

Aminoglycoside Dosing in Adults

Department of Health

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An electronic version of this document is available at www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/safety

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1. Statement

Aminoglycosides are highly effective agents for the treatment of Gram-negative infections. However, their use is associated with significant toxicities including vestibular, auditory and renal toxicity. To maximise efficacy and safety, extended duration (once daily or less frequent) dosing is now the recommended method for dosing aminoglycosides in most clinical settings. These guidelines have been developed by the Queensland Health Statewide Aminoglycoside Working Party to assist clinicians to safely manage aminoglycoside therapy. This guideline covers both empiric short-term (less than 72 hours) use and directed therapy with aminoglycosides and is in concordance with Therapeutic Guidelines – Antibiotic 15th edition.

2. Scope

This guideline provides information for all Queensland Health employees (permanent, temporary and casual) and all organisations and individuals acting as its agents (including Visiting Medical Officers and other partners, contractors, consultants and volunteers). This guideline is for adults and adolescents 18 years and older using aminoglycosides for either empiric, directed or synergistic therapy.

This guideline does not provide guidance on the use of aminoglycosides in:

- surgical prophylaxis (refer to local guidelines if available or eTG [Topic | Therapeutic Guidelines](#)),
- peritonitis in peritoneal dialysis patients (refer to statewide clinical pathway [Peritonitis in PD patients](#))
- use of amikacin in mycobacterial infections (refer to the Tuberculosis Expert Advisory Group (TEAG) guideline [TEAG guidelines](#)).
- patients with cystic fibrosis (refer to individual patient care plan or tertiary referral centre).
- paediatric patients (refer to the Aminoglycoside dosing in paediatric patients guideline [CHQ Paediatric Antimicrobial guidelines](#))

Aminoglycosides are contraindicated in patients who have previously experienced vestibular or auditory toxicity whilst on aminoglycosides, have experienced a serious hypersensitivity reaction to aminoglycosides or have myasthenia gravis.

Aminoglycosides should be used with caution in patients with pre-existing auditory, vestibular or renal impairment, patients that have a family history of aminoglycoside induced auditory toxicity or a maternal relative with deafness due to mitochondrial mutation A1555G or, in patients of advanced age (80 years or over). Use an alternative class of antibiotic if available.

Aminoglycosides are category D in pregnancy and should only be used in pregnancy for life threatening conditions under specialist advice. For information on gentamicin for the

treatment of chorioamnionitis see Queensland Clinical Guideline: Preterm labour and birth (Preterm labour and birth).

Compliance with this guideline is not mandatory, but sound reasoning must exist for departing from the recommended principles within this guideline.

3. Legislation/Standards

The following National Safety and Quality Health Service Standards (NSQHSS) standards (second edition) apply:

- Standard 3 – Preventing & Controlling Healthcare Associated Infections – Antimicrobial stewardship
 - The health service organisation implements systems for the safe and appropriate prescribing and use of antimicrobials as part of an antimicrobial stewardship program.
- Standard 4 – Medication Safety – Clinical governance and quality improvement to support medication management
 - Organisation-wide systems are used to support and promote safety for procuring, supplying, storing, compounding, manufacturing, prescribing, dispensing, administering and monitoring the effects of medicines

4. Supporting documents

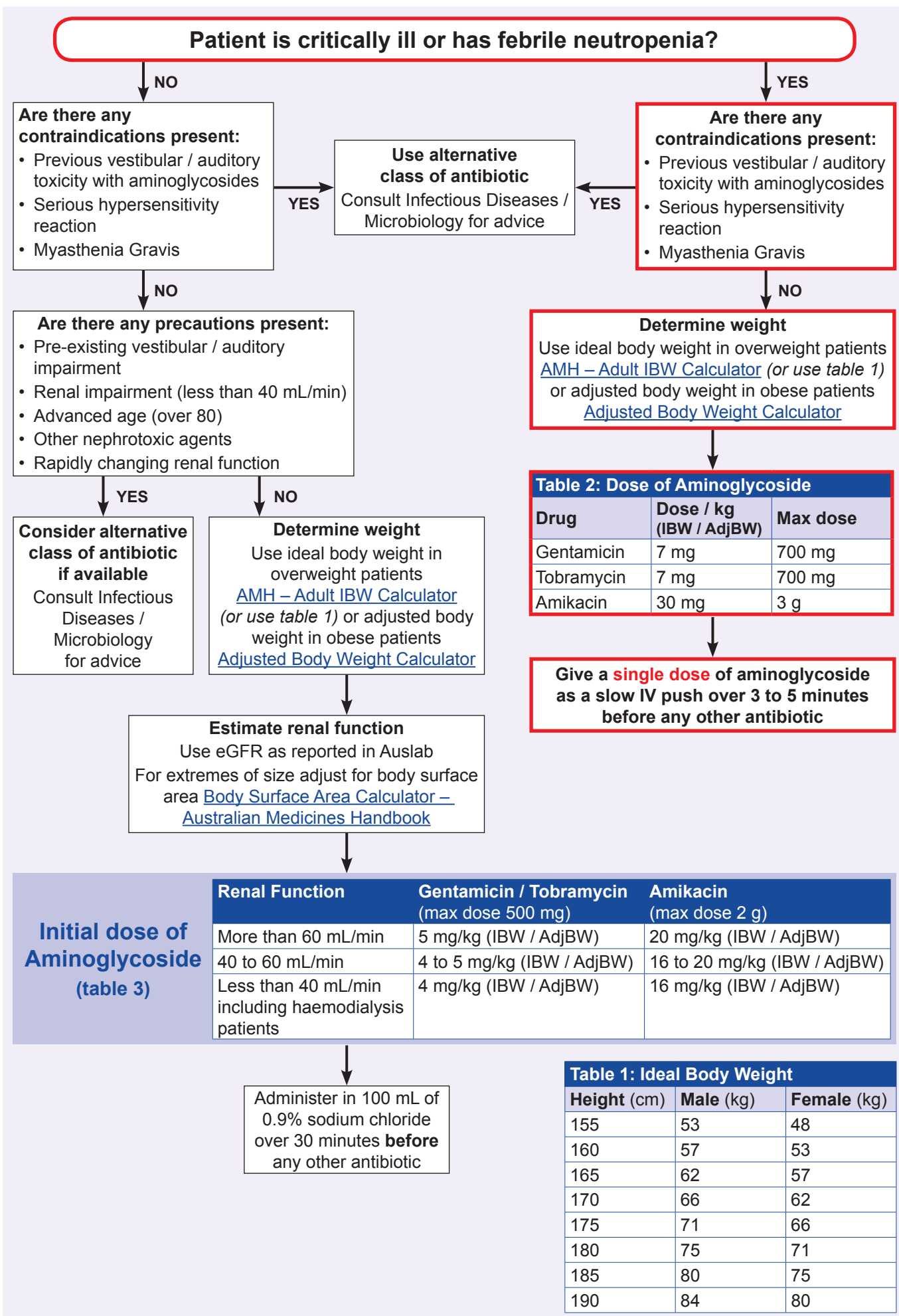
- Queensland Health List of Approved Medicines (LAM)
- National Inpatient Medication Chart (NIMC)
- Therapeutic Guidelines – Antibiotic 15th edition'

