TRAINING WORKBOOK
FOR THERAPEUTIC DRUG MONITORING OF AMINOGLYCOSIDES AND VANCOMYCIN

Fourth edition 2019
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. We hope you find the workbook helpful and that it fulfils your need to be accurate when making dose predictions.

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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 TCIWorks 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 a 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 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. β-lactams (with the exception of 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 (Cmax: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.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>PD index</th>
<th>PAE</th>
<th>Kill classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycosides</td>
<td>fCmax:MIC and fAUC:MIC</td>
<td>prolonged</td>
<td>concentration-dependent</td>
</tr>
<tr>
<td>β-lactams</td>
<td>ft&gt;MIC</td>
<td>minimal (except for carbapenems)</td>
<td>time-dependent</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td>fAUC:MIC and fCmax:MIC</td>
<td>prolonged</td>
<td>concentration-dependent</td>
</tr>
<tr>
<td>glycopeptides</td>
<td>fAUC:MIC</td>
<td>minimal</td>
<td>AUC-dependent</td>
</tr>
<tr>
<td>macrolides</td>
<td>fAUC:MIC</td>
<td>moderate to prolonged</td>
<td>time-dependent</td>
</tr>
</tbody>
</table>
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. As a class 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. This contrasts with β-lactams, where time above the MIC determines rate of kill.

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

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 and measured concentrations. From these, individual pharmacokinetic parameters can be estimated to optimise dose regimens to attain a specific target. Some advantages of the Bayesian approach include faster achievement of target exposure, reduced toxicity and reduced cost.

2.3. Bayesian software: TCIWorks

TCIWorks is a computer programme for Bayesian optimisation of drug dosing. It was created as a part of a joint collaboration between the Schools of Pharmacy and Information Technology and Electrical Engineering, The University of Queensland. The production team consisted of Professor Stephen Duffull, Professor Carl Kirkpatrick and Lionel Van Den Berg. The Bayesian algorithm predicts pharmacokinetic parameters in a patient, by incorporating ‘prior’ population pharmacokinetic information for a drug with patient-specific information i.e. age, sex, weight, renal function and measured drug concentrations. By combining both population and patient-specific information, these algorithms can generate accurate predictions and dosing advice.

To use TCIWorks you will need the patient’s:

- name
- NHI
- age or date of birth
- weight (kg)
- height (cm)
- plasma creatinine (mmol/L)
  - Canterbury Health Laboratories (CHL) report creatinine in micromol/L: divide by 1000 to convert to mmol/L.
- dose (mg)
- dose date and time
- infusion time
  - This is usually 30 minutes. It is important to enter the infusion time that was used in the patient for that dose, because even a difference of 10 minutes can significantly impact on predictions. Thus, entering 30 minutes when the infusion time was actually 40 minutes can lead to significantly erroneous predictions.
- blood sample times
- type of infection being treated to determine target AUC

How to use TCIWorks
- Double click on the TCIWorks icon to open the programme and the following screen will pop up:

If the patient is already in TCIWorks (you can search using the NHI or name) you can select them by clicking on their name. If they are new to TCIWorks click on the ‘Create New Patient’ button – a screen will pop up which you fill in with the patient’s surname, first name, age...
and/or date of birth (format DD/MM/YYYY), sex, height and NHI. Their name will then be added to the patient list so that they can be selected.

- Click on the ‘Select Drug for Patient’ button, which brings up a list of drugs (amikacin, endocarditis once daily gentamicin, enoxaparin, gentamicin, tobramycin and vancomycin). Select the appropriate drug from the list by clicking on the drug name and then click either the ‘Start New Course’ or ‘Continue Course’ button as appropriate).

- If continuing a course, check to see if the previous doses have been inputted and if not add them in using the following steps:
  - Click on the ‘Add Dose’ button, adjust the date and time by clicking in the boxes (you can tab to move between fields); then fill in the infusion time, patient’s weight and creatinine in mmol/L.

  CHL reports creatinine in micromol/L – divide by 1000 to convert to mmol/L
Click on the ‘Plasma Concentrations’ button, adjust the date and time and fill in the concentration for the drug. Remember to change the date and time as necessary for each concentration you add.

If the time reported on the concentration is 0000 or 0001, this very likely means that no time was written on the sample tube. Confirm the correct time with ward staff.

TCIWorks can predict how a patient would handle a drug based on no concentrations to several. The more concentrations you have, the more accurate the prediction is likely to be.

For a given drug, the prediction for a given patient is based on 1) the drug model that is implemented into TCIWorks, 2) the patient’s characteristics, and 3) the drug concentrations.

Note that in addition to these, some Bayesian methods can account for 4) the cumulative data from all the other patients in the local installation of TCIWorks i.e. the predictions change as more patients are added to the local installation.
When ticked, the predictions are based on the model (‘population prior’) for that drug, patient characteristics and drug concentrations (if measured), and do not account for the cumulative data from other patients in the local installation. When not ticked, the predictions also account for the cumulative data. The tick box is usually greyed and ticked i.e. not able to be toggled. However, TCIWorks will untick this box by default for Course 2 and subsequent Courses. When unticked, this box is able to be toggled.

- An example of the drug concentration–time curve is displayed below.

- A patient is a close fit to the prior model (red line on the curve) if the ‘Initial’ and the ‘Optimised (Bayesian)’ patient parameter estimates are similar. Initial and optimised parameter estimates will be similar if the measured concentrations are similar to the concentrations predicted by the prior model. The more similar these are, the better the fit. You
would also expect the estimated AUC (blue line generated from the patient’s concentrations) to be similar to the prior model’s AUC (red line based on the patient’s characteristics in relation to the population data).

- Discrepancies between the model predicted (initial) parameter estimates and the optimised (Bayesian) estimates are not necessarily ‘incorrect’ – unpredictable individual pharmacokinetic variability is why we need to need to measure concentrations in an individual patient. As a rule of thumb, a discrepancy of more than 20% in concentrations may be considered a ‘bad’ fit. Such discrepancies may be due to:
  - Incorrect data:
    - Sampling error (see 2.6)
    - Documentation error e.g. times or doses (either by ward staff or transcription error into TCIWorks)
    - Laboratory error in measurement of creatinine or drug concentration
  - Covariates 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 of a surgical drain: increases 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.

- An example of the ‘Predict Next Dose’ screen is displayed below. The previous dose’s AUC, C_{max} and C_{min} are displayed on the left. For gentamicin, select your target AUC at the top and adjust the start date and time as necessary by clicking in the box. For other drug models adjust the dose and click the ‘Calculate’ button to see the predicted parameters from that dose. Remember to enter the correct dose interval. You can then view a graphical representation of this dose and if you are confident the dose will be given click ‘Accept Dose’. This enters the dose in the patient’s history and saves time later as you just have to add in any relevant concentrations – if necessary you can adjust or delete this dose later on.
Once the above data are inputted into TCIWorks the following parameters will be generated, and should be recorded on the aminoglycoside monitoring form:

- AUC
- \( C_{\text{max}} \)
- \( C_{\text{min}} \): this is often erroneously rounded down to zero by TCIWorks on the Next Dose screen. For a more accurate \( C_{\text{min}} \) you can hover the mouse over the concentration-time graph to get the exact \( C_{\text{min}} \) at the time the next dose is due. Note for patients who are receiving 48 hourly dosing you will need to enter in the next dose in order for the graph to display a \( C_{\text{min}} \) at 48 hours (otherwise it will only display the \( C_{\text{min}} \) at 24 hours).

- \( \%C_l \): In adults, \( \%C_l \) is calculated using the aminoglycoside clearance (\( DrCL \) box on the monitoring form and shown on the Concentration-Time Analysis screen on TCIWorks – use the Optimised (Bayesian) value) and the calculated creatinine clearance (\( CrCL \) box on the monitoring form and shown on the Patient Display screen on TCIWorks):

\[
\%C_l = \frac{\text{drug clearance (DrCL)}}{\text{creatinine clearance (CrCL)}} \times 100
\]

The \( \%C_l \) for a 'normal' person is 70%. If the \( \%C_l \) is greater than 85% then this might indicate an additional aminoglycoside clearance mechanism, such as a surgical drain, or that there is a degree of third spacing. High \( \%C_l \) due to third spacing is due to an error in the model i.e. the model misattributes pharmacokinetic changes resulting from third space to a change in Cl, when it is actually a change in Vd.

- Adjusted Vd (L/kg): volume of distribution adjusted for weight is calculated using the volume of distribution (\( VD \) box on the monitoring form and shown on the Concentration-Time Analysis screen on TCIWorks – use the Optimised (Bayesian) value) and the dosing weight (either the ideal or total body weight, whichever is lower – DWT box on the monitoring form and shown on the Patient Display screen on TCIWorks):
\[
\text{Adjusted } Vd = \frac{VD}{\text{dosing weight}}
\]

Monitoring adjusted Vd is particularly important if a patient has third spacing as the Vd could be 50-100% greater than normal (0.4-0.5 L/kg vs. approximately 0.27 L/kg, in the normal adult patient). If Vd is high then monitoring every one to two days would be appropriate as Vd is related to the Cmax.

- \( t_{1/2} \): calculated using volume of distribution (VD box on the monitoring form and shown on the Concentration-Time Analysis screen on TCIWorks – use the Optimised (Bayesian) value) and aminoglycoside clearance (DrCL box on the monitoring form and shown on the Concentration-Time Analysis screen on TCIWorks – use the Optimised (Bayesian) value):

\[
t_{1/2} = \frac{0.693 \times VD}{\text{drug clearance (DrCl)}}
\]

Monitoring \( t_{1/2} \) is helpful when considering dosing intervals. Practically, if patients have a \( t_{1/2} \) greater than five hours or so then 48 hourly aminoglycoside dosing may provide a better Cmax while also reducing the risk of toxicity (allows more time for the aminoglycoside to be eliminated). Knowledge of \( t_{1/2} \) is also useful in cases where the patient’s \( C_{\text{min}} \) necessitates withholding the next dose. For example, if the \( C_{\text{min}} \) is 2 mg/L and the patient’s half-life is 5 hours, you could withhold the next dose for ~15 hours (3 half-lives) in order to reach a \( C_{\text{min}} \) of 0.25 mg/L before the next dose is given.

