the children's hospital at Westmead

AMINOGLYCOSIDE DOSING AND MONITORING - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- In suspected sepsis, particularly in immunocompromised patients, the first dose of aminoglycoside therapy should not be delayed pending results of blood tests.
- Electrolytes, urea and creatinine (EUC) must be monitored at commencement and during aminoglycoside therapy.
- Dosage should be based on the patient's adjusted body weight (AdjBW) in obese children with BMI ≥95th percentile
- 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.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st April 2021	**Review Period**: 3 years
Team Leader:	Antimicrobial Stewardship Pharmacist	**Area/Dept.**: Infectious Diseases/Pharmacy

Date of Publishing: 13 April 2021 8:05 AM Date of Printing: 13 April 2021

CHANGE SUMMARY

- Neonatal dosing of aminoglycosides updated (refer to table 1)
- Changes in dosing for obesity to adjusted body weight
- Therapeutic drug monitoring recommendations updated (refer to table 5)
- 13/04/21: Minor review. Changed "ideal body weight (AdjBW)" to "adjusted body weight (AdjBW)", pg 4.

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 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 relate 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 10 mg/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 or empirical therapy for severe febrile neutropenia with risk of gram-negative resistance)

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 ≥95th percentile), dose must be calculated based on adjusted body weight (AdjBW) because aminoglycosides distribute minimally in adipose tissue.

$$Adjusted\ Body\ Weight = IBW + 0.4 \times (\text{Measured weight} - \text{IBW})$$

- Ideal body weight (IBW) 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.

$$Ideal\ Body\ Weight\ (kg) = Height\ (cm)^2\ x\ 1.65/1000$$

Table 1: Dosing recommendations for infants, children, and adults [1-5]

Age	Gentamicin or Tobramycin	Amikacin
1 month–18 years	7.5 mg/kg/dose 24 hourly (max starting dose 320 mg)	15-30 mg/kg/dose 24 hourly (max starting dose 1.5 g) [NB1]
Children with cystic fibrosis [NB2]	10-12 mg/kg/dose 24 hourly (max starting dose 600 mg)	30 mg/kg/dose 24 hourly (max starting dose 1.5 g)
Children with endocarditis [NB2] [NB3]	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 [6-9].

[NB2]: There is no maximum dose.

[NB3]: Used only in combination with beta-lactam for enterococcal and streptococcal synergy. Consult ID Team for advice. The frequency may be reduced to facilitate HITH.

Table 2: Dosing recommendations for neonates <28 days old [1, 2]

Age	Postnatal age	Gentamicin or Tobramycin	Amikacin
Neonate ≤29 weeks postmenstrual age [NB4]	0-7 days	5 mg/kg/dose 48 hourly	14 mg/kg/dose 48 hourly
	8-28 days	5 mg/kg/dose 48 hourly	12 mg/kg/dose 36 hourly
	≥ 29 days	5 mg/kg/dose 48 hourly	12 mg/kg/dose 24 hourly
Neonate 30-34 weeks postmenstrual age [NB4]	0-7 days	5 mg/kg/dose 36 hourly	12 mg/kg/dose 36 hourly
	≥8 days	5 mg/kg/dose 36 hourly	12 mg/kg/dose 24 hourly
Neonate ≥35 weeks postmenstrual age [NB4]		5 mg/kg/dose 24 hourly	12 mg/kg/dose 24 hourly

[NB4]: postmenstrual age= gestational age + postnatal age

Table 3: Dosing recommendations for renal impairment [1, 10]

Less nephrotoxic alternatives should be considered in patients with renal impairment

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^2	Normal dosing (refer to Table 1)	
	30-50 mL/min/1.73m^2	2.5 mg/kg/dose 12 hourly	7.5 mg/kg/dose 12 hourly
	10-29 mL/min/1.73m^2	2.5 mg/kg/dose 24 hourly	7.5 mg/kg/dose 24 hourly
	<10 mL/min/1.73m^2	2.5 mg/kg/dose 48-72 hourly	7.5 mg/kg/dose 48-72 hourly

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

$$eGFR\ (mL/min\ /1.73\ \mathrm{m}^2) = \frac{36.2 \times\ height\ (cm)}{serum\ creatinine\ (micromol/L)}$$

Evidence summary of once daily dosing in children:

- 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) [11-23].
- 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 [4].
- 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 [15] (Figure 1).

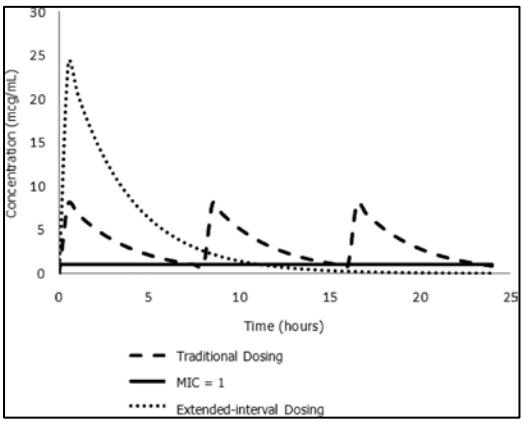

Figure 1: Traditional dosing (8 hourly dosing) versus extended-interval dosing (24 hourly) of aminoglycosides. MIC indicates minimum inhibitory concentration.

