

# AMINOGLYCOSIDE DOSING AND MONITORING - CHW

## PRACTICE GUIDELINE<sup>®</sup>

### DOCUMENT SUMMARY/KEY POINTS

- Once daily dosing is the recommended method of administration for aminoglycosides in most clinical settings at CHW.
- In suspected sepsis, particularly in immunocompromised patients, the first dose of aminoglycoside therapy should not be delayed pending results of blood tests.
- EUCs must be monitored at commencement and during aminoglycoside therapy.
- Initial starting dose should not exceed the maximum dose for that age group as specified in Table 1.
- Dosage should be based on the patient's ideal body weight (IBW) if BMI >30.
- Dosing in empirical therapy should not continue beyond 48 hours (i.e. a maximum of three empirical doses at 0, 24 and 48 hours); given the 'post-antibiotic effect' of aminoglycosides, this effectively provides 72 hours of therapy.
- Monitoring of aminoglycoside plasma concentrations is not required if therapy is ceased within 48 hours of commencement.
- Aminoglycosides are indicated for more prolonged directed therapy in only a few circumstances. If continued beyond 48 hours, plasma concentrations of aminoglycosides are required.
- Gentamicin should be administered by direct IV injection over 3 – 5 minutes irrespective of final concentration and volume of administered dose (*except in patients with neuromuscular disorders such as myasthenia gravis who should ideally receive aminoglycosides via 30 minute infusion*).
- Clinicians administering neuromuscular blocking agents in the first few hours after aminoglycoside dosing, while plasma levels are high, should be aware that there is a theoretical possibility of enhanced or prolonged paralysis.

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

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This Guideline may be varied, withdrawn or replaced at any time.

## CHANGE SUMMARY

- Maximum dosing of aminoglycosides updated (refer to table 1)
- Therapeutic drug monitoring recommendations updated (refer to table 5)

## READ ACKNOWLEDGEMENT

- Local manager to determine which nursing/medical or pharmacy staffs are to read and acknowledge they understand the contents of this document.

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## Introduction

Aminoglycoside antibiotics are used to treat serious infections caused by Gram-negative bacteria. The bactericidal effect is related to inhibition of protein synthesis and also to their effect on bacterial cell wall integrity.

The primary indication for aminoglycosides is as **short-term empirical therapy** pending the outcome of microbiological investigations. Their value as empirical drugs relates to their rapid bactericidal activity and the comparatively low levels of resistance in many community and health care-associated Gram-negative pathogens.

Aminoglycosides given beyond 48 hours (i.e. more than three empirical doses at 0, 24 and 48 hours) are only indicated for directed therapy in only a few circumstances. These include:

- Multi-resistant infections that are not susceptible to alternative antimicrobial classes
- Patients with allergies or other contraindications to first-line agents.
- Initial combination therapy for *Pseudomonas aeruginosa* until susceptibility to alternative antibiotics are known
- Combination therapy for brucellosis and mycobacterial infections

Longer courses of aminoglycosides, usually in combination with a beta-lactam antibiotic, may be utilised for synergistic activity in a few specific clinical settings such as endocarditis, cystic fibrosis, and serious enterococcal and group B streptococcal (*Streptococcus agalactiae*) infections.

### ***The available parenteral aminoglycosides at CHW:***

- **Gentamicin** – 80 mg/2 mL ampoules and 10mg/mL ampoules
- **Tobramycin** – 80 mg/2 mL vials (used mainly for cystic fibrosis patients)
- **Amikacin** – 500 mg/2 mL vials (reserved for proven resistance to other aminoglycosides)

## Initial dose for empirical and directed intravenous therapy

- The initial dose for empirical and directed therapy in infants, children, and adults with **normal renal function** is as follows ([Table 1](#)).
- For neonates, please refer to [Table 2](#).
- For patients with renal impairment, please refer to [Table 3](#).
- For obese patients (e.g. BMI >30), dose must be calculated based on ideal body weight (IBW) because aminoglycosides distribute minimally in adipose tissue.
- Ideal body weight can be estimated using the 50th centile weight for height, or from the formula of Traub and Johnson. This formula is suitable for patients aged 1-18 years.

$$\text{Ideal Body Weight (kg)} = \text{Height (cm)}^2 \times 1.65/1000$$

**Table 1: Dosing recommendations for infants, children, and adults** <sup>(1-5)</sup>

Age	Gentamicin or Tobramycin	Amikacin
1 month–18 years	7.5 mg/kg/dose 24 hourly (max starting dose 320 mg/dose)	15-30 mg/kg/dose 24 hourly (max starting dose 1.5 g/dose) <a href="#">[NB1]</a>
Children with cystic fibrosis <a href="#">[NB2]</a>	10-12 mg/kg/dose 24 hourly	30 mg/kg/dose 24 hourly
Children with endocarditis <a href="#">[NB2]</a> <a href="#">[NB3]</a>	1 mg/kg/dose 8 hourly	Seek ID advice

[\[NB1\]](#): Doses of 15-25 mg/kg/dose 3x weekly are used for mycobacterial infections under ID advice <sup>(6-9)</sup>.