Correct calculations are important. However, it is important to interpret these in light of the patient’s characteristics (age, renal function, type of infection) before making a dose prediction. If the increase from the previous dose is very large, then consider whether a more conservative dose increase may be appropriate. It is also important to think about the practical aspect of administration such as vial size. Gentamicin and tobramycin both come as 80 mg/2 mL, while amikacin is 500 mg/2 mL.
- For patients on longer courses of aminoglycosides (e.g. Endocarditis) there is an electronic dosing record stored in TCI works called ‘Course Report’ – see below. This is a useful adjunct to the aminoglycoside dosing form, and displays AUC, $C_{max}$, $C_{min}$ (see below). Note sometimes the course report will not work (error message).

- **Observation Report**

**Drug Model**

\[ F = 1 \]

\[ Cl \text{ (L/h)} = \text{THETA}(1) \times \text{CLCR} + 0.009 \times \text{DWT} \]

\[ Vd \text{ (Litres)} = \text{THETA}(2) \times \text{DWT} \]

**Optimised Parameters**

\[ Cl \text{ (L/h)}: 4.48 \]

\[ Vd \text{ (Litres)}: 37.4 \]

**Dosing History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose (mg)</th>
<th>Inf Time (min)</th>
<th>Weight (kg)</th>
<th>SCr (mM)</th>
<th>Conc (mg/L)</th>
<th>$C_{max}$ (mg/L)</th>
<th>$C_{min}$ (mg/L)</th>
<th>AUC (mg/L)</th>
<th>Optim. Conc (mg/L)</th>
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</thead>
<tbody>
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<td>0.121</td>
<td>14.3</td>
<td>0.834</td>
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<td>5.76</td>
</tr>
</tbody>
</table>
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.

![Graph showing concentration over time with key terms: T₀, T_max, T₁, T₂, T_min, C_min, C_max, AUC, k, C₁, C₂, t₁/₂.]

<table>
<thead>
<tr>
<th>Key</th>
<th>Known values</th>
<th>Calculated values</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₀</td>
<td>infusion start time</td>
<td>C_max maximum concentration</td>
</tr>
<tr>
<td>T_max</td>
<td>time at the end of the infusion (usually 0.5 hours after T₀)</td>
<td>C_min minimum concentration</td>
</tr>
<tr>
<td>T₁</td>
<td>time of first sample</td>
<td>k elimination rate constant</td>
</tr>
<tr>
<td>T₂</td>
<td>time of second sample</td>
<td>AUC area under the curve</td>
</tr>
<tr>
<td>T_min</td>
<td>time at the end of dosing interval (usually 24 hours after T₀ unless the dosing interval is extended beyond this)</td>
<td>t₁/₂ half-life</td>
</tr>
<tr>
<td>C₁</td>
<td>sample concentration at T₁</td>
<td></td>
</tr>
<tr>
<td>C₂</td>
<td>sample concentration at T₂</td>
<td></td>
</tr>
<tr>
<td>T₂ - T₁</td>
<td>time between T₁ and T₂ (hours)</td>
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<tr>
<td>T₁ - T_max</td>
<td>time between T_max and T₁ (hours)</td>
<td></td>
</tr>
<tr>
<td>T_min - T₂</td>
<td>time between T₂ and T_min (hours)</td>
<td></td>
</tr>
</tbody>
</table>

To obtain the calculated values you will need two sample concentrations (C₁ and C₂), the infusion start and stop times (T₀ and T_max), the times that the two samples were taken (T₁ and T₂) 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)
- $T_{\text{max}}$ and $T_1$ (depicted as $T_1 - T_{\text{max}}$ in the equations below)
- $T_2$ and $T_{\text{min}}$ (depicted as $T_{\text{min}} - T_2$ 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**

$$k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1}$$

$$t_{\frac{1}{2}} = \frac{0.693}{k}$$

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

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

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

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

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

### 2.5. What happens in the laboratory and how long will results take?

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.
2.6. 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.
- 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:
  
  \[
  IBW = 50 \, kg + \left((195 \, cm - 150 \, cm) \times 0.9\right) = 90.5 \, kg 
  \]

- Females: 45 kg + 0.9 kg 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:
  
  \[
  IBW = 45 \, kg + \left((165 \, cm - 150 \, cm) \times 0.9\right) = 58.5 \, kg 
  \]
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).

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

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 takes into account the patient’s age and gender; however, it does not take into account size and thus the units are mL/min/1.73m², 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)

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

\(\alpha\) and \(\beta\) are sex and [creatinine] dependent constants.
4. Adult aminoglycosides

4.1. How is gentamicin/tobramycin dosed and monitored in adults?

All patients, except those with tetraplegia and some patients with endocarditis, 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
- $C_{\text{max}}$: 10-30 mg/L (preferably >20 mg/L)
- $C_{\text{min}}$: as close to zero as possible (<0.5 mg/L)
- $\text{AUC over 24 hours (AUC}_{24})$:

<table>
<thead>
<tr>
<th>Infection</th>
<th>Target $\text{AUC}_{24}$ (mg/L.h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>30-50</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>70</td>
</tr>
<tr>
<td>Other non-life threatening infections</td>
<td>85</td>
</tr>
<tr>
<td>Pseudomonas in cystic fibrosis patients</td>
<td>90-100</td>
</tr>
<tr>
<td>Sepsis</td>
<td>100</td>
</tr>
<tr>
<td>Other life-threatening infections</td>
<td>100</td>
</tr>
</tbody>
</table>
4.2. How is amikacin dosed and monitored in adults?

Amikacin is typically dosed once daily, although often patients with atypical mycobacterium infections are dose 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:

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Dose in mg/kg (IBW)</th>
<th>Time of second blood sample (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;66</td>
<td>15-20 depending on infection severity</td>
<td>6-14</td>
</tr>
<tr>
<td>55-66</td>
<td>12</td>
<td>8-16</td>
</tr>
<tr>
<td>41-54</td>
<td>10</td>
<td>10-18</td>
</tr>
<tr>
<td>31-40</td>
<td>8</td>
<td>12-20</td>
</tr>
<tr>
<td>20-30</td>
<td>not recommended</td>
<td>14-20</td>
</tr>
<tr>
<td>&lt;20</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- 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:

- $C_{\text{max}}$: 20-40 mg/L
- $C_{\text{min}}$: as close to zero as possible (<1 mg/L)
- $\text{AUC}_{24}$: 160-200 mg/L.h

Targets may differ for thrice weekly dosing – seek specialist advice in these cases.

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 not be 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 (AUC48) is double that of AUC24 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.

TCIWorks has a separate profile for endocarditis (Endocarditis once daily gentamicin). The target AUC24 is between 30 to 50 mg/L h and Cmin <0.5 mg/L. The Cmax 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 T1 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:

- Cmax: 6-10 mg/L
- Cmin: <1 mg/L
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 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

Example 1: Home IV cystic fibrosis patient

<table>
<thead>
<tr>
<th>Name</th>
<th>GM Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>TGM1234</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>24 years</td>
</tr>
<tr>
<td>Weight</td>
<td>47 kg</td>
</tr>
<tr>
<td>Height</td>
<td>163 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>78 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>tobramycin</td>
</tr>
<tr>
<td>Dose</td>
<td>660 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC(_{24})</td>
<td>90-100</td>
</tr>
</tbody>
</table>

GM is a cystic fibrosis patient who is currently on home IV therapy with tobramycin. 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 TCIWorks:

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

New dose = \frac{90}{151} \times 660 = 393 \text{ mg} \text{ or } \text{New dose} = \frac{100}{151} \times 660 = 437 \text{ mg}
Calculated by hand:

\[ k = \frac{lnC_1 - lnC_2}{T_2 - T_1} \]
\[ T_2-T_1 \text{ (time between } T_1 \text{ and } T_2) = 5 \text{ hours} \]

\[ k = \frac{ln39.3 - ln7.4}{5} \]
\[ k = 0.3339 \]

\[ t_{1/2} = \frac{0.693}{k} \]
\[ t_{1/2} = \frac{0.693}{0.3339} \]
\[ t_{1/2} = 2.1 \text{ hours} \]

\[ C_{max} = C_1 \times e^{k(T_1-T_{max})} \]
\[ T_1-T_{max} \text{ (time between } T_{max} \text{ and } T_1) = 0.5 \text{ hours} \]

\[ C_{max} = 39.3 \times e^{0.3339(0.5)} \]
\[ C_{max} = 46.4 \text{ mg/L} \]

\[ C_{min} = C_2 \times e^{-k(T_{min}-T_2)} \]
\[ T_{min}-T_2 \text{ (time between } T_2 \text{ and } T_{min}) = 18 \text{ hours} \]

\[ C_{min} = 7.4 \times e^{-0.3339(18)} \]
\[ C_{min} = 0.018 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{max} - C_{min}}{k} \]
\[ AUC_{24} = \frac{46.4 - 0.018}{0.3339} \]
\[ AUC_{24} = 139 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose} \]

\[ \text{New dose} = \frac{90}{139} \times 660 = 427 \text{ mg or New dose} = \frac{100}{139} \times 660 = 475 \text{ mg} \]

Recommendation:
Taking into account the 80 mg/2 mL vial size, and the fact that the patient is an outpatient and not critically unwell, reduce the dose to 400 mg. If the patient was more unwell, a dose of 440 mg would also be reasonable to obtain an AUC\textsubscript{24} closer to 100 mg/L.h. GM is a good fit to the model i.e. the actual and computer-predicted concentrations based on patient demographics are very similar. Repeat samples twice weekly as normal for home IV therapy.
Example 2 – resistant UTI – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>MB Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>TMB1234</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>86 years</td>
</tr>
<tr>
<td>Weight</td>
<td>47.5 kg</td>
</tr>
<tr>
<td>Height</td>
<td>153 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>110 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>240 mg 48 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>UTI</td>
</tr>
<tr>
<td>Target $AUC_{48}$</td>
<td>140</td>
</tr>
</tbody>
</table>

