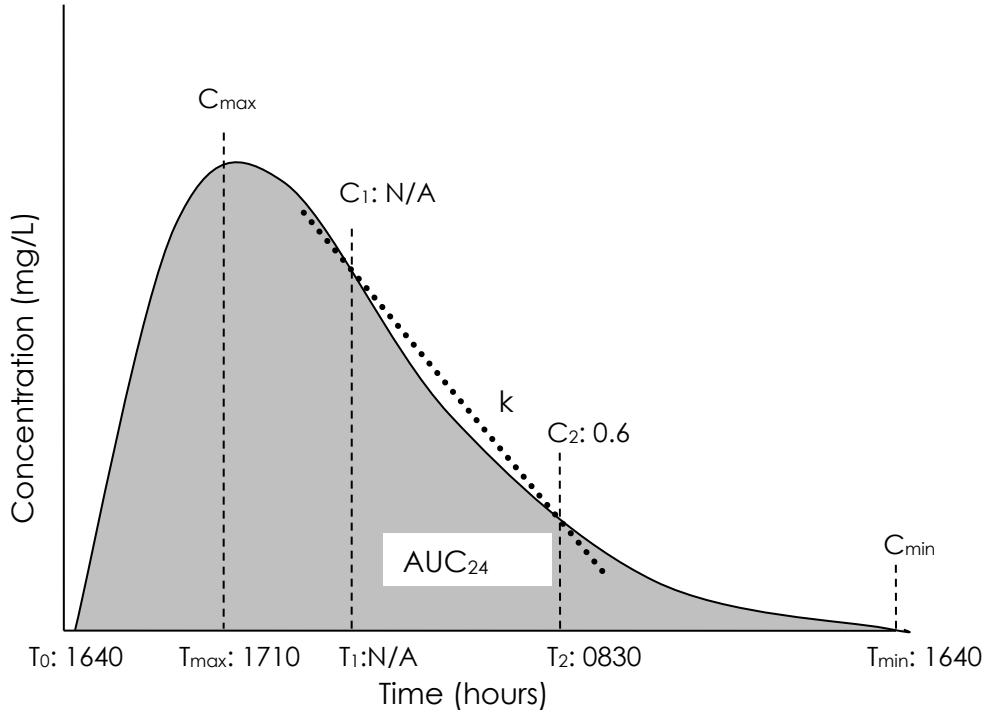
$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{90}{89} \times 420$$

$$New\ dose = 425\ mg$$

Example 4 – suspected peritonitis – in hospital

Name	Test Test
NHI	ZZZ1009
Sex	Male
Age	64 years
Weight	91 kg
Height	180 cm
Creatinine	80 micromol/L
Drug	gentamicin
Dose	240 mg 24 hourly over 30 minutes
Infection	peritonitis
Target AUC_{24}	85-95



Test is a patient with suspected peritonitis who is receiving IV gentamicin. Only one blood sample has been taken, what would you now recommend?

Answer

Calculated by NextDose:

https://www.nextdose.org/#/6043/34642/results

Observations (dependent variables) available for calculation: Concentration
NextDose 1.7.12
Execution time: 2.7 s
Run used actual data

Perform another calculation

NextDose TCI gentamicin 3639 2020-11-06-140145_conc_holfordGAV2020_AVG
Target: AUC 90 mg/L*h per 24 hours (Css avg 3.75 mg/L) at steady state

Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	375 mg every 1 day	240 mg	07/11/2020 08:30

Proposed IV maintenance dose 375 mg every 1 day (Bayesian)
Warning: A predicted dose differs from actual dose by more than 50% (56%). Check input data carefully before using proposed dose.

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology □ Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
4.16	-0.4	26.3	0	1	0	66.2	57.7	4.58	7.95	367	75.9	5.60	448

C_{max} (mg/L)	8.6
C_{min} (mg/L)	0.3

$$AUC\ achieved = \frac{actual\ dose}{proposed\ dose} \times\ target\ AUC$$

$$AUC\ achieved = \frac{240\ mg}{375\ mg} \times\ 90\ = 58$$

Recommendation:

Increase dose to 400 mg, given the C_{max} and AUC_{24} are well below target. This estimate is likely to be less accurate as we only have one sample, so repeat concentrations after this dose to get a more accurate prediction.

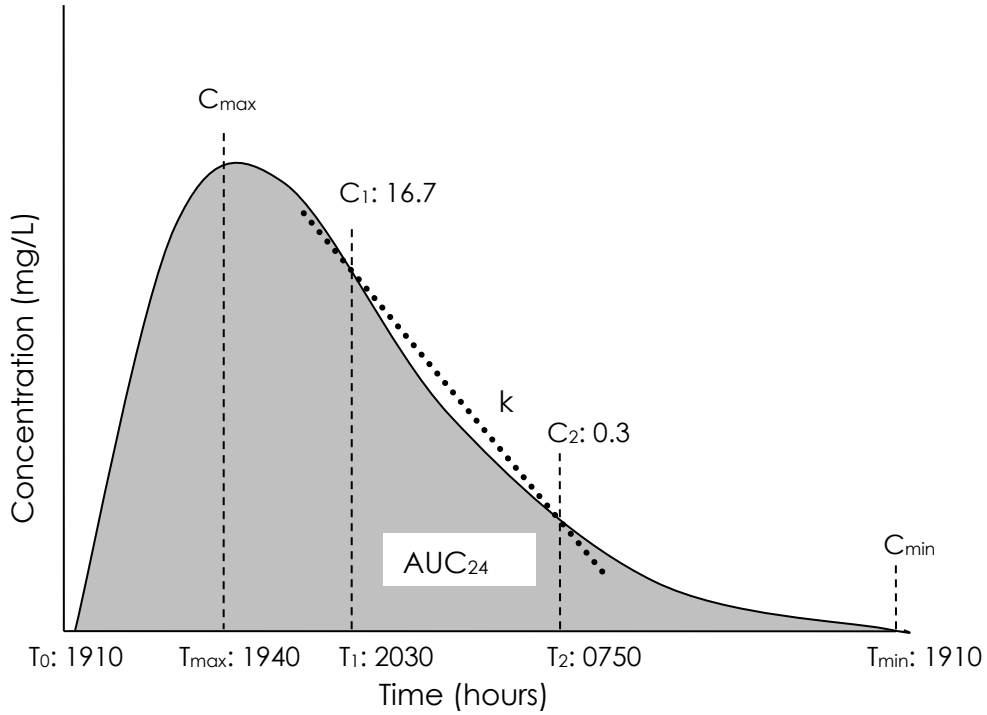
Calculated by hand:

We only have one blood sample, so this is not possible.

7.2. Paediatrics

Example 1 – gentamicin for an abdominal abscess

Name	Test Test
Sex	Female
Age	5 years
Weight	30 kg
Height	
Creatinine	34 micromol/L
Drug	gentamicin
Dose	240 mg 24 hourly over 30 minutes
Infection	abdominal abscess
Target AUC_{24}	90



Test presented with an abdominal abscess that is being treated with IV gentamicin and IV clindamycin. This is her second dose of gentamicin, what would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 11.33 hours

$$k = \frac{ln16.7 - ln0.3}{11.33}$$

$$k = 0.3548$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.3548}$$

$$t_{½} = 1.95\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 0.83 hours

$$C_{max} = 16.7 \times e^{0.3548(0.83)}$$

$$C_{max} = 22.4\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 11.33 hours

$$C_{min} = 0.3 \times e^{-0.3548(11.33)}$$

$$C_{min} = 0.005\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{22.4 - 0.005}{0.3548}$$