5. Definitions

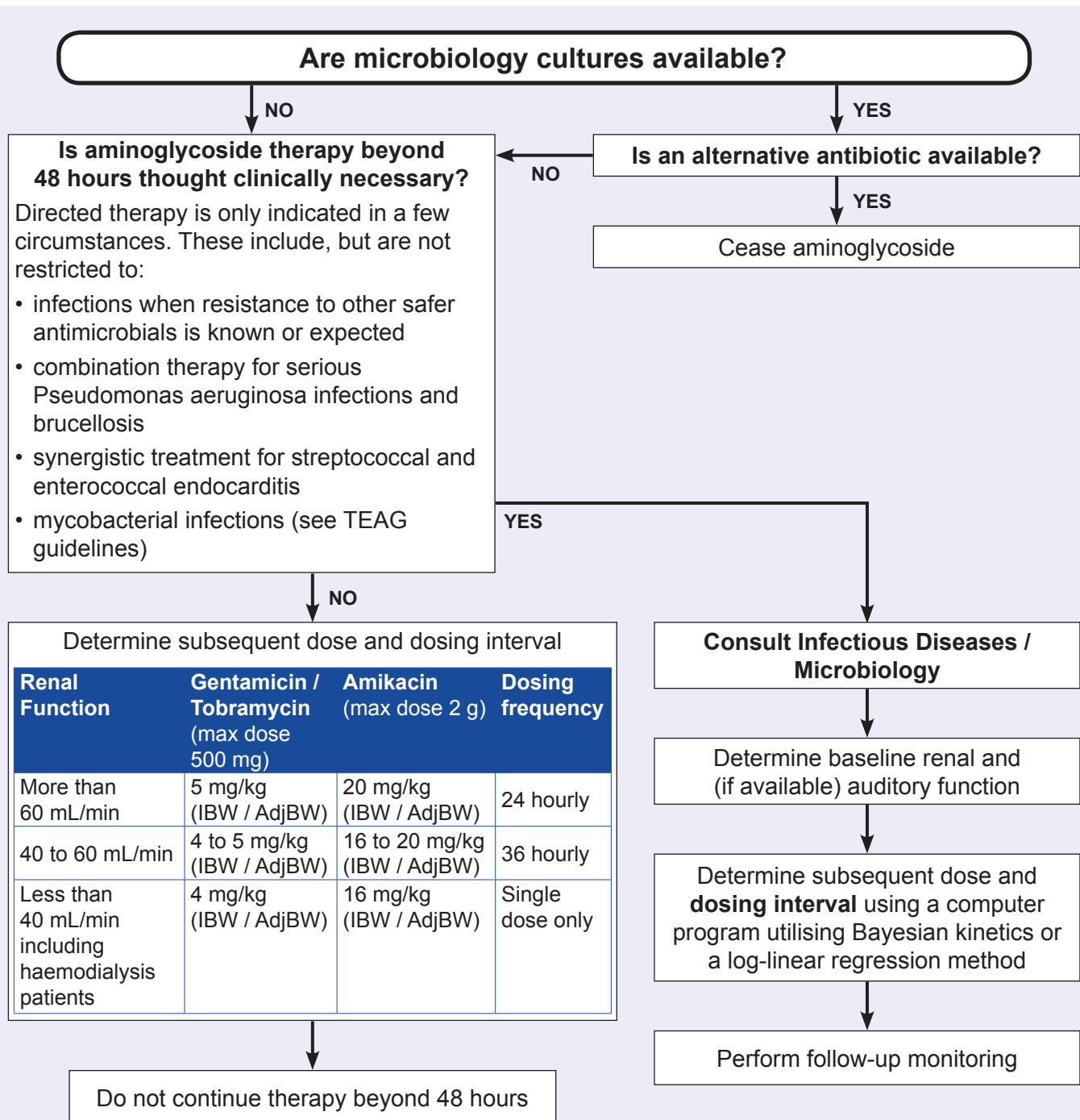
Term	Definition
eTG	Electronic Therapeutic Guidelines
PD	Peritoneal dialysis
NSQHSS	National Safety and Quality Health Service Standards
LAM	List of Approved Medicines
ID	Infectious Diseases
IBW	Ideal body weight
AdjBW	Adjusted body weight
CrCl	Creatinine clearance
eGFR	Estimated glomerular filtration rate
AMH	Australian Medicines Handbook
BSA	Body surface area
TDM	Therapeutic drug monitoring
C _{max}	Maximum concentration
MIC	Minimum inhibitory concentration
AUC	Area under the curve
NIMC	National Inpatient Medication Chart
HIT	Head impulse test
DVA	Dynamic visual acuity
AMS	Antimicrobial Stewardship
EMM	Electronic medication management
VOR	Vestibulo-ocular reflex
TEAG	Tuberculosis Expert Advisory Group
CHQ	Children's Health Queensland
C _{min}	Minimum concentration (trough concentration)
T _{>MIC}	Time above the minimum inhibitory concentration
IV	Intravenous
SPV	Slow phase velocity
MCA	Mono-thermal caloric asymmetry
GP	General Practitioner