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 TCIWorks:

\[ \text{New dose} = \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose} \]

\[ \text{New dose} = \frac{140}{168} \times 240 \]

\[ \text{New dose} = 200 \text{ mg} \]

Note to obtain the AUC_{48} and C_{min} at 48 hours you will need to enter a second dose at 48 hours in order for TCIWorks to display these parameters (otherwise it reverts to 24 hour parameter values).
Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 19.8 - \ln 4.2}{13.42} \]

\[ k = 0.1155 \]

\[ t_{\frac{1}{2}} = \frac{0.693}{k} \]

\[ t_{\frac{1}{2}} = \frac{0.693}{0.1155} \]

\[ t_{\frac{1}{2}} = 6 \text{ hours} \]

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

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

\[ C_{\text{max}} = 19.8 \times e^{0.1155(0.5)} \]

\[ C_{\text{max}} = 21 \text{ mg/L} \]

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

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

\[ C_{\text{min}} = 4.2 \times e^{-0.1155(33.58)} \]

\[ C_{\text{min}} = 0.09 \text{ mg/L} \]

\[ AUC_{48} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{48} = \frac{21 - 0.09}{0.1155} \]

\[ AUC_{48} = 181 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{140}{181} \times 240 = 186 \text{ mg} \]

Recommendation:
Reduce the dose to 200 mg 48 hourly, given the \( AUC_{48} \) is currently above the target. The hand calculations and TCIWorks are a close match in this example. The main reason for this is that the patient is a good fit to the model (i.e. the patient’s actual aminoglycoside concentrations and computer-predicted aminoglycoside concentrations based on patient demographics are very similar). Repeat samples after this dose.
Example 3 – UTI in a paraplegic patient – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>OA Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>TOA1234</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>60 years</td>
</tr>
<tr>
<td>Weight</td>
<td>94 kg</td>
</tr>
<tr>
<td>Height</td>
<td>169 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>78 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>290 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>UTI</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>70</td>
</tr>
</tbody>
</table>

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 TCIWorks:

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

New dose = \frac{70}{53} \times 290

New dose = 383 \text{ mg}
Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\[ T_2-T_1 \text{ (time between } T_1 \text{ and } T_2) = 10.42 \text{ hours} \]

\[ k = \frac{\ln 9.8 - \ln 0.9}{10.42} \]

\[ k = 0.2292 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.2292} \]

\[ t_{1/2} = 3 \text{ hours} \]

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

\[ T_1-T_{\text{max}} \text{ (time between } T_{\text{max}} \text{ and } T_1) = 0.58 \text{ hours} \]

\[ C_{\text{max}} = 9.8 \times e^{0.2292(0.58)} \]

\[ C_{\text{max}} = 11.2 \text{ mg/L} \]

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

\[ T_{\text{min}}-T_2 \text{ (time between } T_2 \text{ and } T_{\text{min}}) = 12.5 \text{ hours} \]

\[ C_{\text{min}} = 0.9 \times e^{-0.2292(12.5)} \]

\[ C_{\text{min}} = 0.05 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{11.2 - 0.05}{0.2292} \]

\[ AUC_{24} = 49 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose} \]

\[ \text{New dose} = \frac{70}{49} \times 290 \]

\[ \text{New dose} = 414 \text{ mg} \]

**Recommendation:**

Increase dose to 380 mg, as the AUC_{24} is low enough to allow a substantial dose increase i.e. resulting in a higher C_{\text{max}} and greater bacterial kill. The hand calculations and TCIWorks are a relatively close match in this example. As the infection is a simple UTI a conservative dose increase is a reasonable option. Repeat samples after this dose.
Example 4 – Home IV cystic fibrosis

<table>
<thead>
<tr>
<th>Name</th>
<th>CL Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHl</td>
<td>TCL1234</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>36 years</td>
</tr>
<tr>
<td>Weight</td>
<td>70 kg</td>
</tr>
<tr>
<td>Height</td>
<td>183 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>98 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>amikacin</td>
</tr>
<tr>
<td>Dose</td>
<td>1100 mg 24 hourly over 60 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>180</td>
</tr>
</tbody>
</table>

CL is a patient with cystic fibrosis who is receiving IV amikacin. What would you now recommend?
\[
\text{New dose} = \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose}
\]

\[
\text{New dose} = \frac{180}{211} \times 1100
\]

\[
\text{New dose} = 938 \text{ mg}
\]
Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 49.7 - \ln 2.2}{9.25} \]

\[ k = 0.3370 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = 0.693 \]

\[ t_{1/2} = 0.3370 \]

\[ t_{1/2} = 2.1 \text{ hours} \]

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

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

\[ C_{\text{max}} = 49.7 \times e^{0.3370(0.75)} \]

\[ C_{\text{max}} = 64 \text{ mg/L} \]

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

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

\[ C_{\text{min}} = 2.2 \times e^{-0.3370(13)} \]

\[ C_{\text{min}} = 0.03 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{64 - 0.03}{0.3370} \]

\[ AUC_{24} = 190 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose} \]

\[ \text{New dose} = \frac{180}{190} \times 1100 \]

\[ \text{New dose} = 1042 \text{ mg} \]

Recommendation:
Reduce dose to 1000 mg. The hand calculations and TCIWorks are a relatively close match in this example. The predicted AUC_{24} is slightly high and, therefore, a small dose reduction is recommended to get the AUC_{24} below the maximum of 200 mg/L.h. Generally in patients with cystic fibrosis you want to aim for the highest dose possible without overly increasing the risk of toxicity.
Example 5 – Endocarditis

<table>
<thead>
<tr>
<th>Name</th>
<th>MW Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>TCI5678</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>26 years</td>
</tr>
<tr>
<td>Weight</td>
<td>85 kg</td>
</tr>
<tr>
<td>Height</td>
<td>181 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>86 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>200 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>30-50</td>
</tr>
</tbody>
</table>

MW is receiving synergistic gentamicin along with benzylpenicillin for treatment of endocarditis. What would you recommend for her next dose?
New dose = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose}

New dose = \frac{50}{49} \times 200

New dose = 204 mg
Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 6 - \ln 2.9}{5.25} \]

\[ k = 0.1385 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.1385} \]

\[ t_{1/2} = 5 \text{ hours} \]

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

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

\[ C_{\text{max}} = 6 \times e^{0.1385(1.5)} \]

\[ C_{\text{max}} = 7.4 \text{ mg/L} \]

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

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

\[ C_{\text{min}} = 2.9 \times e^{-0.1385(16.75)} \]

\[ C_{\text{min}} = 0.29 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{7.4 - 0.29}{0.1385} \]

\[ AUC_{24} = 51 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose} \]

\[ \text{New dose} = \frac{50}{51} \times 200 \]

\[ \text{New dose} = 196 \text{ mg} \]

Recommendation:

MW has achieved an \( AUC_{24} \) close to the maximum target of 50 mg/L.h, and is a reasonably close fit to the TCIWorks model. Suggest continuing on the same dose of 200 mg 24 hourly. Repeat concentrations in three days or so.
4.8. Examples to work through

Example 1 – cystic fibrosis – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1111</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>28 years</td>
</tr>
<tr>
<td>Weight</td>
<td>61 kg</td>
</tr>
<tr>
<td>Height</td>
<td>185 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>48 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>tobramycin</td>
</tr>
<tr>
<td>Dose</td>
<td>680 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>80-100</td>
</tr>
</tbody>
</table>

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 TCIWorks:

<table>
<thead>
<tr>
<th>%Cl</th>
<th>adjusted Vd (L/kg)</th>
<th>C_{max} (mg/L)</th>
<th>C_{min} (mg/L)</th>
<th>t_{1/2} (hours)</th>
<th>AUC_{24} (mg/L.h)</th>
</tr>
</thead>
</table>

Calculated by hand:

Recommendation:
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 TCIWorks:

<table>
<thead>
<tr>
<th>%Cl</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>adjusted Vd (L/kg)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (mg/L)</td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hours)</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;24&lt;/sub&gt; (mg/L.h)</td>
<td></td>
</tr>
</tbody>
</table>

Calculated by hand:

Recommendation:
Example 3 – urosepsis – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1113</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>57 years</td>
</tr>
<tr>
<td>Weight</td>
<td>89.9 kg</td>
</tr>
<tr>
<td>Height</td>
<td>183 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>109 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>420 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Urosepsis</td>
</tr>
<tr>
<td>Target $AUC_{24}$</td>
<td>85-95</td>
</tr>
</tbody>
</table>

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 TCIWorks:

<table>
<thead>
<tr>
<th>%Cl</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>adjusted Vd (L/kg)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{min}}$ (mg/L)</td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (hours)</td>
<td></td>
</tr>
<tr>
<td>$\text{AUC}_{24}$ (mg/L.h)</td>
<td></td>
</tr>
</tbody>
</table>

Calculated by hand:

Recommendation:
Example 4 – suspected peritonitis – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1114</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>64 years</td>
</tr>
<tr>
<td>Weight</td>
<td>91 kg</td>
</tr>
<tr>
<td>Height</td>
<td>180 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>80 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>240 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Peritonitis</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;24&lt;/sub&gt;</td>
<td>85-95</td>
</tr>
</tbody>
</table>

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 TCIWorks:

<table>
<thead>
<tr>
<th>%Cl</th>
<th>adjusted Vd (L/kg)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (mg/L)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (hours)</th>
<th>AUC&lt;sub&gt;24&lt;/sub&gt; (mg/L.h)</th>
</tr>
</thead>
</table>

#### Calculated by hand:

#### Recommendation:
4.9. Troubleshooting

What to do if the patient is not a good fit to the Bayesian model i.e. there are discrepancies between the model predicted (initial) parameter estimates and the optimised (Bayesian) estimates that are greater than 20%:

1. Check the data that has been inputted into TCIWorks is correct – often a bad fit is the result of transcription errors in times, concentrations, doses, weight, height, creatinine etc.
   i) Where height has not been entered, TCIWorks will sometimes calculate a negative prediction as per graph below. This can occur when the drug model is dependent upon ideal body weight.