[\[NB2\]](#): There is no maximum dose.

[\[NB3\]](#): Used only in combination with beta-lactam for enterococcal and streptococcal synergy.

Consult ID Team for advice.

**Table 2: Dosing recommendations for neonates <28 days old** <sup>(1, 2)</sup>

Age	Postnatal age	Gentamicin or Tobramycin	Amikacin
Neonate <30 weeks postmenstrual age <a href="#">[NB4]</a>	0-7 days	5 mg/kg/dose 48 hourly	20 mg/kg/dose 48 hourly
	8-28 days	5 mg/kg/dose 36 hourly	20 mg/kg/dose 36 hourly
	≥ 28 days	5 mg/kg/dose 24 hourly	20 mg/kg/dose 24 hourly
Neonate 30-34 weeks postmenstrual age <a href="#">[NB4]</a>	0-7 days	5 mg/kg/dose 36 hourly	20 mg/kg/dose 36 hourly
	≥8 days	5 mg/kg/dose 24 hourly	20 mg/kg/dose 24 hourly
Neonate ≥35 weeks postmenstrual age <a href="#">[NB4]</a>		5 mg/kg/dose 24 hourly	20 mg/kg/dose 24 hourly

[\[NB4\]](#): postmenstrual age= gestational age + postnatal age

**Table 3: Dosing recommendations for renal impairment** <sup>(1, 10)</sup>

Age	eGFR [NB5]	Gentamicin or Tobramycin	Amikacin
Neonate (<1 month)	Seek infectious diseases advice for alternative antibiotic		
Infant, children and Adolescents (1 month-18 years)	≥50 mL/min/1.73m <sup>2</sup>	Normal dosing (refer to <a href="#">Table 1</a> )	
	30-50 mL/min/1.73m <sup>2</sup>	2.5 mg/kg/dose 12 hourly	7.5 mg/kg/dose 12 hourly
	10-29 mL/min/1.73m <sup>2</sup>	2.5 mg/kg/dose 24 hourly	7.5 mg/kg/dose 24 hourly
	<10 mL/min/1.73m <sup>2</sup>	2.5 mg/kg/dose 48-72 hourly	7.5 mg/kg/dose 48-72 hourly

[NB5]: For children, the Bedside Schwartz formula is recommended for the estimated glomerular filtration rate (eGFR).

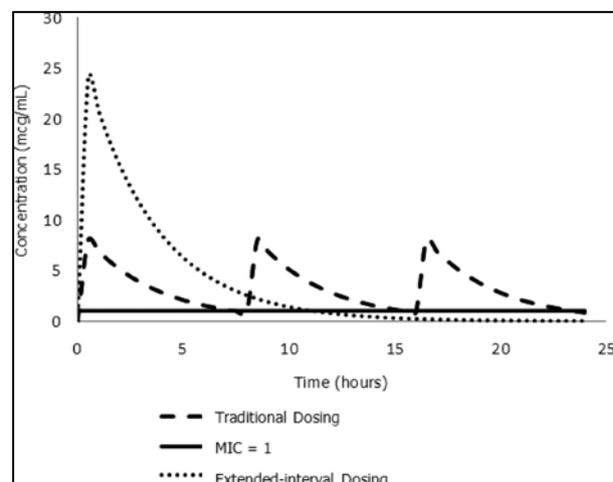
$$eGFR \text{ (mL/min /1.73 m}^2\text{)} = \frac{36.5 \times \text{height (cm)}}{\text{serum creatinine (micromol/L)}}$$

## Dosing and administration

### Dosing

Once daily dosing of aminoglycosides is the recommended frequency of administration in patients with normal renal function in most clinical settings. Numerous adult and paediatric studies suggest that once daily dosing results in improved clinical efficacy and reduced toxicity compared to multiple daily dosing (e.g. 8-12 hourly)<sup>(11-23)</sup>. The difference in nephrotoxicity is more difficult to detect in paediatric populations due to the lower incidence of nephrotoxicity in children compared to adults <2% vs. 8% respectively<sup>(4)</sup>.