6. Summary of Recommendations

Considering Aminoglycoside Therapy



Ongoing Therapy



7. Recommendations

7.1 Determine patient weight and height

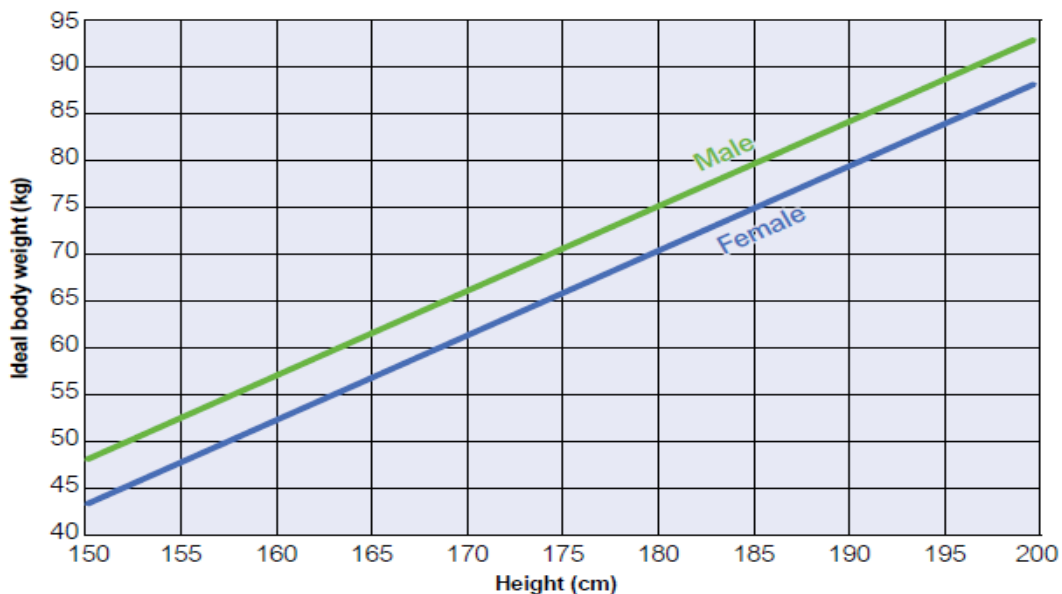
Use Ideal Body Weight (IBW) or actual body weight, whichever is less. In cases of extremes of actual body weight where actual body weight is greater than 20% above ideal, use adjusted body weight (AdjBW).

To calculate IBW see Figure 1, use medication dosing calculators [AMH – Adult IBW Calculator](#) or:

IBW for male = 50 kg + 0.9 kg/each cm over 152 cm

IBW for female = 45.5 kg + 0.9 kg/each cm over 152 cm

Figure 1 Estimation of Ideal body weight for adult males and females based on height



To calculate Adjusted Body Weight (AdjBW) use the equation below or an AdjBW calculator (e.g. [Adjusted body weight calculator](#))

AdjBW = Ideal Body Weight + (0.4*(Actual body weight – Ideal Body Weight))

To determine the ideal body weight for amputees the table below shows the percentage of total body weight contributed by individual body parts⁽¹⁾.

Table 1 Percentage of total body weight contributed by individual body parts

Body Part	Percentage loss
Hand	0.7%
Lower arm and hand	2.3%
Entire arm	5%
Foot	1.5%

Body Part	Percentage loss
Lower leg and foot	5.9%
Entire leg	16%

7.2 Estimate patient's renal function using estimated glomerular filtration rate (eGFR)

For patients who are critically ill or have febrile neutropenia, treatment with an aminoglycoside should not be delayed until renal function can be calculated as prompt initiation of antimicrobials confers a survival benefit(2). The initial dose of aminoglycoside for critically ill/febrile neutropenia patients who have a history of renal impairment should be as for patients without chronic renal impairment(3).

No method of estimating renal function is appropriate for use in patients with rapidly changing renal function or extremes of muscle mass (see Table 2)(4). In such patients therapeutic drug monitoring from the first dose is recommended (see section 6.6).

Table 2 Patients in whom estimates of renal function are unreliable

Unstable creatinine concentrations	Extremes in muscle mass and diet
pregnant women	amputees
patients with serious co-morbidities e.g. in intensive care	paraplegics
patients with acute renal impairment	bodybuilders
patients with febrile neutropenia	obesity
renal dialysis patients	patients with muscle wasting diseases/neuromuscular disorders
	cachectic/malnourished patients
	vegetarian/low meat diets
	patients taking creatine dietary supplements

7.2.1 Calculating eGFR corrected for body surface area

Estimated glomerular filtration rate (eGFR) as reported in pathology results is standardised to a body surface area of 1.73 m². For extremes of body size the value reported needs to be adjusted for actual body surface area. This is achieved by multiplying the eGFR by the patient's body surface area (in m²) and dividing by 1.73 m². Body surface area can be calculated using the equation below (Figure 2) or the body surface calculator available in AMH [Body surface area calculator– Australian Medicines Handbook](#)