2. Double check documentation on lab form (especially sample times as per the example below).

3. Infusion time: TCIWorks will often display strange results if the infusion time entered is anything other than 30 minutes (e.g. 40 minutes). Usually in these cases the predicted $C_{\text{max}}$ is displayed as being less than the actual measured $C_1$. Try entering 30 minutes in these cases.

4. Sampling error e.g. specimen taken from same line antibiotic infused in: see examples below in which much higher than expected concentrations were reported. In these cases it is generally better to obtain another sample before advising on the dose.
5. Extremes of body weight: TCIWorks will often display strange results if the patient is very low or high body weight.

6. Patient variables: changing patient clinical characteristics during the aminoglycoside course e.g. removal of a drain, improvement in condition, change in renal function etc. can affect the patient’s clearance and volume of distribution and hence lead to unexpected results compared to previous dosing.
4.10. TCIWorks bugs

1. TCIWorks often rounds the predicted $C_{\text{min}}$ down to zero on the Predict Next Dose screen. You can obtain a more accurate figure by looking at the time-concentration graph instead (hover over $T_{\text{min}}$). Note this might entail entering a future dose as if it had been administered e.g. in the case of 48 hourly dosing.

2. If the prior and estimated curves completely overlap, and the estimated does not appear to have taken the measured concentration(s) into account, TCIWorks may be performing erroneously - try changing dosing or concentration times by one minute, as this sometimes fixes the problem.

3. The observation report sometimes cannot be generated and will display an error message. This is unpredictable; try removing a dose or concentration to limit the number of data points entered to obtain the report.
5. Paediatric aminoglycosides

5.1. How is gentamicin/tobramycin dosed and monitored 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
As a general rule of thumb 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. As a consequence of this they are generally monitored twice weekly, on Thursdays and Sundays. TCIWorks does not currently contain a reliable paediatric aminoglycoside model. Therefore, 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:

<table>
<thead>
<tr>
<th>Infection</th>
<th>Target AUC&lt;sub&gt;24&lt;/sub&gt; (mg/L.h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>70</td>
</tr>
<tr>
<td>Other non-life threatening infections</td>
<td>85</td>
</tr>
<tr>
<td>Pseudomonas in cystic fibrosis patients</td>
<td>90-100</td>
</tr>
<tr>
<td>Sepsis</td>
<td>100</td>
</tr>
<tr>
<td>Other life-threatening infections</td>
<td>100</td>
</tr>
</tbody>
</table>

### 5.2. How is amikacin dosed and monitored 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<sub>24</sub> range for amikacin is 160 to 200 mg/L. For severe infections aim for an AUC<sub>24</sub> of up to 200 mg/L. C<sub>max</sub> should be approximately double that of gentamicin/tobramycin i.e. 20 to 40 mg/L or more and C<sub>min</sub> should be as low as possible and <1 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 using home IV therapy. 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

<table>
<thead>
<tr>
<th>Name</th>
<th>LK Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>TLK1234</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>5.25 kg</td>
</tr>
<tr>
<td>Creatinine</td>
<td>normal</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>60 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>UTI</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;24&lt;/sub&gt;</td>
<td>70</td>
</tr>
</tbody>
</table>

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 22 - \ln 4.9}{7} \]

\[ k = 0.2145 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.2145} \]

\[ t_{1/2} = 3.2 \text{ hours} \]

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

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

\[ C_{\text{max}} = 22 \times e^{0.2145(0.5)} \]

\[ C_{\text{max}} = 24.5 \text{ mg/L} \]

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

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

\[ C_{\text{min}} = 2.2 \times e^{-0.2145(16)} \]

\[ C_{\text{min}} = 0.16 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{24.5 - 0.16}{0.2145} \]

\[ AUC_{24} = 113 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{70}{113} \times 60 \]

\[ \text{New dose} = 37 \text{ mg} \]

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

<table>
<thead>
<tr>
<th>Name</th>
<th>GI Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHl</td>
<td>TGI1234</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>15 years</td>
</tr>
<tr>
<td>Weight</td>
<td>55.9 kg</td>
</tr>
<tr>
<td>Height</td>
<td>156 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>57 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>tobramycin</td>
</tr>
<tr>
<td>Dose</td>
<td>440 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>90-100</td>
</tr>
</tbody>
</table>

![Concentration vs. Time Graph](image)

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 33.5 - \ln 1}{10.33} \]

\( k = 0.3399 \)

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.3399} \]

\( t_{1/2} = 2 \) hours

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

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

\[ C_{\text{max}} = 33.5 \times e^{0.3399(0.58)} \]

\( C_{\text{max}} = 40.8 \) mg/L

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

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

\[ C_{\text{min}} = 1 \times e^{-0.3399(12.58)} \]

\( C_{\text{min}} = 0.014 \) mg/L

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{40.8 - 0.014}{0.3399} \]

\( AUC_{24} = 120 \) mg/L h

New dose = \( \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \)

New dose = \( \frac{90}{120} \times 440 = 330 \) mg 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

<table>
<thead>
<tr>
<th>Name</th>
<th>FF Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>TFF1234</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>12 years</td>
</tr>
<tr>
<td>Weight</td>
<td>40.2 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>53 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>amikacin</td>
</tr>
<tr>
<td>Dose</td>
<td>600 mg 24 hourly over 60 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;24&lt;/sub&gt;</td>
<td>170</td>
</tr>
</tbody>
</table>

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\[ T_2 - T_1 \text{ (time between } T_1 \text{ and } T_2) = 8.75 \text{ hours} \]

\[ k = \frac{\ln 34.6 - \ln 1.4}{8.75} \]

\[ k = 0.3666 \]

\[ t_{\frac{1}{2}} = \frac{0.693}{k} \]

\[ t_{\frac{1}{2}} = \frac{0.693}{0.3666} \]

\[ t_{\frac{1}{2}} = 1.89 \text{ hours} \]

\[ C_{\text{max}} = C_1 e^{k(T_1 - T_{\text{max}})} \]

\[ T_1 - T_{\text{max}} \text{ (time between } T_{\text{max}} \text{ and } T_1) = 1 \text{ hour} \]

\[ C_{\text{max}} = 34.6 e^{0.3666(1)} \]

\[ C_{\text{max}} = 49.9 \text{ mg/L} \]

\[ C_{\text{min}} = C_2 e^{-k(T_{\text{min}} - T_2)} \]

\[ T_{\text{min}} - T_2 \text{ (time between } T_2 \text{ and } T_{\text{min}}) = 12.75 \text{ hours} \]

\[ C_{\text{min}} = 1.4 e^{-0.3666(12.75)} \]

\[ C_{\text{min}} = 0.013 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{49.9 - 0.013}{0.3666} \]

\[ AUC_{24} = 136 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{170}{136} \times 600 \]

\[ \text{New dose} = 750 \text{ mg} \]

Recommendation:
Increase dose to 750 mg. The AUC_{24} is below target; a dose increase (and resultant C_{\text{max}} increase) will increase efficacy.
Example 3 continued – Six weeks of amikacin therapy for a patient with cystic fibrosis

<table>
<thead>
<tr>
<th>Name</th>
<th>FF Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHU</td>
<td>TFF1234</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>12 years</td>
</tr>
<tr>
<td>Weight</td>
<td>40.2 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>53 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>amikacin</td>
</tr>
<tr>
<td>Dose</td>
<td>750 mg 24 hourly over 60 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC_{24}</td>
<td>170</td>
</tr>
</tbody>
</table>

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

Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 32.5 - \ln 1.5}{9.25} \]

\( k = 0.3325 \)

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.3325} \]

\( t_{1/2} = 2.08 \text{ hours} \)

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

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

\[ C_{\text{max}} = 32.5 \times e^{0.3325(1)} \]

\( C_{\text{max}} = 45.3 \text{ mg/L} \)

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

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

\[ C_{\text{min}} = 1.5 \times e^{-0.3325(12.75)} \]

\( C_{\text{min}} = 0.022 \text{ mg/L} \)

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{45.3 - 0.022}{0.3325} \]

\( AUC_{24} = 136 \text{ mg/L.h} \)

New dose = \( \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \)

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ZZZ1111</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>5 years</td>
</tr>
<tr>
<td>Weight</td>
<td>30 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>34 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>240 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>abdominal abscess</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;24&lt;/sub&gt;</td>
<td>90</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1115</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>9 years</td>
</tr>
<tr>
<td>Weight</td>
<td>35 kg</td>
</tr>
<tr>
<td>Height</td>
<td>140 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>72 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>tobramycin</td>
</tr>
<tr>
<td>Dose</td>
<td>220 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target $AUC_{24}$</td>
<td>90-100</td>
</tr>
</tbody>
</table>

![Graph of concentration over time](graph.png)

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ZZZ1112</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>2 years</td>
</tr>
<tr>
<td>Weight</td>
<td>15.5 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>30 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>220 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Cholangitis</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;24&lt;/sub&gt;</td>
<td>85-95</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>ABC1116</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>15 years</td>
</tr>
<tr>
<td>Weight</td>
<td>53.8 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>61 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>tobramycin</td>
</tr>
<tr>
<td>Dose</td>
<td>380 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>90-100</td>
</tr>
</tbody>
</table>

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 on the basis of 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. How are aminoglycosides dosed 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, Cmax, Cmin 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>
<thead>
<tr>
<th>Dosage/Interval</th>
<th>Weight (kg)</th>
<th>First Dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose to be given as shown in table. Subsequent doses to be advised by Pharmacy</td>
<td>&gt; 1500g</td>
<td>10mg/kg</td>
<td>6hrs</td>
</tr>
<tr>
<td></td>
<td>750 - 1500g</td>
<td>7.5mg/kg</td>
<td>6hrs</td>
</tr>
<tr>
<td></td>
<td>&lt;750g</td>
<td>Use cefotaxime unless treating pseudomonas or an organism sensitive only to gentamicin. If need to use gentamicin give 8mg/kg/dose</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>IV by infusion pump over 30 minutes</td>
<td>Do not give IM (see Neonatal Handbook)</td>
<td></td>
</tr>
</tbody>
</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. How are aminoglycosides monitored in neonates?