$$AUC_{24} = 63\ mg/L.h$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

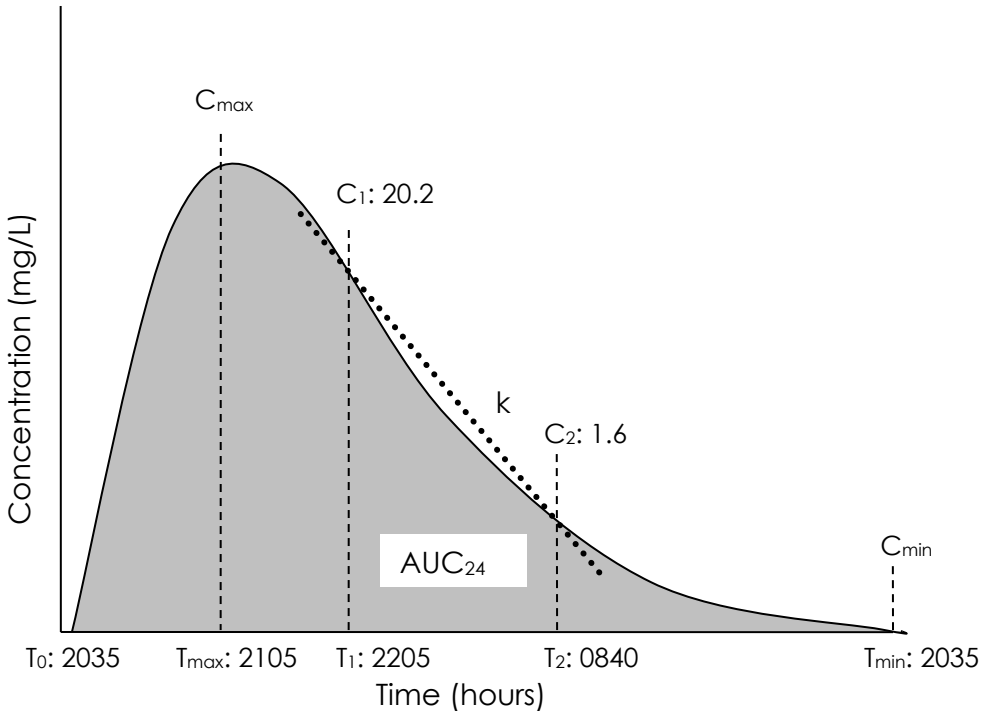
$$New\ dose = \frac{90}{63} \times 240 = 343\ mg$$

Recommendation:

Increase to 280 mg. The patient has achieved a good C_{max} and low C_{min}, which demonstrates that they are clearing gentamicin well. However, the AUC_{24} is much lower than the target of 90. Suggest a more conservative increase rather than the calculated new dose of 340 mg, as this is higher than the usual maximum of 10 mg/kg for paediatrics, especially if the patient is clinically doing well. If we 'overshoot' then we may put the patient at risk of toxicity. Repeat concentrations next dose.

Example 2 – cystic fibrosis patient with pseudomonas

Name	Test Test
Sex	Female
Age	9 years
Weight	35 kg
Height	140 cm
Creatinine	72 micromol/L
Drug	tobramycin
Dose	220 mg 24 hourly over 30 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	90-100



Test has cystic fibrosis and is receiving tobramycin, ceftazidime and clindamycin for pseudomonas as an outpatient. This is the end of the second week of therapy, what would you recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 10.58 hours

$$k = \frac{ln20.2 - ln1.6}{10.58}$$

$$k = 0.240$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.240}$$

$$t_{½} = 2.89\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1 hour

$$C_{max} = 20.2 \times e^{0.240(1)}$$

$$C_{max} = 25.7\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 11.92 hours

$$C_{min} = 1.6 \times e^{-0.240(11.92)}$$

$$C_{min} = 0.09\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{25.7 - 0.09}{0.240}$$

$$AUC_{24} = 107\ mg.h/L$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

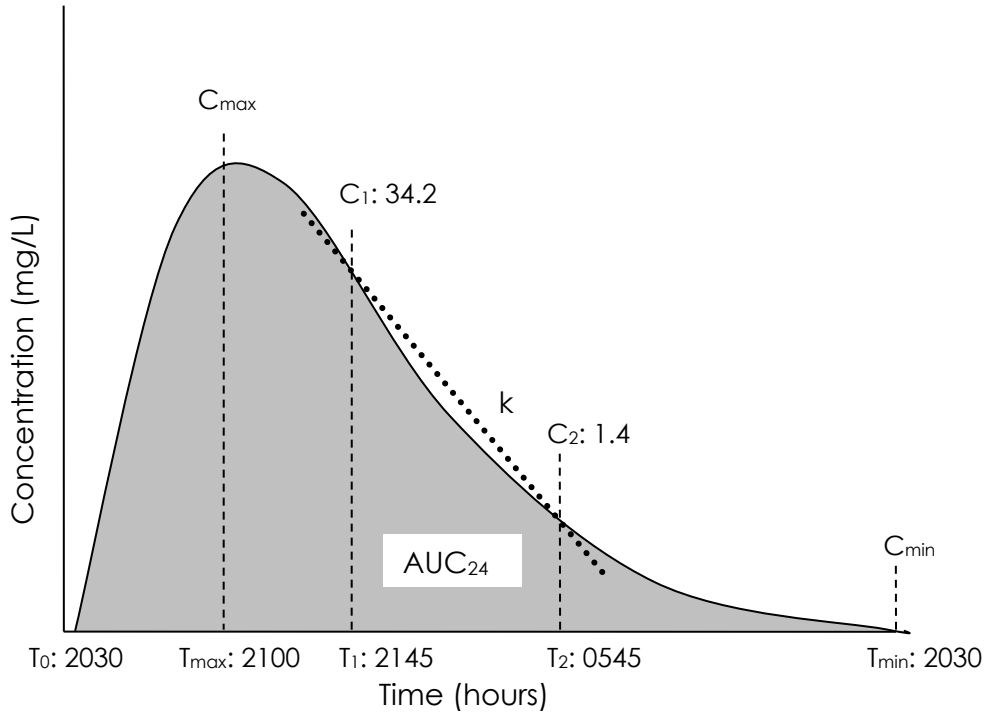
$$New\ dose = \frac{95}{107} \times 220 = 195\ mg$$

Recommendation:

Give the same dose (220 mg). The patient has achieved a good C_{max} and has a low C_{min}, which demonstrates that they are clearing tobramycin well. Repeat concentrations Sunday and Thursday (if therapy is continuing for longer than two weeks). As this patient is having home IV therapy, more frequent concentration monitoring is difficult.

Example 3 – gentamicin for cholangitis

Name	Test Test
Sex	Male
Age	2 years
Weight	15.5 kg
Height	
Creatinine	30 micromol/L
Drug	gentamicin
Dose	220 mg 24 hourly over 30 minutes
Infection	Cholangitis
Target AUC_{24}	85-95



PB has cholangitis that is being treated with gentamicin. This is his third dose (previous doses were 150 mg and 190 mg). What would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 8 hours

$$k = \frac{ln34.2 - ln1.4}{8}$$

$$k = 0.399$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.399}$$

$$t_{½} = 1.74\ hours$$

$$C_{max} = C_1\ x\ e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 0.75 hours

$$C_{max} = 34.2\ x\ e^{0.399(0.75)}$$

$$C_{max} = 46\ mg/L$$

$$C_{min} = C_2\ x\ e^{-k^{(T_{min} - T_2)}}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 14.75 hours

$$C_{min} = 1.4\ x\ e^{-0.399^{(14.75)}}$$

$$C_{min} = 0.004\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{46 - 0.004}{0.399}$$

$$AUC_{24} = 115\ mg.h/L$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC}\ x\ current\ dose$$

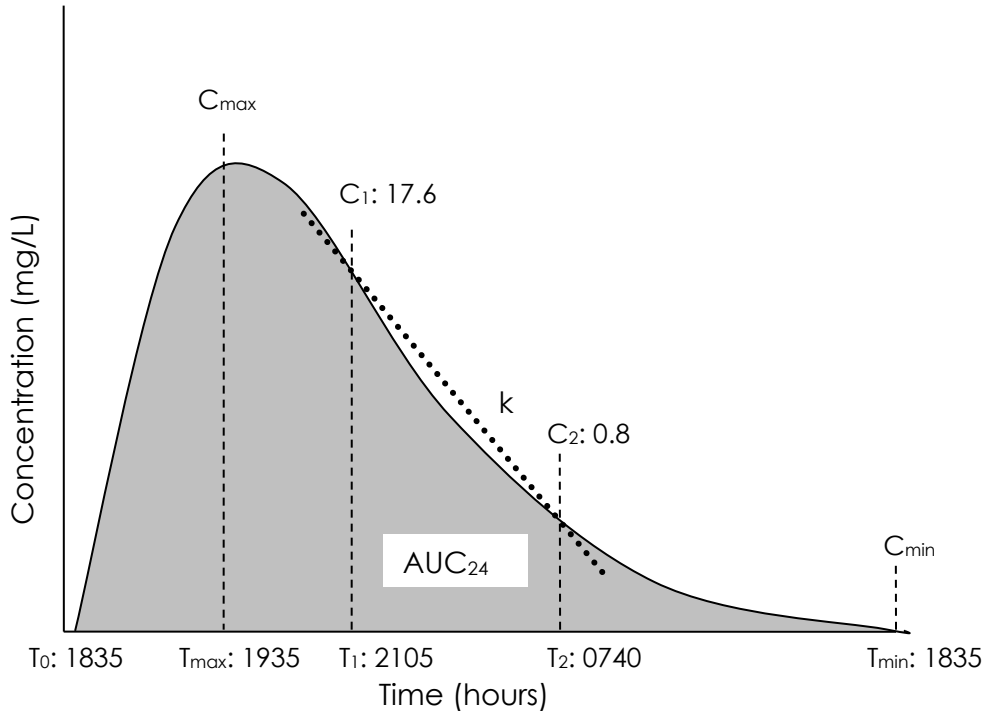
$$New\ dose = \frac{90}{115}\ x\ 220 = 172\ mg$$

Recommendation:

The C_{max} and AUC_{24} are both high but the C_{min} is very low, meaning PB is clearing gentamicin well. Choosing the dose to recommend is tricky. We need to balance the fact that PB is unwell and has good clearance but is also only weighs 15.5 kg (10 mg/kg = 155 mg). For the next dose, you could choose 160 mg, 170 mg or 180 mg, resulting in a C_{max} of 33-36. Repeat concentrations on the next dose.