Figure 2 Body Surface Area (BSA) equation

$$BSA(m^2) = \sqrt{\frac{HEIGHT(cm) \times WEIGHT(kg)}{3600}}$$

7.2.2 Estimating creatinine clearance (CrCl) using the Cockcroft-Gault equation

The use of the Cockcroft and Gault equation as a means of estimating renal function has been excluded from this guideline on the written advice of Kidney Health Australia and the Queensland Health Statewide Renal Clinical Network. Kidney Health Australia states that the use of eGFR to estimate kidney function for drug dosing is endorsed by domestic and international renal clinical guidelines, and the Statewide Renal Clinical Network support utilising the easily available eGFR (as reported in Queensland Health pathology programs AUSLAB/AUSCARE) as a valid measure of renal function for drug dosing (for access to the complete written advice contact medicationsafety@health.qld.gov.au).

7.3 Dosing of aminoglycosides

7.3.1 Critically ill and febrile neutropenic patients

Table 3 Dosing of aminoglycosides in critically ill and/or febrile neutropenic patients

Renal function	Gentamicin and Tobramycin (IBW or AdjBW – maximum dose 700 mg)	Amikacin (IBW or AdjBW – maximum dose 3 g)	Dosing frequency ⁽⁵⁾
Greater than 40 mL/min	7 mg/kg (IBW or AdjBW)	30 mg/kg (IBW or AdjBW) ⁽⁶⁾	Single dose and monitor concentrations
Less than 40 mL/min including haemodialysis patients [#]	7 mg/kg (IBW or AdjBW)	30 mg/kg (IBW or AdjBW)	Single dose only ^{\$}

*The following patient groups may have altered pharmacokinetics (e.g. increased clearance, altered drug distribution); modified aminoglycoside doses may be required and increased monitoring is necessary⁽⁷⁾. Seek advice regarding **ongoing** doses:

- critically ill patients with severe sepsis or septic shock
- patients receiving renal replacement therapy
- patients with severe burns
- patients with cystic fibrosis
- pregnant women
- patients with ascites
- morbidly obese patients

In patients receiving haemodialysis the dose of aminoglycoside should be given immediately and preferably pre- rather than post-dialysis ⁽⁸⁾

\$ Further doses should be under the guidance of ID/Microbiology with TDM

7.3.2 In all other patients or for empirical treatment of endocarditis

Table 4 Dosing of aminoglycosides in non-critically ill patients or for empirical treatment of endocarditis

Renal function	Gentamicin and Tobramycin (IBW or AdjBW – maximum dose 500 mg)	Amikacin (IBW or AdjBW – maximum dose 2 g)	Dosing Frequency
More than 60 mL/min	5 mg/kg (IBW or AdjBW)	20 mg/kg (IBW or AdjBW)	24 hourly
40 to 60 mL/min	4 to 5 mg/kg (IBW or AdjBW)	16 to 20 mg/kg (IBW or AdjBW)	36 hourly
Less than 40 mL/min including haemodialysis patients [#]	4 mg/kg (IBW or AdjBW)	16 mg/kg (IBW or AdjBW)	Single dose only \$

In patients receiving haemodialysis the dose of aminoglycoside should be given immediately and preferably pre- rather than post-dialysis⁽⁸⁾

\$ Further doses should be under the guidance of ID/Microbiology with TDM

NB1: Consider vial concentration e.g. Gentamicin/Tobramycin: 80 mg/2 mL round to nearest 40 mg; Amikacin: 500 mg/2 mL round to nearest 250 mg

NB2: Using a single dose of an aminoglycoside as initial therapy for presumptive Gram-negative sepsis is appropriate in patients with renal failure (CrCl less than 40 mL/min). Treatment in this group may be best continued with non-aminoglycoside antimicrobials. If ongoing therapy with an aminoglycoside is indicated seek ID/Microbiology advice.

Careful monitoring and care not to under dose need to be the principles guiding dose and frequency determination.

7.4 Indications for Aminoglycosides

7.4.1 Empirical therapy

- The primary indication for aminoglycosides is as short-term empirical therapy for suspected Gram-negative infections pending the outcome of microbiological investigations.
- When used empirically, no further doses of aminoglycoside should be given beyond 48 hours when an alternative agent chosen according to susceptibility testing should be commenced. Continue the aminoglycoside only when an alternative agent is not available. If further dosing is thought clinically necessary, seek Infectious Diseases (ID)/Microbiology advice.
- The dose and dosing interval for subsequent empirical dosing is based on the patient's renal function.
- When used empirically in **endocarditis** aminoglycosides synergise with cell-wall inhibitors (i.e. beta-lactams and glycopeptides) for bactericidal activity and are useful

for shortening the duration of therapy (e.g. oral streptococci) and eradicating problematic organisms (e.g. Enterococcus).

- Dosing of gentamicin for the empirical treatment of endocarditis is as for non-critically ill patients (see Table 4)

7.4.2 Directed therapy

Aminoglycosides are indicated for directed therapy in only a few circumstances. These include, but are not restricted to:

- infections when resistance to other safer antimicrobials is known or expected;
- combination therapy for serious *Pseudomonas aeruginosa* infections and brucellosis;
- low doses as synergistic treatment for streptococcal and enterococcal endocarditis;
- mycobacterial infections (see TEAG guidelines).

In **confirmed**, streptococcal or enterococcal endocarditis directed synergistic gentamicin therapy may need to be continued for 2 or more weeks.

For directed synergistic therapy (in combination with other antimicrobials) gentamicin is traditionally given at a dose of 1 mg/kg IV, 8 to 12 hourly depending on renal function ⁽⁶⁾. Some international guidelines ⁽⁸⁾ endorse once daily dosing (at a dose of 3 mg/kg) for:

- non-complicated native valve streptococcal endocarditis
- relatively resistant streptococcal endocarditis
- Enterococcal endocarditis

Evidence for once daily gentamicin dosing for enterococcal endocarditis is limited. Discuss with ID/Microbiology.