**Monitoring targets for gentamicin**
- $C_{\text{max}}: \geq 12 \text{ mg/L}$
- $C_{\text{min}}: <0.5 \text{ mg/L}$
- $\text{AUC}_{60}: 250 \text{ mg/L.h}$

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](#):

<table>
<thead>
<tr>
<th>Monitoring and Further Doses</th>
<th>Levels required – Gentamicin week 1 of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 48 \text{ hrs}$ ie: 1 dose</td>
<td>No levels in most instances but see below for exceptions$^*$</td>
</tr>
<tr>
<td>$\geq 5 \text{ days}$</td>
<td>Dose 1</td>
</tr>
<tr>
<td>1$^\text{st}$ Level – When decision is made to give $\geq 1$ dose:</td>
<td></td>
</tr>
<tr>
<td>Call lab to retrospectively analyse a level or the CCRP blood test taken after gentamicin was given</td>
<td></td>
</tr>
<tr>
<td>If there is no blood in the lab to do this then take a level immediately</td>
<td></td>
</tr>
<tr>
<td>2$^\text{nd}$ Level - At 24-48hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Further Doses</strong></td>
<td></td>
</tr>
<tr>
<td>No levels required if it is a 5 day course</td>
<td></td>
</tr>
<tr>
<td>Pharmacist advises if more levels are required if $\geq 7$ day course and if they are taken:</td>
<td></td>
</tr>
<tr>
<td>1$^\text{st}$ Level – At 1hr after completion of the dose</td>
<td></td>
</tr>
<tr>
<td>2$^\text{nd}$ Level – At 24-36hrs</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Name</th>
<th>LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>27 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>1.3 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>9.65 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>empirical for respiratory distress</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;60&lt;/sub&gt;</td>
<td>250</td>
</tr>
</tbody>
</table>

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

Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 14.3 - \ln 2.6}{23} \]

\( k = 0.0741 \)

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.0741} \]

\( t_{1/2} = 9.35 \) hours

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

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

\[ C_{\text{max}} = 14.3 \times e^{0.0741(1.08)} \]

\[ C_{\text{max}} = 15.5 \text{ mg/L} \]

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

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

\[ C_{\text{min}} = 2.6 \times e^{-0.0741(35.42)} \]

\[ C_{\text{min}} = 0.19 \text{ mg/L} \]

\[ AUC_{60} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{60} = \frac{15.5 - 0.19}{0.0741} \]

\[ AUC_{60} = 207 \text{ mg/L.h} \]

New dose = \( \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose} \)

New dose = \( \frac{250}{207} \times 9.65 \text{ mg} = 11.6 \text{ mg} \)

Recommendation:
LC has received sufficient gentamicin (i.e. \( C_{\text{max}} > 12 \text{ mg/L} \)) and is clearing it adequately (\( C_{\text{min}} < 0.5 \text{ mg/L} \)). 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

<table>
<thead>
<tr>
<th>Name</th>
<th>BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>41 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>4.05 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>40.5 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>suspected sepsis</td>
</tr>
<tr>
<td>Target AUC$_{60}$</td>
<td>250</td>
</tr>
</tbody>
</table>

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

Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 26.9 - \ln 1.2}{24} \]

\( k = 0.1296 \)

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.1296} \]

\( t_{1/2} = 5.35 \) hours

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

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

\[ C_{\text{max}} = 26.9 \times e^{0.1296(1.83)} \]

\( C_{\text{max}} = 34.1 \text{ mg/L} \)

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

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

\[ C_{\text{min}} = 1.2 \times e^{-0.1296(33.67)} \]

\( C_{\text{min}} = 0.015 \text{ mg/L} \)

\[ AUC_{60} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{60} = \frac{33.67 - 0.015}{0.1296} \]

\( AUC_{60} = 260 \text{ mg/L.h} \)

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{250}{260} \times 40.5 \]

\[ \text{New dose} = 38 \text{ mg} \]

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

<table>
<thead>
<tr>
<th>Name</th>
<th>BS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>38 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>2.98 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>29.8 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>empirical respiratory distress</td>
</tr>
<tr>
<td>Target AUC$_{60}$</td>
<td>250</td>
</tr>
</tbody>
</table>

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

**Calculated by hand:**

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 19.9 - \ln 2.4}{24.17} \]

\[ k = 0.0875 \]

\[ t_{\frac{1}{2}} = \frac{0.693}{k} \]

\[ t_{\frac{1}{2}} = \frac{0.693}{0.0875} \]

\[ t_{\frac{1}{2}} = 7.92 \text{ hours} \]

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

\( T_{\text{max}} - T_2 \) (time between \( T_2 \) and \( T_{\text{max}} \)) = 1.33 hours

\[ C_{\text{max}} = 19.9 \times e^{0.0875(1.33)} \]

\[ C_{\text{max}} = 22.4 \text{ mg/L} \]

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

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

\[ C_{\text{min}} = 2.4 \times e^{-0.0875(34)} \]

\[ C_{\text{min}} = 0.13 \text{ mg/L} \]

\[ AUC_{60} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{60} = \frac{22.4 - 0.13}{0.0875} \]

\[ AUC_{60} = 255 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{250}{255} \times 29.8 \]

\[ \text{New dose} = 29 \text{ mg} \]

**Recommendation:**

BS has achieved a good peak and a low \( C_{\text{min}} \). 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

<table>
<thead>
<tr>
<th>Name</th>
<th>FG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>29 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>0.77 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>5.7 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>suspected sepsis</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;60&lt;/sub&gt;</td>
<td>250</td>
</tr>
</tbody>
</table>

![Graph showing concentration over time](image)

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

Calculated by hand:

\[
k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1}
\]

\[T_2 - T_1 \ (time \ between \ T_1 \ and \ T_2) = 24.17 \ hours\]

\[k = \frac{\ln 12.6 - \ln 3}{24.17} \]

\[k = 0.0593\]

\[t_{\frac{1}{2}} = \frac{0.693}{k}\]

\[t_{\frac{1}{2}} = \frac{0.693}{0.0593} = 11.7 \ hours\]

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

\[T_2 - T_{\text{max}} \ (time \ between \ T_{\text{max}} \ and \ T_2) = 1.33 \ hours\]

\[C_{\text{max}} = 12.6 \times e^{0.0593(1.33)}\]

\[C_{\text{max}} = 13.8 \ mg/L\]

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

\[T_{\text{min}} - T_2 \ (time \ between \ T_2 \ and \ T_{\text{min}}) = 34 \ hours\]

\[C_{\text{min}} = 3 \times e^{-0.0593(34)}\]

\[C_{\text{min}} = 0.4 \ mg/L\]

\[AUC_{60} = \frac{C_{\text{max}} - C_{\text{min}}}{k}\]

\[AUC_{60} = \frac{13.8 - 0.4}{0.0593} = 226 \ mg/L \cdot h\]

\[New \ dose = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose}\]

\[New \ dose = \frac{250}{226} \times 5.7\]

\[New \ dose = 6.3 \ mg\]

Recommendation:

FG has achieved a \(C_{\text{max}} > 12 \ mg/L\), a \(C_{\text{min}} < 0.5 \ mg/L\), 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

<table>
<thead>
<tr>
<th>Name</th>
<th>JB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>31 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>1.55 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>15.5 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>suspected sepsis</td>
</tr>
<tr>
<td>Target AUC(_{60})</td>
<td>250</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Name</th>
<th>JC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>39 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>3.6 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>36 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>meconium aspiration</td>
</tr>
<tr>
<td>Target AUC$_{60}$</td>
<td>250</td>
</tr>
</tbody>
</table>

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?

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Answer

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

<table>
<thead>
<tr>
<th>Name</th>
<th>BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>33 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>1.48 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>11.1 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>empirical respiratory distress</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;60&lt;/sub&gt;</td>
<td>250</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Name</th>
<th>BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>36 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>2.78 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>27.8 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>suspected sepsis</td>
</tr>
<tr>
<td>Target $AUC_{60}$</td>
<td>250</td>
</tr>
</tbody>
</table>

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?
Recommendation:
7. Answers

7.1. Adults

Example 1 – cystic fibrosis – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1111</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>28 years</td>
</tr>
<tr>
<td>Weight</td>
<td>61 kg</td>
</tr>
<tr>
<td>Height</td>
<td>185 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>48 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>tobramycin</td>
</tr>
<tr>
<td>Dose</td>
<td>680 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>80-100</td>
</tr>
</tbody>
</table>

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 TCIWorks:

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

New dose = \frac{90}{96} \times 680 = 638 mg
Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\[ T_2 - T_1 \text{ (time between } T_1 \text{ and } T_2) = 7.08 \text{ hours} \]

\[ k = \frac{\ln 22.7 - \ln 2.6}{7.08} \]

\[ k = 0.3061 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.3061} \]

\[ t_{1/2} = 2.3 \text{ hours} \]

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

\[ T_1 - T_{\text{max}} \text{ (time between } T_{\text{max}} \text{ and } T_1) = 0.5 \text{ hours} \]

\[ C_{\text{max}} = 22.7 \times e^{0.3061(0.5)} \]

\[ C_{\text{max}} = 26.5 \text{ mg/L} \]

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

\[ T_{\text{min}} - T_2 \text{ (time between } T_2 \text{ and } T_{\text{min}}) = 15.92 \text{ hours} \]

\[ C_{\text{min}} = 2.6 \times e^{-0.3061(15.92)} \]

\[ C_{\text{min}} = 0.02 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{26.5 - 0.02}{0.3061} \]

\[ AUC_{24} = 87 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{90}{87} \times 680 = 703 \text{ mg} \]

Recommendation:

No change needed as the AUC_{24} is within range (80-100). The hand calculations and TCIWorks are a close match in this example. The main reason for this is probably due to the patient being a close fit to the model i.e. the patient’s actual aminoglycoside concentrations and computer-predicted aminoglycoside concentrations based on patient demographics are very similar. Repeat samples twice weekly.
Example 2 – suspected perforated appendix – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHl</td>
<td>ABC1112</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>37 years</td>
</tr>
<tr>
<td>Weight</td>
<td>83.3 kg</td>
</tr>
<tr>
<td>Height</td>
<td>187 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>77 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>400 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Perforated appendix</td>
</tr>
<tr>
<td>Target $AUC_{24}$</td>
<td>85</td>
</tr>
</tbody>
</table>