Example 4 – cystic fibrosis with pseudomonas

Name	Test Test
Sex	Female
Age	15 years
Weight	53.8 kg
Height	
Creatinine	61 micromol/L
Drug	tobramycin
Dose	380 mg 24 hourly over 30 minutes
Infection	Pseudomonas in lungs
Target AUC_{24}	90-100



Test is a patient with cystic fibrosis who is on tobramycin in the community. What would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 10.58 hours

$$k = \frac{ln17.6 - ln0.8}{10.58}$$

$$k = 0.2921$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.2921}$$

$$t_{½} = 2.37\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.5 hours

$$C_{max} = 17.6 \times e^{0.2921(1.5)}$$

$$C_{max} = 27\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 10.92 hours

$$C_{min} = 0.8 \times e^{-0.2921(10.92)}$$

$$C_{min} = 0.03\ mg/L$$

$$AUC_{24} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{24} = \frac{27 - 0.03}{0.2921}$$

$$AUC_{24} = 92\ mg/L.h$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{95}{92} \times 380$$

$$New\ dose = 392\ mg$$

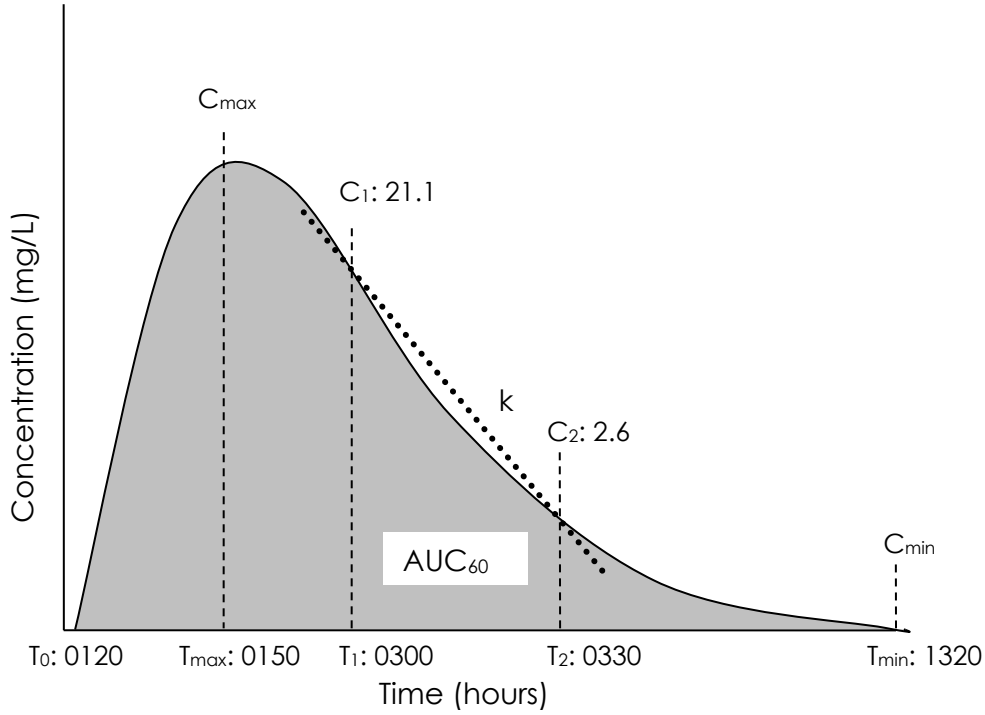
Recommendation:

Give the same dose (380 mg). The AUC_{24}, C_{max} and C_{min} are all satisfactory meaning no dose change is required. Repeat concentrations twice weekly (Sunday or Thursday).

7.3. Neonates

Example 1 – suspected sepsis, five-day treatment course

Name	JB
Sex	Male
Age	31 weeks
Weight	1.55 kg
Drug	gentamicin
Dose	15.5 mg 60 hourly over 30 minutes
Infection	suspected sepsis
Target AUC_{60}	250



JB is being treated with gentamicin for suspected sepsis and has had two doses. What would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 24.5 hours

$$k = \frac{ln21.1 - ln2.6}{24.5}$$

$$k = 0.0855$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.0855}$$

$$t_{½} = 8.1\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and $T_{1)}$ = 1.17 hours

$$C_{max} = 21.1 \times e^{0.0855(1.17)}$$

$$C_{max} = 23\ mg/L$$

$$C_{min} = C_2\ x\ e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 33.83 hours

$$C_{min} = 2.6 \times e^{-0.0855(33.83)}$$

$$C_{min} = 0.14\ mg/L$$

$$AUC_{60} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{60} = \frac{23 - 0.14}{0.0855}$$

$$AUC_{60} = 267\ mg/L.h$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

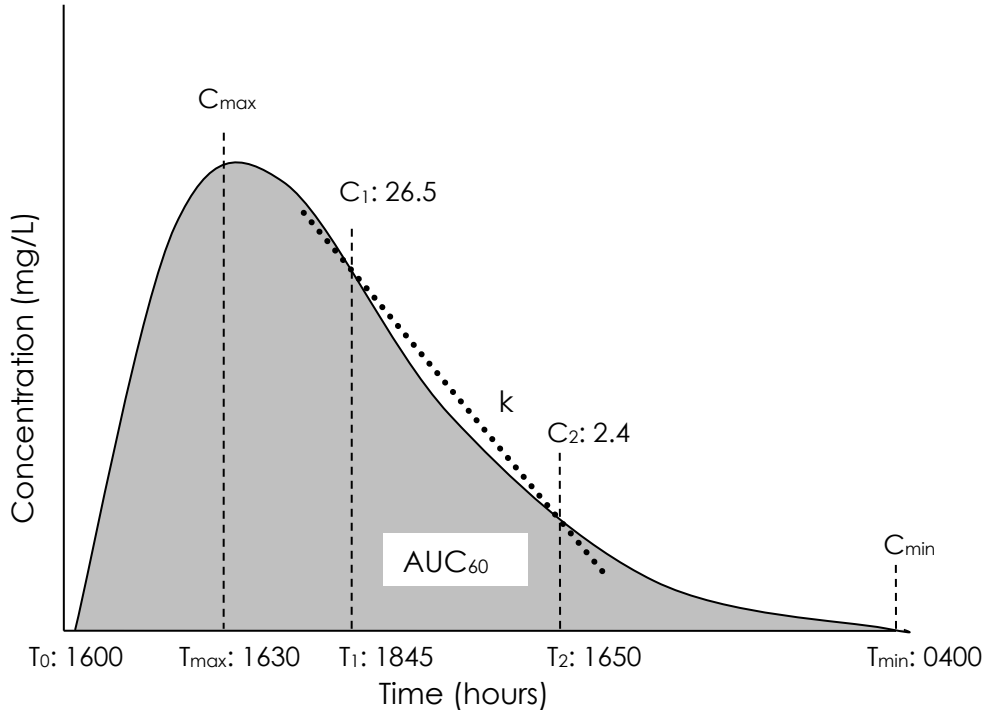
$$New\ dose = \frac{250}{267} \times 15.5 = 14.5\ mg$$

Recommendation:

JB has achieved a good C_{max} and low C_{min}. However, the AUC_{60} is higher than the maximum of 250. A small dose reduction should still achieve a good C_{max} and low C_{min} but reduce the AUC_{60} closer to 250. Neonates generally have large fluid shifts in the first few days of life, and JB may have a degree of third spacing due to sepsis. Kidney function should be improving steadily with age. If further doses are needed, then measure concentrations following the next dose.