7.5 Therapeutic drug monitoring, pharmacokinetic and pharmacodynamic considerations

7.5.1 Monitoring of extended duration (once daily) aminoglycoside dosing

- The aims of monitoring aminoglycoside plasma concentrations are to ensure adequate dosing and to avoid excessive drug exposure, which can be associated with renal and audio-vestibular toxicity.
- High trough concentrations have been associated with an increased risk of toxicity.
- Monitoring of aminoglycoside plasma concentrations is not generally required for non-critically ill patients with normal renal function receiving **empiric** therapy if the plan is to cease treatment within 72 hours of commencement.
- Monitoring the aminoglycoside plasma concentration is recommended from the first dose of **directed therapy** or if therapy is planned for longer than 48 hours.
- Monitoring may also be considered for patients receiving empirical therapy (up to 48 hours of therapy) if renal function is unstable (e.g. critically ill patients with severe sepsis, suspected acute renal failure) or in patients with altered pharmacokinetics

(see 6.3.1 for list of such patients). Appendix 1 provides a summary of this information.

- It is recommended that the information below be provided with the pathology request to accurately calculate the subsequent dose:
 - Dose administered
 - Time dose was administered plus the infusion duration (start and finish times)
 - Time concentration(s) was taken

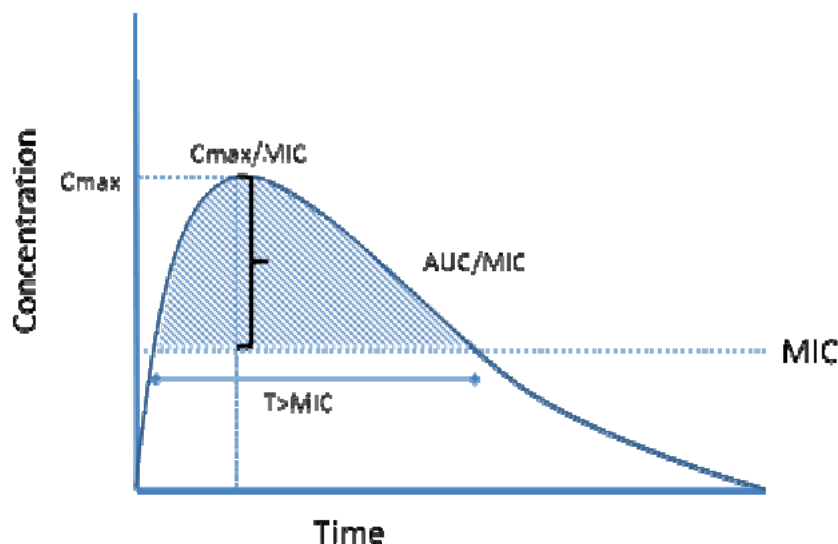
7.5.2 Monitoring in endocarditis

- To mitigate the risk of acute renal failure, renal function and serum gentamicin concentrations (trough) should be monitored, as a minimum, twice a week. More frequent monitoring is required initially and in patients with renal dysfunction or risk factors for nephrotoxicity or ototoxicity.
- A trough concentration (C_{min}) of less than 1 mg/L is required for synergistic dosing of aminoglycosides irrespective of the dosing frequency employed.

7.5.3 Pharmacokinetic and pharmacodynamics considerations for extended duration (once daily) aminoglycoside dosing

- Extended duration e.g. once-daily dosing of aminoglycosides is as effective (and less toxic) than conventional multiple-daily dosing regimens.
- The advantages of extended duration include optimisation of:
 - the maximum concentration (C_{max}) to minimum inhibitory concentration (MIC) ratio ^(9, 10)
 - area under the concentration time curve (AUC),
 - post-antibiotic effect ⁽¹¹⁾, and
 - reduction in costs of medication administration ⁽¹²⁻¹⁴⁾.

Figure 3 Pharmacokinetic and pharmacodynamic parameters



- Where feasible, and when treatment will not be delayed, it is recommended that a computer program utilising Bayesian principles be used. Such software programs can be used to calculate both initial dosing and subsequent doses. Dose calculation by these methods have been shown to result in significantly better achievement of target exposure earlier in the course of therapy and a reduction in the number of

subsequent concentration measurements ^(16, 17 18). Examples of such Bayesian programs currently available include (but are not limited to) TDMx, RxKinetics, ID ODS and DoseMe. Such software should be used by a clinician experienced with the particular platform.

- For those that are unable that to access a Bayesian program a log-linear regression method could be considered but requires at least two serum concentrations per dosing interval ⁽¹⁶⁾.
- The use of the nomogram in version 2 of these guidelines is no longer supported.
- Trough plasma concentrations cannot be used to monitor once-daily or less frequent dosing in adults because they are often below the laboratory detection limit and correlate poorly with overall exposure.
- Table 5 provides the therapeutic drug monitoring targets for extended duration e.g. once daily aminoglycoside administration

Table 5 Therapeutic drug monitoring targets for extended duration (once daily) aminoglycoside administration

Parameter	Gentamicin, Tobramycin	Amikacin
Cmax (peak)	16 to 20 mg/L ^{#1}	45 to 60 mg/L ^{#2}
Cmin (trough)	Less than 0.5 mg/L ^{#3}	Less than 2 mg/L ^{#3}
AUC ₀₋₂₄	70 to 100 mg*hr/L	Seek advice

#1 For Pseudomonas Isolates with MIC > 2 mg/L a higher Cmax may be required to achieve optimal Cmax:MIC target. Seek expert advice.