The rationale for once daily dosing is based on the pharmacokinetic and pharmacodynamic parameter of aminoglycosides. The bactericidal activity of aminoglycosides is concentration-dependent. Optimising the ratio of peak plasma concentrations over the minimum inhibitory concentration maximises the bactericidal activity of aminoglycosides<sup>(15)</sup> (Figure 1).



**Figure 1: Traditional dosing (8 hourly dosing) versus extended-interval dosing (24 hourly) of aminoglycosides. MIC indicates minimum inhibitory concentration.**

Source: Jenh, A. M., et al. (2011). "Pediatric Infectious Disease Journal 30(4): 338-339.

## Administration

- Gentamicin (**but NOT amikacin**) can be safely administered **by IV bolus over 3-5 minutes** <sup>(24-31)</sup>. This is preferred over 30 minute infusions to take advantage of the concentration dependent bactericidal effects <sup>(32-35)</sup>.
- **Dose may be diluted in 5-10 mL of normal saline OR injected directly undiluted.** <sup>(25, 29, 35, 36)</sup>
- Tobramycin is infused over 30 minutes at CHW for AUC calculation.
- Clinicians administering neuromuscular blocking agents in the first few hours after aminoglycoside dosing, while plasma levels are high, should be aware that there is a theoretical possibility of enhanced or prolonged paralysis.
- Aminoglycosides should be used with great caution in patients with neuromuscular disorders (e.g. myasthenia gravis). These patients should be infused over 30 minutes.

### **Amikacin MUST be administered by INFUSION**

Amikacin must be diluted to a maximum concentration of 10 mg/mL and infused over at least 30 minutes.

## Monitoring for patients on aminoglycosides

### Renal function

- Accumulation of aminoglycosides within the kidneys results in reversible nephrotoxicity.
- Elevated trough concentrations, increased frequency, concurrent nephrotoxins (e.g. vancomycin and amphotericin), dehydration and prolonged duration of therapy (>5 days) are risk factors for nephrotoxicity <sup>(3, 11)</sup>.
- Monitoring of plasma aminoglycoside levels is required to minimise the risk of accumulation and toxicity if therapy is continued beyond 48 hours.
- Before starting therapy, bloods should be collected for measurement of electrolytes, urea and creatinine.
- In suspected sepsis (particularly in immunocompromised patients) the first dose of aminoglycoside therapy should not be delayed pending results of these blood tests (urea, creatinine etc.), give doses recommended in [Table 3](#).
- Electrolytes, urea and creatinine (EUC) must be monitored at baseline and during aminoglycoside therapy. An alternative antibiotic is to be considered if urea and/or creatinine are not within the normal range.
- **Twice weekly** EUC monitoring is required in clinically stable patients and should be performed more frequently if renal impairment exists.

- For patients on aminoglycoside therapy for more than a month, the frequency of EUC is the following:

1 <sup>st</sup> month	Twice a week
2 <sup>nd</sup> month	Weekly
3 <sup>rd</sup> month until end of treatment	Fortnightly*
*Consider reducing to monthly if renal function remains stable. Consider increasing frequency of monitoring if evidence of renal impairment.	

## Therapeutic drug monitoring

- Accurate documentation of **sample collection time** and **time of last dose** **MUST** always be recorded on the request form.
- Trough levels are measured within 30 minutes before the next dose
- Inpatients on a stable aminoglycoside regimen should continue to be monitored **twice weekly** if renal function is normal and stable and more frequently when impaired renal function exists or is potentially unstable.
- Trough level monitoring should be done following each dosing adjustment.
- Trough levels are used **only** to monitor toxicity, not efficacy.
- Refer the Table 5 for targets, timing and frequency of therapeutic drug monitoring