Example 2 – meconium aspiration and ventilated neonate

Name	JC
Sex	Male
Age	39 weeks
Weight	3.6 kg
Drug	gentamicin
Dose	36 mg 60 hourly over 30 minutes
Infection	meconium aspiration
Target AUC_{60}	250



JC aspirated meconium during labour and is now requiring ventilation. As a precaution he is being treated with gentamicin. The doctors do not want to use an alternative antibiotic. What would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 22.08 hours

$$k = \frac{ln26.5 - ln2.4}{22.08}$$

$$k = 0.1088$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.1088}$$

$$t_{½} = 6.37\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and $T_{1)}$ = 2.25 hours

$$C_{max} = 26.5 \times e^{0.1088(2.25)}$$

$$C_{max} = 33.9\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 35.17 hours

$$C_{min} = 2.4 \times e^{-0.1088(35.17)}$$

$$C_{min} = 0.05\ mg/L$$

$$AUC_{60} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{60} = \frac{33.9 - 0.05}{0.1088}$$

$$AUC_{60} = 311\ mg/L.h$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{250}{311} \times 36$$

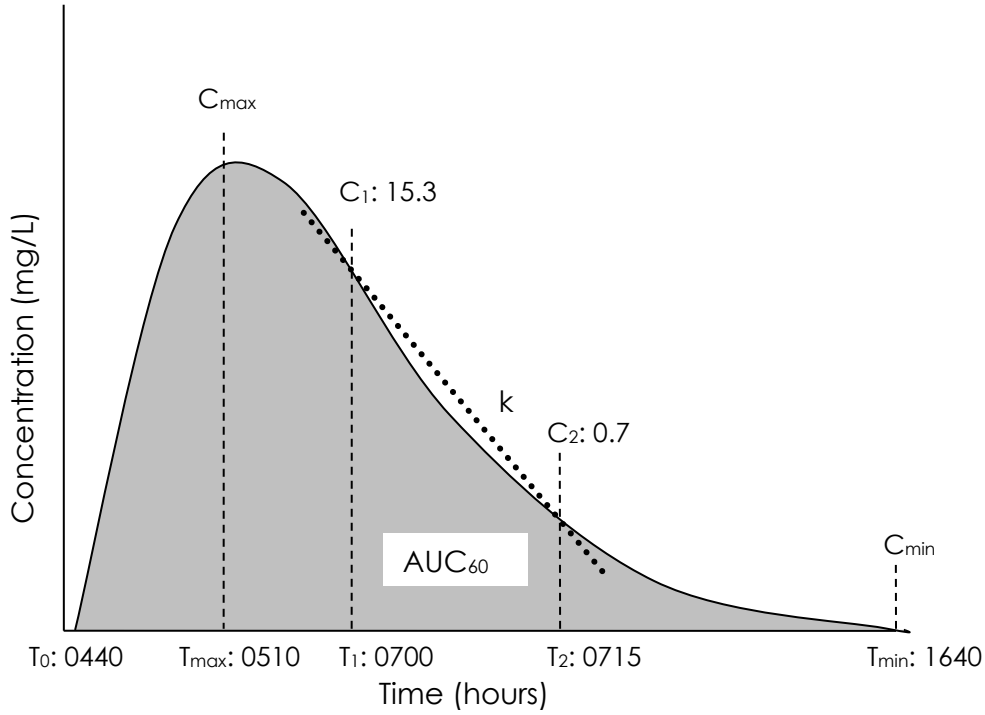
$$New\ dose = 28\ mg$$

Recommendation:

JC has achieved a high C_{max} and a low C_{min}; however, the AUC_{60} is too high. If gentamicin is to continue, the dose should be reduced to 28 mg to achieve an AUC_{60} of 250.

Example 3 – 60-hour empirical treatment for respiratory distress immediately after birth

Name	BM
Sex	Female
Age	33 weeks
Weight	1.48 kg
Drug	gentamicin
Dose	11.1 mg 60 hourly over 30 minutes
Infection	empirical respiratory distress
Target AUC_{60}	250



BM is a premature neonate with respiratory distress at birth. As a precaution she has been started on 60-hour empirical treatment. What would you now recommend?

Answer:

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 24.25 hours

$$k = \frac{ln15.3 \ - ln0.7}{24.25}$$

$$k = 0.1272$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.1272}$$

$$t_{½} = 5.45 \ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.83 hours

$$C_{max} = 15.3 \times e^{0.1272(1.83)}$$

$$C_{max} = 19.3 \ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 33.42 hours

$$C_{min} = 0.7 \times e^{-0.1272(33.42)}$$

$$C_{min} = 0.01 \ mg/L$$

$$AUC_{60} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{60} = \frac{19.3 - 0.01}{0.1272}$$

$$AUC_{60} = 152 \ mg/L.h$$

$$New \ dose = \frac{target \ AUC}{calculated \ AUC} \times current \ dose$$

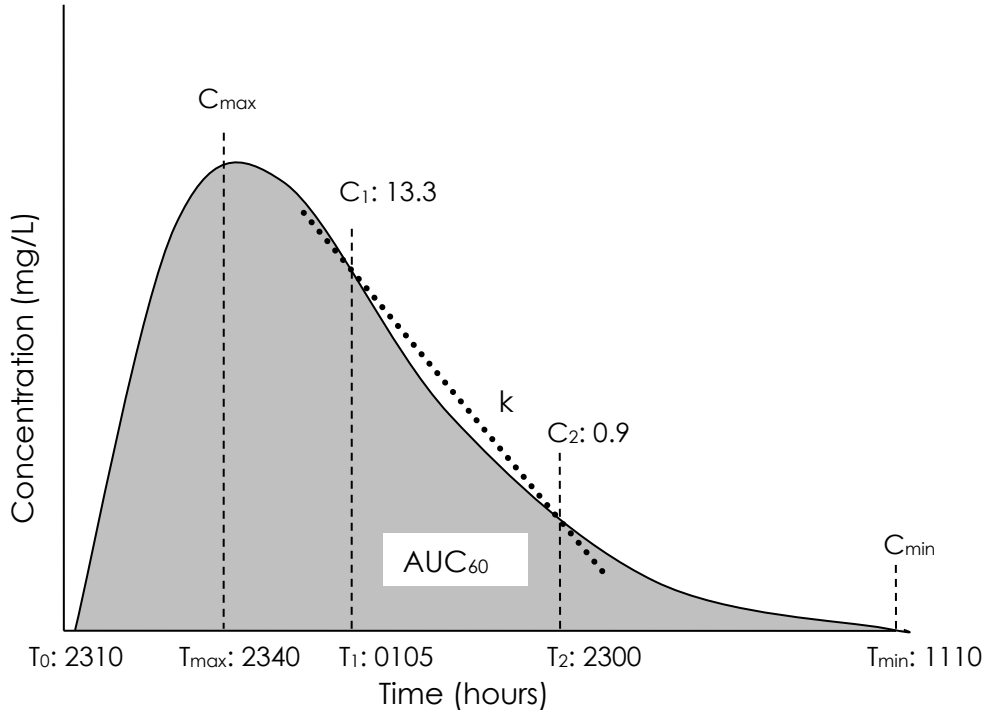
$$New \ dose = \frac{250}{152} \times 11.1 = 18.2 \ mg$$

Recommendation:

BM has a good C_{max} and low C_{min} and no further dose is needed for empirical therapy. However, if BM had confirmed sepsis then we could increase the dose as the AUC_{60} is much lower than the target. Suggest a conservative dose increase to 15 mg (close to the 10 mg/kg maximum). BM is clearing gentamicin quickly for her age and weight, suggesting a degree of third spacing. This may be due to sepsis, a surgical drain or a blood transfusion with a dose of furosemide causing fluid balance disruption.

Example 4 – five-day treatment for suspected sepsis

Name	BF
Sex	Female
Age	36 weeks
Weight	2.78 kg
Drug	gentamicin
Dose	27.8 mg 60 hourly over 30 minutes
Infection	suspected sepsis
Target AUC_{60}	250



BF had respiratory distress at birth and was showing signs of suspected sepsis. A five-day treatment course including gentamicin was started. What would you now recommend?