#2 For Pseudomonas Isolates with MIC > 4 mg/L a higher Cmax may be required to achieve optimal Cmax:MIC target. Seek expert advice.

#3. If unable to achieve Cmin targets while also achieving Cmax and AUC₀₋₂₄ targets with 24 hourly dosing, consider increasing the dosage interval to every 36 or 48 hours dosing. Seek expert advice.

7.6 Documenting the aminoglycoside order

7.6.1 On the National Inpatient Medication Chart (NIMC)

- All patients requiring aminoglycosides should receive the initial dose as soon as possible after microbiology samples are taken.
- Refer to section 6.3 – Dosing of aminoglycosides for timing of subsequent dose(s).
- The **initial** dose of aminoglycoside should be documented on the ‘Once Only’ section of the NIMC and communicated as part of the clinical handover to nursing staff (See Figure 4a).
- For patients requiring more than one dose of aminoglycoside (e.g. patient with intra-abdominal infections) where the **subsequent dose** is documented is determined by the dosing frequency.
- For patients requiring **daily dosing**, subsequent doses should be recorded in the ‘Variable dose’ section of the NIMC (see Figure 4b)
- For patients requiring **36 hourly dosing** (i.e. patients with a renal function of 40 to 60 mL/min) subsequent doses should be recorded in the ‘Regular Medication’ section of the NIMC and cross referenced to the variable dose section of the NIMC for drug concentrations (see Figure 4c).

Figure 4 Documenting aminoglycoside orders on the NIMC

a) Single/initial dose

ONCE ONLY, PRE-MEDICATION, TELEPHONE ORDERS AND NURSE INITIATED MEDICINES (Telephone orders MUST be signed within 24 hours of order)								
Date Prescribed	Medication (Print Generic Name)	Route	Dose	Date / Time of dose	Prescriber / Nurse Initiator (NI)		Given by	Time Given
					Signature	Print Your Name		
dd/MM	Gentamicin	IV	280mg	DD 06:00	<i>[Signature]</i>	QOIN		

b) Daily dosing

YEAR <u>YY</u> DATE and MONTH →		DD/MM	+1	+2
VARIABLE DOSE MEDICATION			Drug level	
Date	Medication (Print Generic Name)	When level taken		
DD/MM	Gentamicin			
Route	Frequency	Dose		
IV	Daily	360 mg	360 mg	
Prescriber to enter dose times and individual doses		Prescriber		
Indication	Pharmacy	Time to be given:		
Pyelonephritis				
Prescriber Signature	Print Your Name	Contact	Time given	
<i>[Signature]</i>	QOIN	591		

c) 36 hourly dosing

REGULAR MEDICATIONS					DD	DD	DD		
YEAR: <u>YY</u> DATE and MONTH →		DOCTORS MUST ENTER administration times			DD	DD	DD		
Date	Medication (Print Generic Name)	Frequency and Enter Times			Tick if Slow Release				
DD/MM	Gentamicin	08:00							
Route	Dose	every 36 hours			X	X			
IV	280 mg								
Indication	Pharmacy	20:00			X	X			
Pyelonephritis									
Prescriber Signature	Print Your Name	Contact							
<i>[Signature]</i>	QOIN	591							

7.6.2 In the digital environment

- Electronic prescribing is progressively being introduced across Queensland. It is recommended that each Antimicrobial Stewardship (AMS) program develop a work instruction/standardised order set specific to their EMM system to be used in conjunction with this guideline.

7.7 Administration of aminoglycosides

- In general aminoglycosides should be given via the intravenous (IV) route. If IV access is unavailable contact ID/Microbiology for advice.
- When used in combination with other IV antibiotics, **aminoglycosides** should be administered **first**.
- Patients in the emergency department or who are critically ill, aminoglycosides (any dose) may be given as a slow IV bolus over 3 to 5 minutes⁽⁹⁾.

- Administration of aminoglycosides via this technique often results in transient arm discomfort that resolves within 15 minutes⁽¹⁰⁾. Patients receiving aminoglycosides as a slow IV bolus should be closely monitored for other signs of extravasation or infiltration e.g. swelling, redness, coolness or blanching at the cannula insertion site.
- For all other patients it is preferable to administer the aminoglycoside as an IV infusion in 100mL 0.9% sodium chloride over 30 minutes.
- Do not administer at the same time as penicillins or cephalosporins as they may inactivate one another. Administer via separate peripheral cannulas or separate lumens of a central venous catheter if possible. If this is not possible, flush the line well before and after giving each drug.
- For patients receiving directed therapy with aminoglycosides, or in those patients where therapeutic drug monitoring may be required, ensure the exact time the infusion started and finished is recorded on the medication chart.

7.8 Monitor renal, hearing and vestibular function

Patients and/or guardians/carers should be informed of the potential toxicities of aminoglycoside therapy and documentation of this discussion should be recorded in the patient's clinical notes. For more information on what to discuss with patients (and a suggested script for the discussion) see Appendix 2.

If audio-vestibular toxicity is suspected during therapy, stop the aminoglycoside and seek advice.

7.8.1 Renal function – Baseline & ongoing monitoring

Serum creatinine should be checked and renal function estimated (eGFR) before commencing an aminoglycoside and then, if therapy is ongoing, two to three times each week or more frequently if renal function is unstable. An increasing serum creatinine concentration may potentially indicate deterioration in renal function. A need to reduce the dose of aminoglycoside could similarly indicate deterioration in renal function.

7.8.2 Audiological Testing – Baseline

- Where prolonged aminoglycoside courses (greater than 5 days of therapy) are anticipated ahead of time, baseline audio-vestibular testing as described in Table 6 should be conducted in all patients, if available (ideally within 72 hours prior to initiation).
- Baseline testing should not delay therapy.