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 TCIWorks:

\[
\text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose}
\]

\[
\text{New dose} = \frac{85}{49} \times 400
\]

\[
\text{New dose} = 694 \text{ mg}
\]
Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\[ T_2 - T_1 \text{ (time between } T_1 \text{ and } T_2 \text{) = 8.5 hours} \]

\[ k = \frac{\ln 9.8 - \ln 0.8}{8.5} \]

\[ k = 0.2948 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.2948} \]

\[ t_{1/2} = 2.4 \text{ hours} \]

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

\[ T_1 - T_{\text{max}} \text{ (time between } T_{\text{max}} \text{ and } T_1 \text{) = 1 hour} \]

\[ C_{\text{max}} = 9.8 \times e^{0.2958(1)} \]

\[ C_{\text{max}} = 13.2 \text{ mg/L} \]

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

\[ T_{\text{min}} - T_2 \text{ (time between } T_2 \text{ and } T_{\text{min}} \text{) = 14 hours} \]

\[ C_{\text{min}} = 0.8 \times e^{-0.2958(14)} \]

\[ C_{\text{min}} = 0.013 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{13.2 - 0.013}{0.2958} \]

\[ AUC_{24} = 45 \text{ mg/L. h} \]

\[ \text{New dose} = \frac{\text{target } AUC \times \text{ current dose}}{\text{calculated } AUC} \]

\[ \text{New dose} = \frac{85}{45} \times 400 \]

\[ \text{New dose} = 756 \text{ mg} \]

**Recommendation:**

Increase dose to 720 mg. The AUC\(_{24}\) at 46 is well below the target of 85. This allows us to increase the dose and therefore \(C_{\text{max}}\), which increases bacterial kill, without overly increasing the risk of toxicity. The hand calculations and TCIWorks are a relatively close match in this example. Repeat sample after next dose.
Example 3 – urosepsis – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1113</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>57 years</td>
</tr>
<tr>
<td>Weight</td>
<td>88.9 kg</td>
</tr>
<tr>
<td>Height</td>
<td>183 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>109 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>420 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Urosepsis</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>85-95</td>
</tr>
</tbody>
</table>

Test is a patient with urosepsis who is receiving IV gentamicin. This is his third dose of gentamicin, what would you now recommend?
New dose = \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose}

New dose = \frac{90}{93} \times 420

New dose = 406 mg
Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 17.9 - \ln 1.9}{10} \]

\( k = 0.2243 \)

\[ t_{1/2} = \frac{0.693}{k} \]

\( t_{1/2} = 0.693 \times \frac{1}{0.2243} \)

\( t_{1/2} = 3.1 \text{ hours} \)

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

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

\[ C_{\text{max}} = 17.9 \times e^{0.2243(0.5)} \]

\( C_{\text{max}} = 20 \text{ mg/L} \)

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

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

\[ C_{\text{min}} = 1.9 \times e^{-0.2243(13)} \]

\( C_{\text{min}} = 0.1 \text{ mg/L} \)

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{20 - 0.1}{0.2243} \]

\( AUC_{24} = 89 \text{ mg/L.h} \)

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{90}{89} \times 420 \]

\( \text{New dose} = 425 \text{ mg} \)

Recommendation:
Continue with the same dose. The AUC_{24} is within the target range, the \( C_{\text{max}} \) and \( C_{\text{min}} \) are adequate and the hand calculations and TCIWorks are similar, meaning that the patient is a reasonable fit to the model. Repeat samples after two doses.
Example 4 – suspected peritonitis – in hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1114</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>64 years</td>
</tr>
<tr>
<td>Weight</td>
<td>91 kg</td>
</tr>
<tr>
<td>Height</td>
<td>180 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>80 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>240 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>peritonitis</td>
</tr>
<tr>
<td>Target AUC$_{24}$</td>
<td>85-95</td>
</tr>
</tbody>
</table>

![Concentration-time graph](image)

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 TCIWorks:**

\[
\text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose}
\]

\[
\text{New dose} = \frac{90}{53} \times 240
\]

\[
\text{New dose} = 408 \text{ mg}
\]

**Calculated by hand:**
We only have one blood sample so this is not possible.

**Recommendation:**
Increase dose to 400 mg. The AUC_{24} is well below the target range. This allows us to increase the dose and therefore the C_{max}, which increases bacterial kill, without overly increasing the risk of toxicity. It is impossible to hand calculate pharmacokinetic parameters with only one concentration. However, TCIWorks can estimate these using population data and fit this patient’s characteristics to that data. Remember that the estimate is likely to be less accurate as we have fewer samples. Repeat samples after this dose so we can try and get a more accurate prediction.
### Example 1 – gentamicin for an abdominal abscess

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ZZZ1111</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>5 years</td>
</tr>
<tr>
<td>Weight</td>
<td>30 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>34 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>240 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>abdominal abscess</td>
</tr>
<tr>
<td>Target $\text{AUC}_{24}$</td>
<td>90</td>
</tr>
</tbody>
</table>

---

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\[ T_2-T_1 \text{ (time between } T_1 \text{ and } T_2) = 11.33 \text{ hours} \]

\[ k = \frac{\ln 16.7 - \ln 0.3}{11.33} \]

\[ k = 0.3548 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.3548} \]

\[ t_{1/2} = 1.95 \text{ hours} \]

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

\[ T_1-T_{\text{max}} \text{ (time between } T_{\text{max}} \text{ and } T_1) = 0.83 \text{ hours} \]

\[ C_{\text{max}} = 16.7 \times e^{0.3548(0.83)} \]

\[ C_{\text{max}} = 22.4 \text{ mg/L} \]

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

\[ T_{\text{min}}-T_2 \text{ (time between } T_2 \text{ and } T_{\text{min}}) = 11.33 \text{ hours} \]

\[ C_{\text{min}} = 0.3 \times e^{-0.3548(11.33)} \]

\[ C_{\text{min}} = 0.005 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{22.4 - 0.005}{0.3548} \]

\[ AUC_{24} = 63 \text{ mg/L. h} \]

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{90}{63} \times 240 = 343 \text{ mg} \]

Recommendation:

Increase to 280 mg. The patient has achieved a good \( C_{\text{max}} \) and low \( C_{\text{min}} \), 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

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1115</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>9 years</td>
</tr>
<tr>
<td>Weight</td>
<td>35 kg</td>
</tr>
<tr>
<td>Height</td>
<td>140 cm</td>
</tr>
<tr>
<td>Creatinine</td>
<td>72 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>tobramycin</td>
</tr>
<tr>
<td>Dose</td>
<td>220 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;24&lt;/sub&gt;</td>
<td>90-100</td>
</tr>
</tbody>
</table>

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 20.2 - \ln 1.6}{10.58} \]

\( k = 0.240 \)

\[ t_{\frac{1}{2}} = \frac{0.693}{k} \]

\( t_{\frac{1}{2}} = \frac{0.693}{0.240} \)

\( t_{\frac{1}{2}} = 2.89 \text{ hours} \)

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

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

\( \text{C}_{\text{max}} = 20.2 \times e^{0.240(1)} \)

\( \text{C}_{\text{max}} = 25.7 \text{ mg/L} \)

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

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

\( \text{C}_{\text{min}} = 1.6 \times e^{-0.240(11.92)} \)

\( \text{C}_{\text{min}} = 0.09 \text{ mg/L} \)

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{25.7 - 0.09}{0.240} \]

\( AUC_{24} = 107 \text{ mg.h/L} \)

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\( \text{New dose} = \frac{95}{107} \times 220 = 195 \text{ mg} \)

Recommendation:

Give the same dose (220 mg). The patient has achieved a good \( C_{\text{max}} \) and has a low \( C_{\text{min}} \), 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

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ZZZ1112</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>2 years</td>
</tr>
<tr>
<td>Weight</td>
<td>15.5 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>30 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>220 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Cholangitis</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;24&lt;/sub&gt;</td>
<td>85-95</td>
</tr>
</tbody>
</table>

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 34.2 - \ln 1.4}{8} \]

\( k = 0.399 \)

\[ t_{\frac{1}{2}} = \frac{0.693}{k} \]

\[ t_{\frac{1}{2}} = \frac{0.693}{0.399} \]

\( t_{\frac{1}{2}} = 1.74 \) hours

\[ C_{\text{max}} = C_1 e^{k(T_1 - T_{\text{max}})} \]

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

\[ C_{\text{max}} = 34.2 e^{0.399(0.75)} \]

\( C_{\text{max}} = 46 \text{ mg/L} \)

\[ C_{\text{min}} = C_2 e^{-k(T_{\text{min}} - T_2)} \]

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

\[ C_{\text{min}} = 1.4 e^{-0.399(14.75)} \]

\( C_{\text{min}} = 0.004 \text{ mg/L} \)

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{46 - 0.004}{0.399} \]

\( AUC_{24} = 115 \text{ mg.h/L} \)

\[ \text{New dose} = \frac{\text{target AUC}}{\text{calculated AUC}} x \text{current dose} \]

\[ \text{New dose} = \frac{90}{115} \times 220 = 172 \text{ mg} \]

Recommendation:
The \( C_{\text{max}} \) and \( AUC_{24} \) are both high but the \( C_{\text{min}} \) 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 \( C_{\text{max}} \) of 33-36. Repeat concentrations on the next dose.
Example 4 – cystic fibrosis with pseudomonas

<table>
<thead>
<tr>
<th>Name</th>
<th>Test Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHI</td>
<td>ABC1116</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>15 years</td>
</tr>
<tr>
<td>Weight</td>
<td>53.8 kg</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>61 micromol/L</td>
</tr>
<tr>
<td>Drug</td>
<td>tobramycin</td>
</tr>
<tr>
<td>Dose</td>
<td>380 mg 24 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>Pseudomonas in lungs</td>
</tr>
<tr>
<td>Target $\text{AUC}_{24}$</td>
<td>90-100</td>
</tr>
</tbody>
</table>