Answer

Calculated by hand:

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 21.92 hours

$$k = \frac{ln13.3 - ln1.9}{21.92}$$

$$k = 0.0888$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.0888}$$

$$t_{½} = 7.8\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.42 hours

$$C_{max} = 13.3 \times e^{0.0888(1.42)}$$

$$C_{max} = 15.1\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 36.16 hours

$$C_{min} = 1.9 \times e^{-0.0888(36.16)}$$

$$C_{min} = 0.08\ mg/L$$

$$AUC_{60} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{60} = \frac{15.1 - 0.08}{0.0888}$$

$$AUC_{60} = 169\ mg.h/L$$

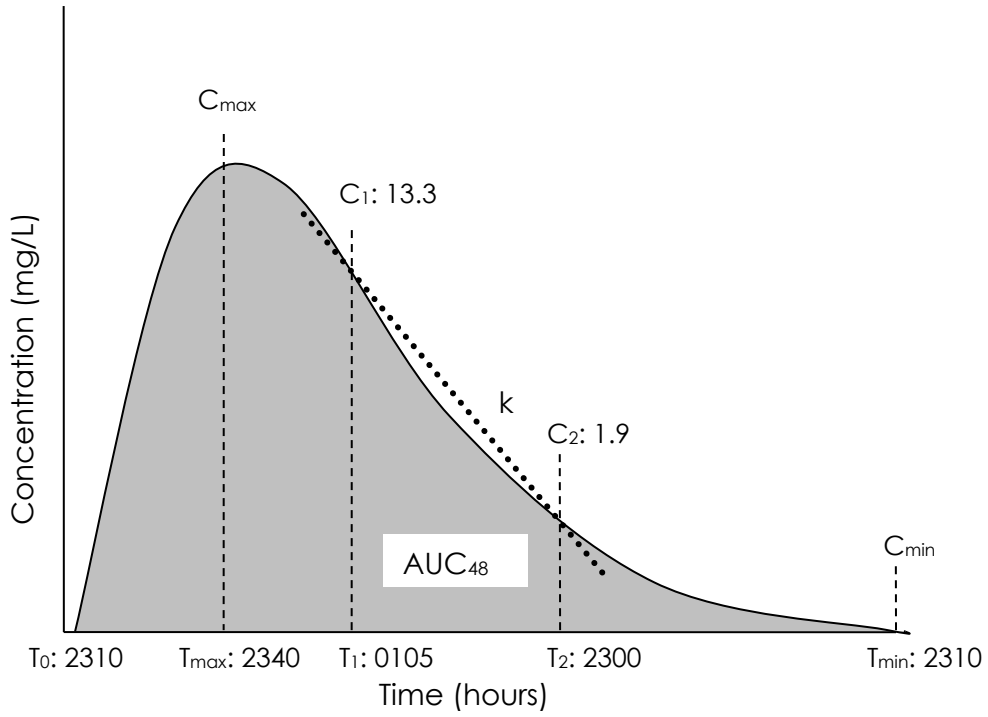
$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{250}{169} \times 27.8$$

$$New\ dose = 41\ mg$$

Recommendation:

BF has achieved a reasonable C_{max}, with a low C_{min} and AUC_{60} indicating minimal potential for toxicity. As BF is a very sick neonate, we could potentially bring the next dose forward and give a higher dose, to achieve a higher C_{max} and better bacterial kill. If dosing 48 hourly, we aim for an AUC_{48} of 200 mg/L.h. See below for 48 hourly dosing calculations.



$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 21.92 hours

$$k = \frac{ln13.3 - ln1.9}{21.92}$$

$$k = 0.0888$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.0888}$$

$$t_{½} = 7.8\ hours$$

$$C_{max} = C_1 \times e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.42 hours

$$C_{max} = 13.3 \times e^{0.0888(1.42)}$$

$$C_{max} = 15.1\ mg/L$$

$$C_{min} = C_2 \times e^{-k(T_{min} - T_2)}$$

T_{min}-T_2 (time between T_2 and T_{min}) = 24.16 hours

$$C_{min} = 1.9 \times e^{-0.0888(24.16)}$$

$$C_{min} = 0.22\ mg/L$$

$$AUC_{48} = \frac{C_{max} - C_{min}}{k}$$

$$AUC_{48} = \frac{15.1 - 0.22}{0.0888}$$

$$AUC_{48} = 168\ mg/L.h$$

$$New\ dose = \frac{target\ AUC}{calculated\ AUC} \times current\ dose$$

$$New\ dose = \frac{200}{168} \times 27.8$$

$$New\ dose = 33\ mg$$

Recommendation:

In this situation we would usually take the conservative approach and switch to 48 hourly dosing. A dose of 33 mg should still achieve a high C_{max} and low C_{min}, and an AUC_{48} around 200. Further concentrations should be taken after this dose as it is likely that a third dose will be required to complete the five-day course.

8. Vancomycin

8.1. What is vancomycin and how does it work?

Vancomycin is a glycopeptide antibiotic that was first isolated in the early 1950s from *Streptomyces orientali*, a bacterium discovered in a soil sample from a jungle path in Borneo. Intravenous vancomycin is used for the treatment of suspected or proven infections with Gram-positive organisms resistant to other antibiotics (e.g. MRSA, coagulase-negative staphylococci and amoxicillin-resistant enterococci), or in patients who cannot tolerate alternatives e.g. severe beta-lactam allergy.

Oral vancomycin is not absorbed and therefore cannot be used to treat systemic infections. It is, however, indicated for the treatment of *Clostridium difficile*-related diarrhoea.

Pharmacokinetics of vancomycin in healthy adults

- Oral bioavailability: 0
- Protein binding: 0.4 (0.3-0.5)
- Volume of distribution (Vd): 0.6 L/kg (0.4-0.9)
- Clearance (CL): 0.085 L/h/kg (0.08-0.09)
- Fraction excreted unchanged by the kidneys (fe): 0.9
- Half-life (t½): 6 hours

8.2. Vancomycin dosing and monitoring in adults

Refer to the CDHB vancomycin dosing guidelines. Most patients will receive vancomycin by intermittent infusion. Occasionally, Infectious Diseases may start patients on continuous infusions, which can help attain therapeutic concentrations and more consistent concentrations over time.

Monitoring

- Vancomycin concentration monitoring helps optimise outcomes with this agent, which has a narrow therapeutic index and wide interindividual variation in pharmacokinetics.
- An AUC_{24} between 400 and 600 is currently considered the optimal monitoring target for vancomycin. This aims to optimise efficacy while minimising the risk of nephrotoxicity.

Target vancomycin AUC_{24} is 400 – 600 mg/L.h:

AUC_{24}	Potential outcome
< 400*	Potential emergence of MRSA resistance (vancomycin-intermediate *S. aureus*)
≥ 400*	Efficacy target
> 600	Increased risk of nephrotoxicity

**Assumes a minimum inhibitory concentration (MIC) by broth microdilution ≤ 1 mg/L*

- An $AUC_{24} \geq 400$ mg/L.h for efficacy is largely derived from retrospective observational studies of invasive infections due to MRSA with a MIC ≤ 1 mg/L. It is not clear how it translates to other organisms or infections, but it is the best option we have currently to guide the likely effectiveness of treatment.
- An $AUC_{24} > 600$ mg/L.h increases the risk of nephrotoxicity but is usually well-tolerated in the short term.

- Dose adjustments based on AUC_{24} should consider the patient's clinical picture including infection (site, severity, improving/deteriorating) and assessment of renal function. Consult Infectious Diseases/Microbiology for severe infections (e.g. endocarditis, meningitis) or when the pathogen has an MIC $\geq$ 2 mg/L. A higher AUC_{24} (above 600 mg/L.h) or alternative agent may be needed.

Adjusting doses:

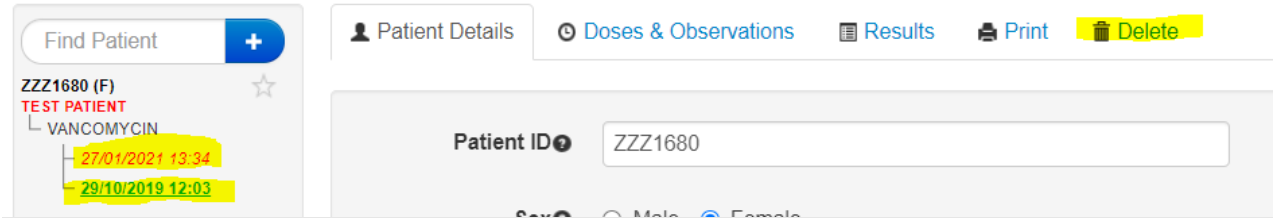
- The dosing of vancomycin can be adjusted either by reducing the dose given to the patient or by altering the dosing frequency. Generally, it is suggested that only one of these parameters is altered at any one time but there may be clinical circumstances which dictate a change to both.
- Bayesian software (e.g. NextDose) can be used to guide vancomycin dosing. This method can both predict vancomycin AUC and detect possible errant concentration results (e.g. samples taken from the same line the vancomycin was given through).
    - It is particularly important to input ALL vancomycin doses into the software programme (including the loading dose) – not just the dose that the given concentrations are based on.
    - Infusion duration for vancomycin may vary between 500 and 1000 mg/hour. It is important to enter an accurate duration when the dose is associated with a measured **peak** concentration. If the intermittent infusion time is unknown, enter a duration that relates to a rate of 750 mg/hour. For continuous infusions, enter 24 hours e.g. 2000 mg with infusion duration 24 hours.
    - If aiming for an AUC of 400–600 mg/L.h, enter "500" as the desired target, unless ID or Micro have suggested otherwise.
    - If you need help with a dose recommendation, contact your Team Leader, Sharon Gardiner, Medicines Information or Paul Chin (in that order).