7.8.3 Audiological Testing – Ongoing monitoring

- It is recommended that monitoring for **cochlear toxicity** should occur weekly during therapy and at follow-up appointments following completion of the aminoglycoside course.
- The treating clinician should order audiological tests as specified in Table 6.
- For **vestibular toxicity** it is recommended that the treating clinician should monitor using the 3-step bedside screening test at least weekly during therapy (see appendix 3).
- Monitoring for vestibular toxicity using the mono-thermal screening caloric test (if available via audiology) should occur:

- if the patient has any signs/symptoms (see Table 7) OR if clinicians involved in the mobilisation of the patient detect any symptoms.
- at the mid-point of their treatment course if this is likely to be protracted (3 to 6 months)
- following completion of aminoglycoside treatment.
- Signs of audio-vestibular toxicity may appear several months after completion of the aminoglycoside course. Clinicians should liaise closely with the audiology department to determine what formal audiology testing is required following the completion of aminoglycoside treatment.

Table 6 Audiological tests to be performed

Cochlear testing (conducted by audiology)	Vestibular testing
<p>Distortion Product OtoAcoustic Emissions 2 to 12 kHz, or to highest frequency equipment allows</p>	<p>Mono-thermal screening caloric test (conducted by audiology): Screen using warm water irrigation for 15 seconds in each ear to maximise patient tolerance. Perform standard bi-thermal test if Slow Phase Velocity (SPV) is less than 8 °/s for either ear or if mono-thermal caloric asymmetry (MCA) is greater than 15%. MCA is calculated using Jongkee's formula: [(Left warm-Right warm) / (Left warm + Right warm)] x 100</p>
<p>Acoustic Immittance: Tympanometry only (stapedial reflex testing is contraindicated in this patient population)</p>	<p>For regional and/or remote settings/or for regular weekly monitoring during therapy (conducted by treating clinician):</p>
<p>High Frequency Pure-Tone Audiometry: § 4 kHz to 20 kHz or to highest frequency equipment allows. Needs to include all inter-octave frequencies. Air-conduction only is appropriate.</p>	<p>Where caloric testing is not available or for regular weekly testing during therapy, 3-step bedside screening for bilateral vestibular hypofunction is recommended. For information on how to perform these tests see Appendix 3)</p>

§ May not be able to perform in critically ill/altered state of conscious.

Table 7 Common signs and symptoms associated with ototoxicity

Cochlear toxicity	Vestibular toxicity
Hearing loss (unilateral or bilateral)	Motion-induced oscillopsia - <i>a visual disturbance in which objects in the visual field appear to oscillate. Often described as “jumping”, “bobbing” or “bouncing” vision.</i>
Tinnitus (unilateral or bilateral)	Postural instability
Aural fullness (unilateral or bilateral)	Unsteadiness of gait

7.9 Version Control

Version No.	Modified by	Amendments authorised by	Approved by
V1	Justin Lee	State-wide Aminoglycoside Working Party	Dr Julie Stokes
V2	Justin Lee	Statewide Aminoglycoside Working Party	Dr Julie Stokes
V3	Josie Quin	Statewide Aminoglycoside Working Party	

Appendix 1 – Summary of monitoring principles of aminoglycosides

Type of therapy	Plasma concentration monitoring
Empirical therapy or directed therapy for up to 48 hours	Not generally required Consider in patients with rapidly or substantially changing renal function (e.g. critically ill or suspected acute renal failure) or in patients with altered pharmacokinetics
Directed therapy for longer than 48 hours	Mandatory Measure plasma concentration on the first dose, a computer program utilising Bayesian principles or a log-linear regression method should be used to determine subsequent dosing
Directed synergistic therapy	Mandatory Monitor trough concentration, as a minimum, twice a week. Trough should be less than 1 mg/L
Surgical prophylaxis	Exclusion from this document Not required

Appendix 2 – Information to be discussed with patient by prescriber prior to initiation of therapy

1. What are aminoglycosides?

Aminoglycosides are a family of antibiotics including the specific drugs:

- Gentamicin (most commonly used)
- Tobramycin
- Amikacin
- Streptomycin (not currently marketed in Australia; imported from overseas)
- Kanamycin (not currently marketed in Australia; imported from overseas)

2. What are aminoglycosides used for?

Aminoglycosides are antibiotics that work by preventing bacteria from growing and by killing them. They are used to treat serious bacterial infections in many different parts of the body such as chest infections, urinary tract infections and infected wounds or burns. Aminoglycosides may be prescribed for other reasons that are not mentioned above.

Before you are given an aminoglycoside, tell me (your doctor) if:

- you have any allergies
- you are/may be pregnant*
- you are breast-feeding*
- you have or have had any of the following medical conditions:
 - kidney disease or any kidney problems
 - hearing problems
 - a maternal relative with deafness resulting from the mitochondrial DNA mutation A1555G or aminoglycoside induced auditory toxicity
 - myasthenia gravis (a muscle disease)
 - Parkinson's disease (a disease affecting movement)

*Pregnancy and breastfeeding are not contraindications to the use of aminoglycosides but an alternative antibiotic (if available) may be more appropriate.

3. Aminoglycoside use in critically ill/febrile neutropenia patient

Sepsis is a life-threatening complication of infection. Sepsis occurs when chemicals released into the bloodstream to fight the infection trigger inflammatory responses

throughout the body. This inflammation can trigger a cascade of changes that can damage multiple organ systems such as the heart, lungs, kidneys and liver, causing them to fail. If sepsis progresses to septic shock, blood pressure drops dramatically and this may lead to death.

The main treatments for these critically ill patients are antibiotics, fluids and medicines to raise blood pressure. Ideally, antibiotic treatment should start within an hour of diagnosis to reduce the risk of serious complications or death. There won't usually be time to wait until a specific type of infection has been identified, so broad-spectrum antibiotics are given first. These are designed to work against a wide range of known infectious bacteria and usually cure most common infections. As these are life threatening conditions the presence of the above conditions (with the exception of a life threatening allergy) may not be considered before the aminoglycoside is given.