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

Administration

Aminoglycosides should be used with great caution in patients with neuromuscular disorders (e.g. myasthenia gravis). These patients should be infused over 30 minutes.

Administration	Gentamicin	Tobramycin	Amikacin
IV injection	****Preferred**** Inject undiluted or diluted in 5-10mL NS slowly over 3-5 minutes		
IV infusion	• Dilute to a convenient volume (20–50 mL G5W or NS). • Infuse over 30 minutes. • Maximum concentration: 10 mg/mL		• Dilute to 0.25–5 mg/mL • Infuse over 30–60 minutes in children and over 1–2 hours in infants. • Maximum concentration:10 mg/mL in G5W, G10W and NS only

Abbreviations: NS: Sodium chloride 0.9%, G5W: Glucose 5% in water, G10W: Glucose 10% in water

- Tobramycin is infused over 30 minutes at CHW for Area Under the Curve (AUC) calculation (Refer to page 10)
- Amikacin can only be given as an IV infusion, there is no evidence to support IV injection for amikacin
- 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.

Monitoring for patients on aminoglycosides

Renal function

Twice weekly EUC monitoring is required in clinically stable patients and should be performed more frequently if renal impairment exists.

- **Accumulation of aminoglycosides within the kidneys results in reversible nephrotoxicity.**
- **Elevated trough concentrations, increased frequency, concurrent nephrotoxins (e.g. vancomycin and amphotericin B), dehydration, severe sepsis, reduced renal perfusion from hypovolemia and prolonged duration of therapy (>5 days) are risk factors for nephrotoxicity [3, 11].**
- 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.
- For patients on aminoglycoside therapy for more than a month, the frequency of EUC is the following:

1st month	Twice a week
2nd month	Weekly
3rd 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.	

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.
Refer to ENT

- 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.

Therapeutic Drug Monitoring (TDM)

- 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 [1, 2, 27]:

<table>
<tr><th rowspan="2">Indication</th><th rowspan="2">Level</th><th rowspan="2">How often</th><th colspan="2">Target level</th></tr>
<tr><th>Gentamicin or Tobramycin</th><th>Amikacin</th></tr>
<tr><td>Empirical therapy ≤48 hours</td><td>Not required</td><td>Not required</td><td>Not applicable</td><td>Not applicable</td></tr>
<tr><td rowspan="2">Empirical therapy >48 hours</td><td>Review use (e.g. cease, switch to a less nephrotoxic agent, or seek ID advice)</td><td rowspan="2">Twice a week</td><td rowspan="2">Trough < 1 mg/L</td><td rowspan="2">Trough < 5 mg/L</td></tr>
<tr><td>If empirical therapy continues >48 hours, before the 4th dose</td></tr>
<tr><td>Febrile neutropenia</td><td>Before the 2nd dose</td><td>Twice weekly</td><td>Trough < 1 mg/L</td><td>Trough < 5 mg/L</td></tr>
<tr><td>Neonate (on general ward)</td><td>Before the 2nd dose</td><td>Twice weekly</td><td>Trough < 1 mg/L</td><td>Trough < 5 mg/L</td></tr>
<tr><td>Neonate (in NICU)</td><td>22 hours after the 2nd dose</td><td colspan="3">Refer to Neomed monograph</td></tr>
<tr><td rowspan="2">Pre-existing renal impairment</td><td rowspan="2">Before the 2nd dose Consider ceasing or changing antibiotic. Seek ID advice.</td><td rowspan="2">At least twice weekly</td><td>Trough < 2 mg/L*</td><td>Trough < 10 mg/L*</td></tr>
<tr><td colspan="2">*The target troughs are higher due to multiple daily dose regimens.</td></tr>
</table>

Directed therapy	Measure Area Under the Curve (see below) ****Preferred****	Twice weekly	AUC: 100 mg.hr/L	Not applicable
	Before the 2nd dose	Twice weekly	Trough < 1 mg/L	Trough < 5 mg/L
Infective exacerbation of Cystic fibrosis	Measure Area Under the Curve (see below)	Twice weekly	AUC: 90-110 mg.hr/L	Not applicable
Endocarditis [2, 5, 37]	Before the 4th dose	At least twice weekly	Trough < 1 mg/L	Not applicable
Amikacin for Mycobacterial infections [6-8]	Measure peak and troughs (see below)			

Area Under the Curve calculations [2, 38-41]:

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 100 mg.hr/L. The range in the literature is between 80-120 mg.hr/L

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

Amikacin for Mycobacterial infections [9, 45, 47]:

- 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.

Level	How often	Target level
AUC **Preferred**	Weekly for 4 weeks then fortnightly (Consider reducing to monthly if renal function remains stable)	320-400 mg.hr/L (depends on MIC)
Peak		25 - 40 mg/L
Trough		< 5 mg/L

- Please contact the Antimicrobial Stewardship/ID Pharmacist on (ext. 52696/pager 6698) for AUC calculations and dose adjustments.

Additional Information

Contacts

- Antimicrobial Stewardship Pharmacist on pager 6658
- Antimicrobial Stewardship Consultant on pager 7092.
- Infectious Diseases Fellow on pager 6675

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