8.3. Worked examples with NextDose

For each example, use Bayesian monitoring software (see 2.2 and 2.3) to determine your next dose recommendation. Worked model answers are provided.

How to use NextDose for the practice patient examples:

1. Search in NextDose for the NHI assigned to that case (note this NHI is different to that used for the model answer for the case, which are designed to be non-editable).
2. Check Patient Details (sex and date of birth) are correct.
3. Add the medicine and enter the data.
   - If the previous person working on the example did not delete their inputted data once they had finished, then the medicine will already be in the patient's record. If this is the case, you can delete their data before you start by clicking on each dataset and deleting it:



4. Once you have finished, delete your dataset/s so that the next person can start fresh.

Example 1 Patient with septic arthritis due to *S aureus*

- NHI: ZZZ1010 (use this for practising in NextDose, or see ZZZ0004 for the model answer)
- 78-year-old male
- Target AUC_{24} 400-600 mg/L.h
- Given a 2000 mg dose, then 1500 mg, then 500 mg 12-hourly before a trough concentration was taken.

https://www.nextdose.org/#/5989/34235/details

Patient Details | Doses & Observations | Results | Print | Delete

☐	21/11/2019	08:20 Height	177 cm
☐	21/08/2020	00:00 Weight	77.1 kg
☐	11/12/2020	00:00 Weight	70 kg
☐	11/12/2020	16:53 IV dose	2000 mg
☐	11/12/2020	18:10 Serum creatinine	96 umol/L
☐	12/12/2020	07:50 Serum creatinine	88 umol/L
☐	12/12/2020	08:48 IV dose	1500 mg
☐	12/12/2020	20:48 IV dose	500 mg
☐	13/12/2020	08:46 IV dose	500 mg
☐	13/12/2020	20:42 Concentration	18.1 mg/L
☐	13/12/2020	21:17 IV dose	500 mg

https://www.nextdose.org/#/5989/34225/results

Observations (dependent variables) available for calculation: Concentration
NextDose 1.7.15
Execution time: 2.0 s
Run used actual data

Perform another calculation

NextDose TCI vancomycin 5989:2021-01-22-112806_conc_holfordGAV2020_AVG
Target: AUC 500 mg/L*h per 24 hours (Css avg 20.8 mg/L) at steady state

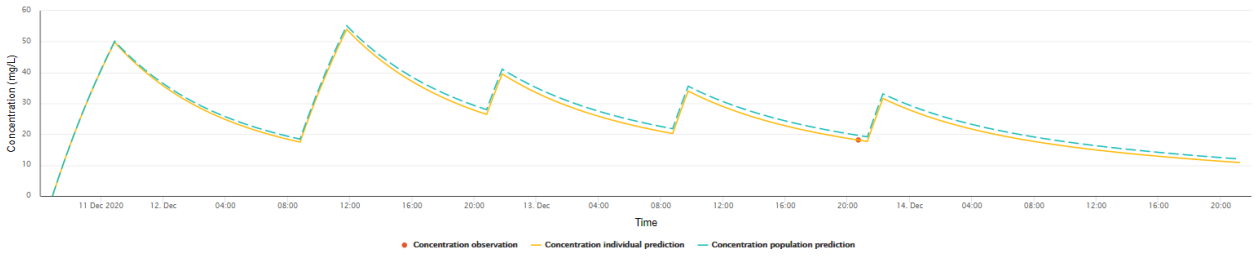
Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	528 mg every 12 hours	500 mg	13/12/2020 20:42

Proposed IV maintenance dose 528 mg every 12 hours (Bayesian)

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology □ Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
2.11	6.4	32.2	0	1	0	56.4	35.3	2.48	7.05	219	42.7	2.74	241



$$AUC\ achieved = (actual\ dose \div proposed\ dose) \times target\ AUC$$

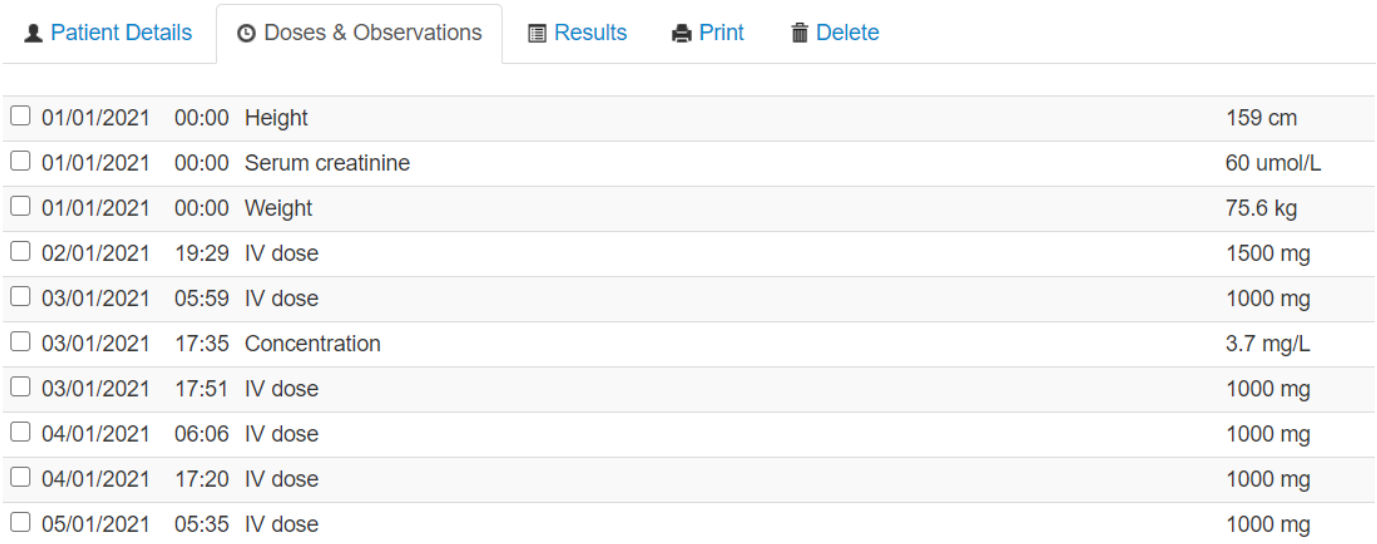
$$AUC\ achieved = (500 \div 528) \times 500 = 473 \text{ mg/L.h}$$

The pharmacist advised to continue the dose and repeat concentrations in a few days.

Example 2 Patient with septic prosthetic knee joint due to *Staphylococcus aureus* and *Corynebacterium striatum*

- NHI: ZZZ1011 (use this for practising in NextDose, or see ZZZ0005 for the model answer)
- 19-year-old female.
- Target AUC_{24} 400-600 mg/L.h
- Given a 1500 mg dose, then 1000 mg 12-hourly before a trough concentration was taken.