4. Side effects of aminoglycosides

These should be discussed with the patient prior to receiving a dose of aminoglycoside if that is practicable or, if not, once the patient is well enough to understand the discussion.

4.1 Auditory (hearing)/vestibular (balance) toxicity

Aminoglycosides can damage your ears resulting in problems with hearing and balance. These are rare side effects and occur in 2 to 3% of patients treated with aminoglycosides⁽¹¹⁾. These side effects are more likely to occur if you receive large cumulative doses of aminoglycosides or receive long courses of aminoglycosides (more than five to seven days of treatment). Tell a doctor/nurse immediately if you have any of the following:

- Visual problems such as blurred vision or vision that seems to oscillate (“jumping”, “bobbing” or “bouncing” vision)
- problems with balance, unsteadiness of gait or vertigo
- dizziness (especially when you sit up, stand up or walk), nausea or vomiting
- hearing problems, ringing in the ears, feeling of fullness in the ears

These symptoms may appear several weeks to months after the medication has stopped. If symptoms develop once you have returned home contact the hospital you were discharged from for advice or see your GP.

4.2 Renal/kidney impairment

Aminoglycosides can impair kidney function. This usually improves again once the aminoglycosides are stopped. As with damage to the ears, kidney damage is more likely to occur if high cumulative doses (added up over the course of treatment) of aminoglycosides are used or treatment lasts more than 7 to 10 days. Regular blood tests are required to detect this complication.

4.3 Neuromuscular blockade (paralysis/muscle weakness)

There have been a few individual patient reports of aminoglycosides causing muscle weakness. This is usually when given with paralyzing medications in surgery or Intensive care. Tell your doctor immediately if you have skin tingling, numbness or muscle twitching.

4.4 Allergy/hypersensitivity

As with any medication, it is possible to develop an allergy. Signs of an allergic reaction include rash, itching, hives, swelling of the lips, tongue or throat, and breathing difficulties. If you experience any of these side effects inform staff immediately.

5. Monitoring of aminoglycosides

5.1 Monitoring for vestibular/auditory toxicity

For patients who are likely to receive more than 5 days of aminoglycoside treatment or who report any of the above visual/balance symptoms discussed above, testing of audio-vestibular function is usually undertaken. Simple testing can be done by the treating team or possibly your GP if you have been discharged from the hospital. If balance or hearing toxicity is suspected, referral to a specialist (e.g. neuro-otologist, otolaryngologist or neurologist) for further investigation and formal audiology testing may be required. This may not be available at your local public facility. You may need to travel to a larger public facility. A private facility may be able to perform the testing but a cost may be incurred. Discuss this with the hospital senior medical staff if you have financial concerns.

In patients who are critically ill, this testing will only be undertaken if the patient reports symptoms and once the patient is alert and able to actively participate in the assessment.

5.2 Monitoring of aminoglycoside blood concentrations (concentration monitoring/therapeutic drug monitoring) and kidney function

As mentioned previously, many of the side effects of aminoglycosides are more likely to occur if the amount of medication in your system is high or you are exposed to the medication for a prolonged period of time. For those patients who it is felt will need more than 2 to 3 days of treatment with an aminoglycoside or in those patients who have poor renal function or altered body parameters (e.g. pregnant women, patients with ascites (fluid in their abdomen), morbidly obese patients) blood levels will be measured. These blood levels will require you to have one or occasionally two blood samples taken depending on the machine used at your facility. The results of these

tests may result in the aminoglycoside being given less frequently. As well as monitoring the level of aminoglycoside, your renal function will be monitored frequently to ensure it is not deteriorating.

Appendix 3 – Three step bedside exam for vestibular toxicity

1. Head impulse test (HIT)

Stand in front of the seated patient and ask the patient to focus on a target directly in front of them (e.g. the examiner's nose). Briskly rotate the patient's head horizontally approximately 10 to 20° amplitude, watching the patient's eyes closely. In normal subjects, the patient's eyes remain still as they remain on target. However, in a patient with impaired vestibulo-ocular reflex (VOR), the patient's eyes drift off the target and require a corrective 'catch-up' saccade to re-fixate on the target and stabilise vision. This catch-up saccade is a small amplitude horizontal eye movement in the opposite direction of the head turn and should occur with every head impulse (repeatable).

If available, video HIT (vHIT) is recommended as this has a higher sensitivity than the traditional bedside head impulse test at detecting impaired VOR. Main benefits include detecting covert (hidden) catch up saccades and peer review

2. Dynamic visual acuity (DVA) during head shaking

Ask the patient to read a visual acuity chart (e.g. Snellen) while sitting still at recommend distance. This result is the static visual acuity.

Repeat task while oscillating the patient's head horizontally or vertically at 1 to 2 Hz. An abnormal DVA is defined as loss of at least three lines of visual acuity compared with static condition (horizontal and/or vertical).

3. Romberg test on foam rubber

3.1 Firm surface

Ask the patient to stand still on the ground with two feet together. The patient should be able to stand steady with their eyes open. If the patient is not able to perform this task, ask them to separate their feet to minimal distance that allows them to do so. Repeat task this time with their eyes closed. Record if patient falls (positive Romberg test) or does not (negative Romberg test).

3.2 Foam surface

Repeat above steps on foam surface. Record if patient falls (positive Romberg test) or does not (negative Romberg test).

Patients who have bilateral vestibulopathy should have a negative Romberg test on a firm surface and positive results on a foam surface.

Practical advice and videos on how to perform these tests are available at:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3526948/pdf/10.1177_1756285612465920.pdf
<https://www.youtube.com/watch?v=AfghWx3IIIE>

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