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

Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 17.6 - \ln 0.8}{10.58} \]

\[ k = 0.2921 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.2921} \]

\[ t_{1/2} = 2.37 \text{ hours} \]

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

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

\[ C_{\text{max}} = 17.6 \times e^{0.2921(1.5)} \]

\[ C_{\text{max}} = 27 \text{ mg/L} \]

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

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

\[ C_{\text{min}} = 0.8 \times e^{-0.2921(10.92)} \]

\[ C_{\text{min}} = 0.03 \text{ mg/L} \]

\[ AUC_{24} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{24} = \frac{27 - 0.03}{0.2921} \]

\[ AUC_{24} = 92 \text{ mg/L.h} \]

New dose = \( \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \)

\[ \text{New dose} = \frac{95}{92} \times 380 \]

\[ \text{New dose} = 392 \text{ mg} \]

Recommendation:

Give the same dose (380 mg). The \( AUC_{24}, C_{\text{max}} \) and \( C_{\text{min}} \) 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

<table>
<thead>
<tr>
<th>Name</th>
<th>JB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>31 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>1.55 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>15.5 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>suspected sepsis</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;60&lt;/sub&gt;</td>
<td>250</td>
</tr>
</tbody>
</table>

![Graph showing concentration over time](image-url)  

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

Calculated by hand:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\[ T_2 - T_1 \text{ (time between } T_1 \text{ and } T_2 \text{) } = 24.5 \text{ hours} \]

\[ k = \frac{\ln 21.1 - \ln 2.6}{24.5} \]

\[ k = 0.0855 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.0855} \]

\[ t_{1/2} = 8.1 \text{ hours} \]

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

\[ T_1 - T_{\text{max}} \text{ (time between } T_{\text{max}} \text{ and } T_1 \text{) } = 1.17 \text{ hours} \]

\[ C_{\text{max}} = 21.1 \times e^{0.0855(1.17)} \]

\[ C_{\text{max}} = 23 \text{ mg/L} \]

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

\[ T_{\text{min}} - T_2 \text{ (time between } T_2 \text{ and } T_{\text{min}} \text{) } = 33.83 \text{ hours} \]

\[ C_{\text{min}} = 2.6 \times e^{-0.0855(33.83)} \]

\[ C_{\text{min}} = 0.14 \text{ mg/L} \]

\[ AUC_{60} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{60} = \frac{23 - 0.14}{0.0855} \]

\[ AUC_{60} = 267 \text{ mg/L.h} \]

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{250}{267} \times 15.5 = 14.5 \text{ mg} \]

Recommendation:

JB has achieved a good \( C_{\text{max}} \) and low \( C_{\text{min}} \). However, the \( AUC_{60} \) is higher than the maximum of 250. A small dose reduction should still achieve a good \( C_{\text{max}} \) and low \( C_{\text{min}} \), 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

<table>
<thead>
<tr>
<th>Name</th>
<th>JC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>39 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>3.6 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>36 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>meconium aspiration</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;60&lt;/sub&gt;</td>
<td>250</td>
</tr>
</tbody>
</table>

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 26.5 - \ln 2.4}{22.08} \]

\[ k = 0.1088 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.1088} \]

\[ t_{1/2} = 6.37 \text{ hours} \]

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

\( T_1-T_{\text{max}} \) (time between \( T_{\text{max}} \) and \( T_1 \)) = 2.25 hours

\[ C_{\text{max}} = 26.5 \times e^{0.1088(2.25)} \]

\[ C_{\text{max}} = 33.9 \text{ mg/L} \]

\[ C_{\text{min}} = C_2 \times e^{-k(T_{\text{max}}-T_2)} \]

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

\[ C_{\text{min}} = 2.4 \times e^{-0.1088(35.17)} \]

\[ C_{\text{min}} = 0.05 \text{ mg/L} \]

\[ AUC_{60} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{60} = \frac{33.9 - 0.05}{0.1088} \]

\[ AUC_{60} = 311 \text{ mg/L.h} \]

New dose = \( \frac{\text{target AUC}}{\text{calculated AUC}} \times \text{current dose} \)

\[ \text{New dose} = \frac{250}{311} \times 36 \]

\[ \text{New dose} = 28 \text{ mg} \]

Recommendation:
JC has achieved a high \( C_{\text{max}} \) and a low \( C_{\text{min}} \); 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

<table>
<thead>
<tr>
<th>Name</th>
<th>BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>33 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>1.48 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>11.1 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>empirical respiratory distress</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;60&lt;/sub&gt;</td>
<td>250</td>
</tr>
</tbody>
</table>

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

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

\[ k = \frac{\ln 15.3 - \ln 0.7}{24.25} \]

\( k = 0.1272 \)

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.1272} \]

\( t_{1/2} = 5.45 \text{ hours} \)

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

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

\[ C_{\text{max}} = 15.3 \times e^{0.1272(1.83)} \]

\( C_{\text{max}} = 19.3 \text{ mg/L} \)

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

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

\[ C_{\text{min}} = 0.7 \times e^{-0.1272(33.42)} \]

\( C_{\text{min}} = 0.01 \text{ mg/L} \)

\[ AUC_{60} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{60} = \frac{19.3 - 0.01}{0.1272} \]

\( AUC_{60} = 152 \text{ mg/L.h} \)

New dose = \( \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \)

New dose = \( \frac{250}{152} \times 11.1 = 18.2 \text{ mg} \)

Recommendation:

BM has a good \( C_{\text{max}} \) and low \( C_{\text{min}} \) 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

<table>
<thead>
<tr>
<th></th>
<th>BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>BF</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>36 weeks</td>
</tr>
<tr>
<td>Weight</td>
<td>2.78 kg</td>
</tr>
<tr>
<td>Drug</td>
<td>gentamicin</td>
</tr>
<tr>
<td>Dose</td>
<td>27.8 mg 60 hourly over 30 minutes</td>
</tr>
<tr>
<td>Infection</td>
<td>suspected sepsis</td>
</tr>
<tr>
<td>Target AUC&lt;sub&gt;60&lt;/sub&gt;</td>
<td>250</td>
</tr>
</tbody>
</table>

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:

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\[ T_2 - T_1 \text{ (time between } T_1 \text{ and } T_2) = 21.92 \text{ hours} \]

\[ k = \frac{\ln 13.3 - \ln 1.9}{21.92} \]

\[ k = 0.0888 \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693}{0.0888} \]

\[ t_{1/2} = 7.8 \text{ hours} \]

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

\[ T_1 - T_{\text{max}} \text{ (time between } T_{\text{max}} \text{ and } T_1) = 1.42 \text{ hours} \]

\[ C_{\text{max}} = 13.3 \times e^{0.0888(1.42)} \]

\[ C_{\text{max}} = 15.1 \text{ mg/L} \]

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

\[ T_{\text{min}} - T_2 \text{ (time between } T_2 \text{ and } T_{\text{min}}) = 36.16 \text{ hours} \]

\[ C_{\text{min}} = 1.9 \times e^{-0.0888(36.16)} \]

\[ C_{\text{min}} = 0.08 \text{ mg/L} \]

\[ AUC_{60} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]

\[ AUC_{60} = \frac{15.1 - 0.08}{0.0888} \]

\[ AUC_{60} = 169 \text{ mg.h/L} \]

\[ \text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose} \]

\[ \text{New dose} = \frac{250}{169} \times 27.8 \]

\[ \text{New dose} = 41 \text{ mg} \]

Recommendation:

BF has achieved a reasonable C_{\text{max}}, with a low C_{\text{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_{\text{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.
\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\( T_{2-T_1} \) (time between \( T_1 \) and \( T_2 \)) = 21.92 hours

\[ k = \frac{\ln 13.3 - \ln 1.9}{21.92} \]

\[ k = 0.0888 \]

\[ t_{\frac{1}{2}} = \frac{0.693}{k} \]

\[ t_{\frac{1}{2}} = \frac{0.693}{0.0888} \]

\[ t_{\frac{1}{2}} = 7.8 \text{ hours} \]

\[ C_{\text{max}} = C_1 \times e^{k(T_{1-T_{\text{max}}})} \]

\( T_{1-T_{\text{max}}} \) (time between \( T_{\text{max}} \) and \( T_1 \)) = 1.42 hours

\[ C_{\text{max}} = 13.3 \times e^{0.0888(1.42)} \]

\[ C_{\text{max}} = 15.1 \text{ mg/L} \]

\[ C_{\text{min}} = C_2 \times e^{-k(T_{\text{max}-T_2})} \]

\( T_{\text{max}-T_2} \) (time between \( T_2 \) and \( T_{\text{max}} \)) = 24.16 hours

\[ C_{\text{min}} = 1.9 \times e^{-0.0888(24.16)} \]

\[ C_{\text{min}} = 0.22 \text{ mg/L} \]

\[ AUC_{48} = \frac{C_{\text{max}} - C_{\text{min}}}{k} \]
\[
AUC_{48} = \frac{15.1 - 0.22}{0.0888}
\]

\[
AUC_{48} = 168 \text{ mg/L.h}
\]

\[
\text{New dose} = \frac{\text{target } AUC}{\text{calculated } AUC} \times \text{current dose}
\]

\[
\text{New dose} = \frac{200}{168} \times 27.8
\]

\[
\text{New dose} = 33 \text{ mg}
\]

**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 \(C_{\text{max}}\) and low \(C_{\text{min}}\), 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. How is vancomycin dosed and monitored 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.

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. Remember that the clearance of vancomycin is directly proportional to renal function. Practically, this means that if you reduce the dose by 25% this will result in a reduction in trough blood concentrations by around 25%, assuming stable renal function and steady state conditions. The decision as to whether you decrease the dose or increase the interval will be based on the individual patient. If you are unsure then seek advice from a more senior pharmacist.
TCIWorks can also be used to guide vancomycin dosing. As well as predicting vancomycin AUC, using TCIWorks can detect possible errant concentration results (e.g. samples taken from the same line the vancomycin was given through). For most indications an AUC$_{24}$ of around 400 mg/L.h is recommended. It is particularly important to input ALL vancomycin doses into TCIWorks (including the loading dose) – not just the dose that the given concentrations are based on.