https://www.nextdose.org/#/6004/34377/records



https://www.nextdose.org/#/6004/34377/results

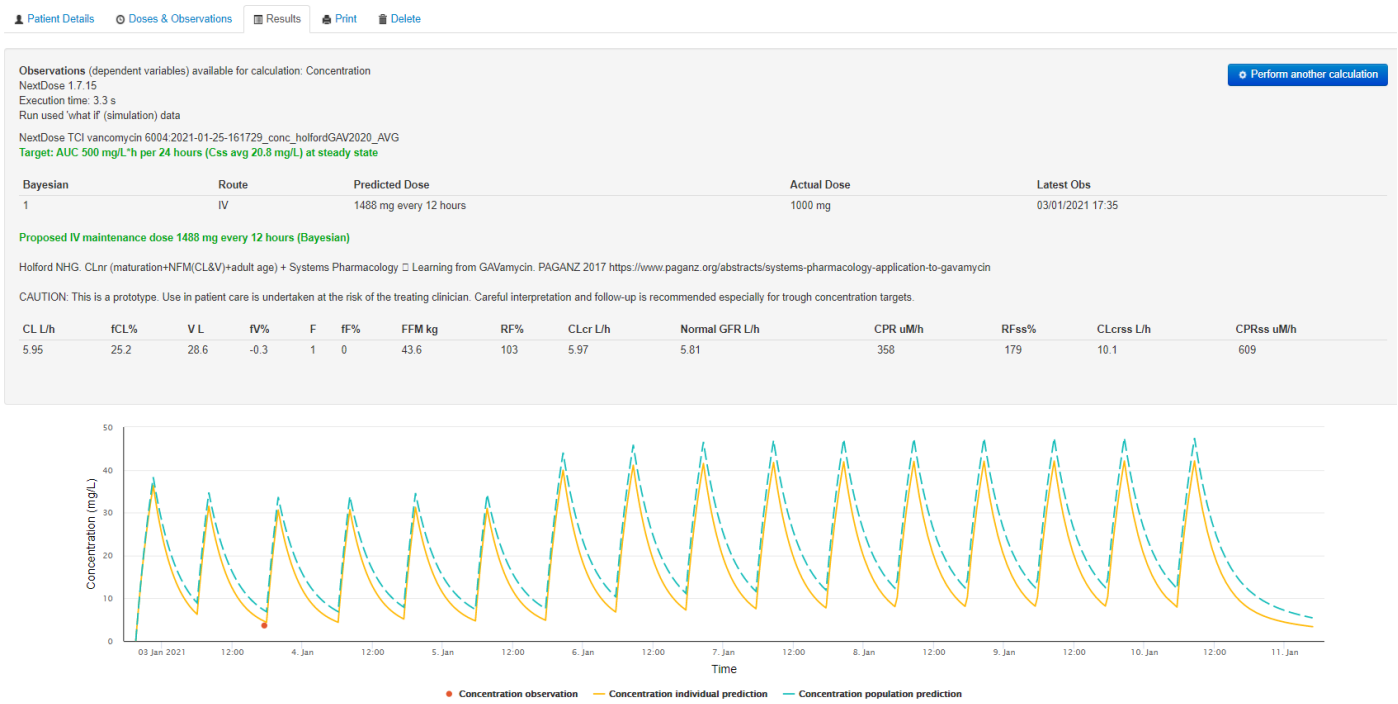
$$AUC\ achieved = (actual\ dose \div proposed\ dose) \times target\ AUC$$

$$AUC\ achieved = (1000 \div 1488) \times 500 = 336 \text{ mg/L.h}$$

The pharmacist tried a 'what-if' scenario for 1500 mg 12-hourly:

https://www.nextdose.org/#/6004/34381/records

https://www.nextdose.org/#/6004/34381/results



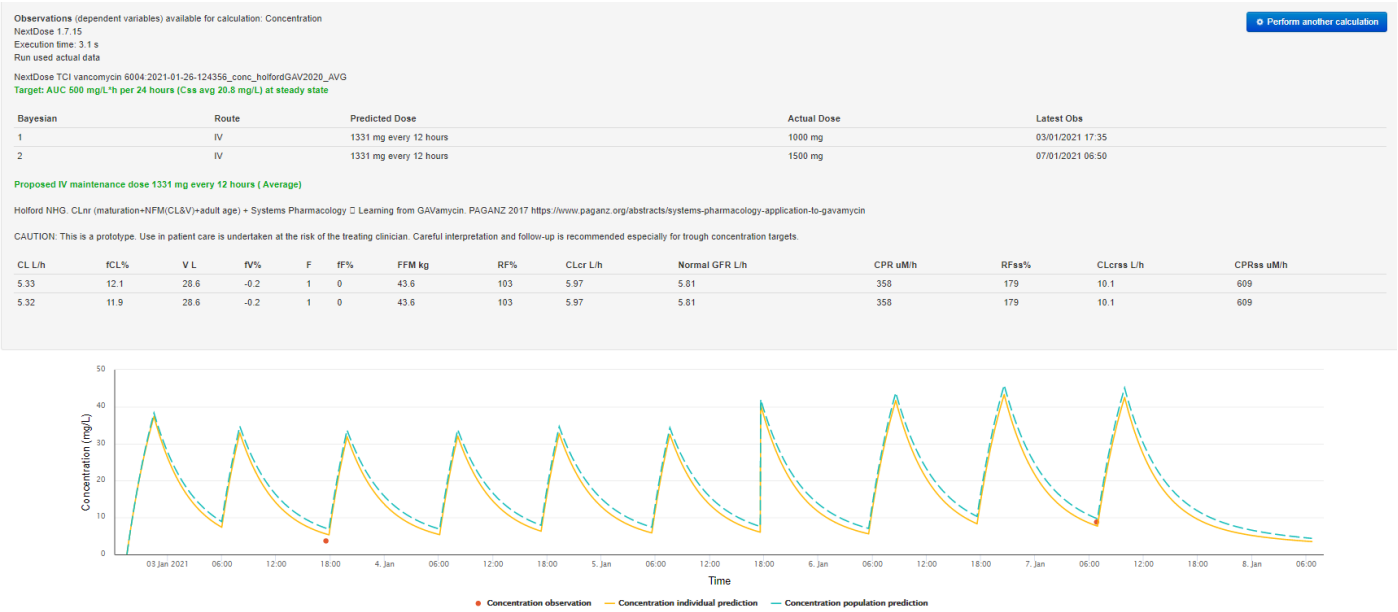
$$AUC\ achieved = (actual\ dose \div proposed\ dose) \times target\ AUC$$

$$AUC\ achieved = (1500 \div 1488) \times 500 \ = 504 \text{ mg/L.h}$$

The dose was increased to 1500 mg 12-hourly and concentrations were rechecked a few days later.

https://www.nextdose.org/#/6004/34409/records

https://www.nextdose.org/#/6004/34409/results



Observations (dependent variables) available for calculation: Concentration
NextDose 1.7.15
Execution time: 3.1 s
Run used actual data

Perform another calculation

NextDose TCI vancomycin 6004:2021-01-26-124356_conc_holfordGAV2020_AVG
Target: AUC 500 mg/L*h per 24 hours (Css avg 20.8 mg/L) at steady state

Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	1331 mg every 12 hours	1000 mg	03/01/2021 17:35
2	IV	1331 mg every 12 hours	1500 mg	07/01/2021 06:50

Proposed IV maintenance dose 1331 mg every 12 hours (Average)

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
5.33	12.1	28.6	-0.2	1	0	43.6	103	5.97	5.81	358	179	10.1	609
5.32	11.9	28.6	-0.2	1	0	43.6	103	5.97	5.81	358	179	10.1	609

$AUC\ achieved = (actual\ dose \div proposed\ dose) \times target\ AUC$

$AUC\ achieved = (1500 \div 1331) \times 500$ = 563 mg/L.h

The pharmacist opted to continue the 1500 mg 12-hourly dose, and the patient remained stable on this dose until she was discharged.

Example 3 Switching a patient from intermittent to continuous vancomycin

- NHI: ZZZ1012 (use this for practising in NextDose, or see ZZZ0006 for the model answer)
- 79-year-old male
- Target AUC_{24} 400-600 mg/L.h
- The patient had been receiving 1000 mg 12-hourly by intermittent infusion as an inpatient, and the medical team asked the pharmacist for their advice on switching to a continuous infusion for discharge. If the patient has been stable and monitored using NextDose then it is generally acceptable to recommend that the same total dose be given (i.e. 2000 mg in this case) and concentrations rechecked. If you're not sure or want to double-check you can try some 'what-if' scenarios as below.

https://www.nextdose.org/#/6012/34451/records

☐	07/09/2020	00:00	Height	170 cm
☐	07/09/2020	00:00	Serum creatinine	75 umol/L
☐	07/09/2020	00:00	Weight	90 kg
☐	07/09/2020	20:00	IV dose	2000 mg
☐	08/09/2020	08:00	IV dose	1000 mg
☐	08/09/2020	20:00	Concentration	13 mg/L
☐	08/09/2020	20:05	IV dose	1000 mg
☐	09/09/2020	08:00	IV dose	1000 mg
☐	09/09/2020	20:00	IV dose	1000 mg
☐	10/09/2020	08:00	Concentration	14 mg/L
☐	10/09/2020	08:00	Serum creatinine	65 umol/L
☐	10/09/2020	08:05	IV dose	1000 mg
☐	10/09/2020	20:00	IV dose	1000 mg

https://www.nextdose.org/#/6012/34450/results

NextDose TCI vancomycin 6012:2021-01-27-082925_conc_holfordGAV2020_AVG
Target: AUC 500 mg/L*h per 24 hours (Css avg 20.8 mg/L) at steady state