**Table 5: Therapeutic drug monitoring of aminoglycosides** <sup>(1, 2, 27)</sup>:

Indication	Level	How often	Target level	
			Gentamicin or Tobramycin	Amikacin
Empirical therapy ≤48 hours	Not required	<b>Not required</b>	Not applicable	Not applicable
Empirical therapy >48 hours	Review use <b>(e.g. cease, switch to a less nephrotoxic agent, or seek ID advice)</b>	Twice a week	Trough < 1 mg/L	Trough < 4 mg/L
	If empirical therapy continues >48 hours, before the 4 <sup>th</sup> dose			
Febrile neutropenia	Before the 2 <sup>nd</sup> dose	Twice weekly	Trough < 1 mg/L	Trough < 4 mg/L
Neonate <b>(not on Grace ward)</b>	Before the 2 <sup>nd</sup> dose	Twice weekly	Trough < 1 mg/L	Trough < 4 mg/L
Neonate <b>(on Grace ward)</b>	22 hours after the of the 2 <sup>nd</sup> dose	<a href="#">Refer to Neomed Gentamicin monograph</a>		
Pre-existing renal impairment	Before the 2 <sup>nd</sup> dose <i>Consider ceasing or changing antibiotic. Seek ID advice.</i>	At least twice weekly	Trough < 2 mg/L*	Trough < 8 mg/L*
			<i>*The target troughs are higher due to multiple daily dose regimens.</i>	
Directed therapy	<b>**Preferred**</b> Measure Area Under the Curve ( <a href="#">see below</a> )	Twice weekly	AUC: 80-100 mg.hr/L	Not applicable
	Before the 2 <sup>nd</sup> dose	Twice weekly	Trough < 1 mg/L	Trough < 4 mg/L
Infective exacerbation of Cystic fibrosis	Measure Area Under the Curve ( <a href="#">see below</a> )	Twice weekly	AUC: 90-110 mg.hr/L	Not applicable
Endocarditis <sup>(2, 5, 37)</sup>	Before the 4 <sup>th</sup> dose	At least twice weekly	Trough < 1 mg/L	Not applicable
Amikacin for Mycobacterial infections <sup>(6-8)</sup>	Measure peak and troughs ( <a href="#">see below</a> )			

## Area Under the Curve calculations <sup>(2, 38-41)</sup>:

Achieving adequate Area Under the Concentration-time curve (AUC) of aminoglycosides is associated with clinical efficacy and minimises toxicity. AUC calculations are recommended for the following patients:

- Directed therapy
- Cystic fibrosis (CF)

The calculation of AUC requires ONE level between 2-6 hours after the second dose.

Record the **EXACT** time of collection and dose on the collection tube **AND** the request form to allow accurate interpretation of results.

The AUC is calculated through a computer program using Bayesian Forecasting software, Dose Me. The target AUC is 80 – 100 mg.hr/L.

Please contact the Antimicrobial Stewardship Pharmacist on (ext. 53226/pager 6658) for advice.

## Amikacin for Mycobacterial infections <sup>(9)</sup>:

- Amikacin is a **RED** restricted antibiotic and requires Antimicrobial Stewardship (AMS) approval. Please discuss with ID/AMS for advice or alternative therapy.
- The rationale for monitoring amikacin for mycobacterial infection is to ensure therapeutic efficacy and avoid accumulation due to drug-induced renal impairment.
- Record the **EXACT** time of collection and dose on the collection tube **AND** the request form to allow accurate interpretation of results.

Target level	Timing	Frequency
Peak: 25 - 40 mg/L	Within 60 minutes after the end of the infusion	Peak level in the 1 <sup>st</sup> week only
	If the peak level is high, reduce the <b><u>dose</u></b> . If the peak level is low, increase the <b><u>dose</u></b> .	
Trough: <4 mg/L	Pre-dose	Weekly for 4 weeks then fortnightly (Consider reducing to monthly if renal function remains stable)
	If the trough level is high, the dosing <b><u>interval</u></b> should be extended	

Please contact the Antimicrobial Stewardship/ID Pharmacist on (ext. 52696/pager 6698) for advice. AUCs can also be measured using DoseMe

## Ototoxicity and vestibular toxicity (2, 9, 42-44):

- Aminoglycosides can cause **irreversible** ototoxicity and vestibular toxicity
- Ototoxicity and vestibular toxicity are **NOT** predicted by plasma concentrations
- Loss of hearing usually occurs first and is detected by regular audiometric testing. Vertigo, loss of balance and auditory disturbances are also signs of ototoxicity.

**Audiograms and vestibular testing should be performed for patient on aminoglycosides longer than 5 days.**

**Prolonged therapy should be discussed with ID/Micro**

**SEEK ID/Micro advice for alternative therapy.**

- Audiograms require cooperation of the subject and reliable results are difficult to obtain for children younger than 2 years of age. Brain-stem-evoked response audiometry (BERA) may be considered in infants as an option.
- Ototoxicity on audiogram is defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies.
- If this occurs, aminoglycoside should be discontinued or dosing reduced in frequency to avoid further hearing loss, although the hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change.
- We recommend that patients have **baseline** audiometry and then **monthly** reviews until treatment with aminoglycoside ceases.
- For patients on aminoglycosides longer than 1 month, audiometric and vestibular testing should be performed 4 months after cessation to detect delayed impairments.
- For vestibular toxicity seek ENT for advice.

## Additional Information

### Contacts

- Antimicrobial Stewardship Pharmacist on pager 6658
- Antimicrobial Stewardship Consultant on pager 7092.
- Infectious Diseases Fellow on pager 6675 or
- After hours or on weekends, Microbiologist on-call via switchboard.

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