**Example**

MD is a 59 year old male with an infected left femur who is being treated with vancomycin. He weighs 90 kg, has a plasma creatinine of 92 micromol/L and is 180 cm tall. He has been given a loading dose of 2000 mg.

**Day 1 (maintenance dose):**
- 750 mg twice daily IV (0800 to 0930) → next dose due at 2000
- trough concentration taken at 2000 = 13.1 mg/L
  → dose increased to 1000 mg twice daily

**Day 3:**
- 1000 mg twice daily IV
- trough concentration = 16.7 mg/L
  → dose kept at 1000 mg twice daily (in range)

8.3. How is vancomycin monitored 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 0430
Day 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

8.4. How is vancomycin dosed and monitored in neonates?
Refer to the vancomycin neonatal drug information sheet on the CDHB Intranet:

<table>
<thead>
<tr>
<th>Dosage / Interval</th>
<th>Indication1,2,3:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>Dose</td>
</tr>
<tr>
<td>micromol/L</td>
<td>(mg/kg)</td>
</tr>
<tr>
<td>20-39</td>
<td>20</td>
</tr>
<tr>
<td>40-49</td>
<td>15</td>
</tr>
<tr>
<td>50-59</td>
<td>12</td>
</tr>
<tr>
<td>60-79</td>
<td>15</td>
</tr>
<tr>
<td>80-100</td>
<td>15</td>
</tr>
<tr>
<td>&gt;100</td>
<td>15</td>
</tr>
</tbody>
</table>

The minimum dose of vancomycin to be used is 10mg/kg.

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>First set of levels take peak and trough levels around the dose due at 36-48 hours, depending on timing of next laboratory run.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Pre-dose level (trough) 5 - 15 mcg/mL Higher troughs may be acceptable in severe sepsis</td>
</tr>
<tr>
<td></td>
<td>Peak level (1hr after end of infusion) 25-40 mcg/mL</td>
</tr>
<tr>
<td></td>
<td>Verbal dose recommendations from Pharmacist must be communicated to the prescriber and the nurse or ACNM</td>
</tr>
</tbody>
</table>

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?

\[ k = \frac{\ln C_1 - \ln C_2}{T_2 - T_1} \]

\( T_2-T_1 \) (time between \( T_1 \) and \( T_2 \)) = 21.12 hours

\[ k = \frac{\ln 30.6 - \ln 2.3}{21.12} \]

\[ k = 0.1225 \]

\[ t_{\frac{1}{2}} = \frac{0.693}{k} \]

\[ t_{\frac{1}{2}} = \frac{0.693}{0.1225} = 5.68 \text{ hours} \]

\[ C_{\text{max}} = C_1 e^{k(T_1-T_{\text{max}})} \]

\( T_1-T_{\text{max}} \) (time between \( T_{\text{max}} \) and \( T_1 \)) = 1.134 hours

\[ C_{\text{max}} = 13.3 \times e^{0.1225(1.134)} \]

\[ C_{\text{max}} = 35.16 \text{ mg/L} \]

\[ C_{\text{min}} = C_2 e^{-k(T_{\text{min}}-T_2)} \]

\( T_{\text{min}}-T_2 \) (time between \( T_2 \) and \( T_{\text{min}} \)) = 0.584 hours

\[ C_{\text{min}} = 1.9 \times e^{-0.1225(0.584)} \]

\[ C_{\text{min}} = 2.1 \text{ mg/L} \]

We are aiming for a \( C_{\text{min}} \) of 5-15 mg/L and a \( C_{\text{max}} < 40 \text{ mg/L} \). Currently the \( C_{\text{max}} \) is satisfactory but the \( C_{\text{min}} \) is too low. There are two methods for increasing the \( C_{\text{min}} \): we can either increase the dose or decrease the dose interval. We need to achieve a \( C_{\text{min}} \) that is at least three times what we have currently, but remember that at the moment, after only one dose, we are not at steady state and if we give three times the current dose then the \( C_{\text{max}} \) 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 \( C_{\text{min}} \) is still low:

\[ C_{18} = 2.3 \times e^{0.1225 \times [23.416 - 18]} = 4.46 \text{ mg/L} \]

Therefore the best course of action would be to reduce the dosing interval to 12 hours:

\[ C_{12} = 2.3 \times e^{0.1225 \times [23.416 - 12]} = 9.3 \text{ mg/L} \]

A further trough level should be taken prior to the third 12 hourly dose.
Appendix 1: CDHB Monitoring forms
(Available in the Clinical Pharmacology common drive or Pharmacy SharePoint)

Adult aminoglycoside monitoring form

G:\Division\CPharm\COMMON\Drug Info\TDM\Aminoglycosides\Monitoring forms\Aminoglycoside monitoring Form_adults_endocarditis_TCIWorks.doc

http://cdhbdelaymedicalandsurgical/CDHBPharmacyTeam/Forms/Aminoglycoside%20monitoring%20Form_adults.doc

| Name: | | Nhs Number: | | | | | | |
|-------|-------|---------------|-------|-------|-------|-------|-------|
| Ward: | Team: | Target AUC: | Gender: | Age: | Dwell: | Other AEC: | |

Aminoglycoside Monitoring Form – Once Daily Dosing:  

<table>
<thead>
<tr>
<th>Dosing / Sampling</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (h)</td>
<td>Concentration (mg/L)</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>72</td>
<td>-</td>
</tr>
</tbody>
</table>

Endocarditis Gentamicin / Gentamicin / Tobramycin / Amikacin

<table>
<thead>
<tr>
<th>Indication:</th>
<th>Sensitivities:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg):</td>
<td>Height (cm):</td>
</tr>
</tbody>
</table>

Notes:

- TDM Done for 5 days post surgery.  
- Serum levels should be measured in the morning prior to the next dose.  
- Stop medication if serum levels are abnormal.  
- Aminoglycosides should be given in a dose of 10mg/kg every 12 hours.  
- Target AUC: 6-10 mg*h/mL.  
- Maintenance dose: 10% of initial dose on day 2.  
- No need for initial loading dose.  
- Aminoglycosides should be given every 12 hours.  
- Target AUC: 6-10 mg*h/mL.  
- Monitoring should be repeated on day 3.  
- TDM Done for 5 days post surgery.  
- Serum levels should be measured in the morning prior to the next dose.  
- Stop medication if serum levels are abnormal.  
- Aminoglycosides should be given in a dose of 10mg/kg every 12 hours.  

Aminoglycoside monitoring Form_adults_endocarditis_TCIWorks.doc

http://cdhbdelaymedicalandsurgical/CDHBPharmacyTeam/Forms/Aminoglycoside%20monitoring%20Form_adults.doc
### Aminoglycoside Monitoring Form (the manual pediatric, neonatal & adult SBC)

**Medication:** Gentamicin / Tobramycin

<table>
<thead>
<tr>
<th>Name:</th>
<th>NH4 Number:</th>
<th>Weight:</th>
<th>Height:</th>
<th>cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ward:</th>
<th>Team:</th>
<th>Indications:</th>
<th>Sensitivities:</th>
<th>Other Abuse:</th>
<th>DOB:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing / Sampling</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Calculation

\[
\text{AUC} = \frac{\text{Cmax} \times \text{tmax}}{\text{Vd}}
\]

\[
\text{t}_{1/2} = \frac{\ln(2) \times \text{Vd}}{\text{Cl}}
\]

**Example:**

\[
\text{AUC} = \frac{5 \times 6000}{1000} = 30 \text{ mg/h/L}
\]

\[
\text{t}_{1/2} = \frac{\ln(2) \times 1000}{500} = 4 \text{ hours}
\]
Neonatal aminoglycoside monitoring form


Canterbury District Health Board

Neonatal Gentamicin Monitoring Form

<table>
<thead>
<tr>
<th>Prescriber/Nurse to Complete</th>
<th>Pharmacist to Complete or Advise by Phone and NICU Staff Can Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOsing</td>
<td>Sampling</td>
</tr>
<tr>
<td>Date</td>
<td>Date and Interval</td>
</tr>
<tr>
<td>Gentamicin Infusion Start Time</td>
<td>Gentamicin Infusion Stop Time</td>
</tr>
<tr>
<td>Time of Peak Level</td>
<td>Peak Level</td>
</tr>
<tr>
<td>Time of Mid-Interval Level</td>
<td>Mid-Interval Level</td>
</tr>
<tr>
<td>h24</td>
<td>Cmax</td>
</tr>
<tr>
<td>AUC</td>
<td>Recommendations</td>
</tr>
<tr>
<td>New Dose</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Working weight:</th>
<th>Indication:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use a new sheet for each gentamicin course and keep in the notes.</td>
<td>Accurate entry of drug infusion times is imperative for dose predictions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>NEw Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Work hours

- The Neonatal Unit pharmacist ( pager 5009) will provide help with gentamicin monitoring and dose predictions between 6.00am-4.30pm Mon-Fri.

After hours

- Contact the on-call pharmacist via the Christchurch Hospital operator. Verbal predictions need to be "witnessed" by two staff members.

Notes:

- This dosing strategy aims to maximise the effectiveness of gentamicin via concentration rather than time-dependent bacterial kill and to minimise toxicity and resistance.
- \( t_{1/2} \) (half-life) – neonates with very long gentamicin half-lives, i.e. > 12 h should not be given subsequent doses (i.e. the Consultant as alternative antibiotics may not be available).
- \( C_{\text{max}} \) (true peak concentration) – needs to be > 12 mg/L. Gentamicin works best with a high \( C_{\text{max}} \) and a very low \( C_{\text{mean}} \).
- \( C_{\text{min}} \) (true trough concentration – at the end of the dosing interval) – needs to be as low as possible and ideally should be < 4.5 mg/L.
- \( AUC \) (area under the concentration-time curve) – should be 250 mg/h/L for a 12hr dosing interval.