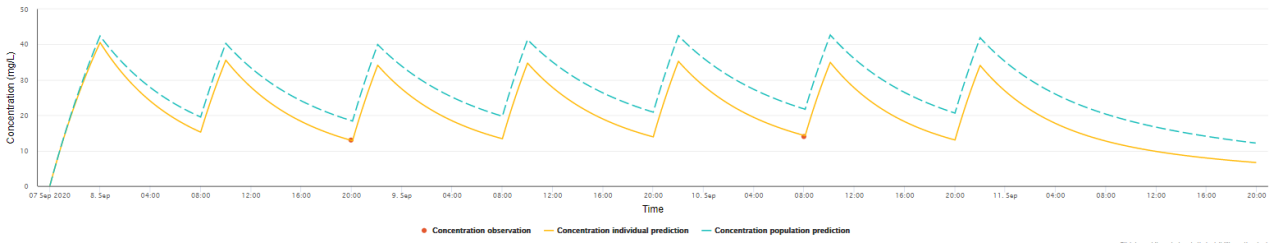
Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	869 mg every 12 hours	1000 mg	08/09/2020 20:00
2	IV	869 mg every 12 hours	1000 mg	10/09/2020 08:00

Proposed IV maintenance dose 869 mg every 12 hours (Average)

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
3.48	39	37.7	-0.3	1	0	62.2	41.3	3.13	7.59	235	56.6	4.02	302
3.48	39.1	37.7	-0.3	1	0	62.2	41.3	3.13	7.59	235	56.6	4.02	302



$$AUC\ achieved = (actual\ dose \div proposed\ dose) \times target\ AUC$$

$$AUC\ achieved = (1000 \div 869) \times 500 \ = 575 \text{ mg/L.h}$$

The pharmacist tried a 'what-if' scenario for 1500 mg 24 hourly:

https://www.nextdose.org/#/6012/34451/records

07/09/2020	00:00	Height	170 cm
07/09/2020	00:00	Serum creatinine	75 umol/L
07/09/2020	00:00	Weight	90 kg
07/09/2020	20:00	IV dose	2000 mg
08/09/2020	08:00	IV dose	1000 mg
08/09/2020	20:00	Concentration	13 mg/L
08/09/2020	20:05	IV dose	1000 mg
09/09/2020	08:00	IV dose	1000 mg
09/09/2020	20:00	IV dose	1000 mg
10/09/2020	08:00	Concentration	14 mg/L
10/09/2020	08:00	Serum creatinine	65 umol/L
10/09/2020	08:05	IV dose	1000 mg
10/09/2020	20:00	IV dose	1000 mg
11/09/2020	08:00	IV dose	1500 mg

https://www.nextdose.org/#/6012/34451/results

NextDose TCI vancomycin 6012:2021-01-27-083357_conc_holfordGAV2020_AVG
Target: AUC 500 mg/L*h per 24 hours (Css avg 20.8 mg/L) at steady state

Bayesian	Route	Predicted Dose	Actual Dose	Latest Obs
1	IV	1738 mg every 1 day	1000 mg	08/09/2020 20:00
2	IV	1738 mg every 1 day	1000 mg	10/09/2020 08:00

Proposed IV maintenance dose 1738 mg every 1 day (Average)
Warning: A predicted dose differs from actual dose by more than 50% (74%). Check input data carefully before using proposed dose.

Holford NHG. CLnr (maturation+NFM(CL&V)+adult age) + Systems Pharmacology □ Learning from GAVamycin. PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin

CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets.

CL L/h	fCL%	V L	fV%	F	fF%	FFM kg	RF%	CLcr L/h	Normal GFR L/h	CPR uM/h	RFss%	CLcrss L/h	CPRss uM/h
3.48	39	37.7	-0.3	1	0	62.2	41.3	3.13	7.59	235	56.6	4.02	302
3.48	39.1	37.7	-0.3	1	0	62.2	41.3	3.13	7.59	235	56.6	4.02	302

$AUC\ achieved = (actual\ dose \div proposed\ dose) \times target\ AUC$

$AUC\ achieved = (1500 \div 1738) \times 500$ = 431 mg/L.h

The pharmacist advised to start a continuous infusion of 1500 mg 24 hourly, with concentrations to be checked twice weekly.

8.4 Vancomycin monitoring in paediatrics

- A trough concentration taken just prior to the third or fourth dose should be 5 to 15 mg/L (10 to 15 mg/mL if the patient is under the care of the CDHB Children's Haematology Oncology Centre (CHOC)).
- Take further trough concentrations every three days or more often depending on the clinical situation.

Example

SP is a male patient with cystic fibrosis who is receiving treatment with vancomycin. He is 15 years old and weights 44 kg.

Day 1:

- 1 g twice daily IV (0830 to 1030) → next dose due at 2030
- trough concentration taken at 2030 = 3.6 mg/L

→ dose increased to 1.5 g twice daily

Day 3:

- 1.5 g twice daily IV (2030 – 2230)
- trough concentration taken at 0844 = 6.6 mg/L

→ dose changed to 800 mg 8 hourly → next dose due at 0430Day 5:

- 800 mg 8 hourly IV (1230 – 1430)
- trough concentration taken at 2030 = 7.3 mg/L

→ dose kept at 800 mg 8 hourly → next dose due at 0430

Day 8:

- 800 mg 8 hourly IV (0430 – 0630)
- trough concentration taken at 1230 = 9.7

→ dose kept at 800 mg 8 hourly

8.5 Vancomycin dosing and monitoring in neonates

Refer to the vancomycin neonatal drug information sheet on the CDHB Intranet:

Dosage / Interval

Indication1,2,3:

Creatinine micromol/L	Dose (mg/kg)	Interval (hourly)
20-39	20	12
40-49	15	12
50-59	12	12
60-79	15	18
80-100	15	24
>100	15	Check trough at 24 hrs Dose according to result

The **minimum dose** of vancomycin to be used is **10mg/kg**.

Monitoring	**First set of levels** take peak and trough levels around the dose due at 36-48 hours, depending on timing of next laboratory run. **For ongoing monitoring** recheck trough levels every 48 to 72 hours, or more frequently if renal function unstable. Recheck peak level only if specifically requested. **Pre-dose level** (trough) **5 - 15 mcg/mL** **Higher troughs** may be acceptable in severe sepsis **Peak level** (1hr after end of infusion) **25-40 mcg/mL** **Verbal dose recommendations from Pharmacist must be communicated to the prescriber and the nurse or ACNM**

Both peak and trough concentrations are taken initially, which allows calculation of an approximate half-life. The reasoning for this is that anecdotally we know that some neonates can have tricky vancomycin kinetics. Samples are usually taken around the dose due at either 36 or 48 hours.

Example

JW is a male infant born at 26 weeks who is prescribed vancomycin for suspected coagulase negative sepsis. He weighs 0.91 kg and has a plasma creatinine of 88 micromol/L.

- Dose: 15 mg/kg = 13.6 mg 24 hourly (1500)
- Day 2: trough concentration at 1425 = 2.3 mg/L
- Day 2: dose 13.6 mg; start time 1500; stop time 1610
- Day 2: peak concentration at 1720 = 30.6 mg/L

What advice would you give for the next dose due on day 3?

$$k = \frac{lnC_1 - lnC_2}{T_2 - T_1}$$

T_2-T_1 (time between T_1 and T_2) = 21.12 hours

$$k = \frac{ln30.6 - ln2.3}{21.12}$$

$$k = 0.1225$$

$$t_{½} = \frac{0.693}{k}$$

$$t_{½} = \frac{0.693}{0.1225}$$

$$t_{½} = 5.68\ hours$$

$$C_{max} = C_1\ x\ e^{k(T_1 - T_{max})}$$

T_1-T_{max} (time between T_{max} and T_1) = 1.134 hours

$$C_{max} = 13.3\ x\ e^{0.1225(1.134)}$$

$$C_{max} = 35.16\ mg/L$$

$C_{min} = C_2 \, x \, e^{-k^{(T_{min} - T_2)}}$

T_{min}-T_2 *(time between* T_2 *and* T_{min}*)* $= 0.584$ *hours*

$C_{min} = 1.9 \, x \, e^{-0.1225^{(0.584)}}$

$C_{min} = 2.1 \, mg/L$

We are aiming for a C_{min} of 5-15 mg/L and a C_{max} < 40 mg/L. Currently the C_{max} is satisfactory but the C_{min} is too low. There are two methods for increasing the C_{min}: we can either increase the dose or decrease the dose interval. We need to achieve a C_{min} that is at least three times what we have currently, but remember that now, after only one dose, we are not at steady state and if we give three times the current dose then the C_{max} is likely to go too high. The best solution is therefore to decrease the dosing interval.

If we reduce the dosing interval to 18 hours the C_{min} is still low:

$C_{18} = 2.3 \times e^{0.1225 \times (23.416 - 18)} = 4.46$ mg/L

Therefore, the best course of action would be to reduce the dosing interval to 12 hours:

$C_{12} = 2.3 \times e^{0.1225 \times (23.416 - 12)} = 9.3$ mg/L

A further trough concentration should be taken prior to the third 12 hourly dose.