AMINOGLYCOSIDE THERAPY -SCH

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Aminoglycosides, such as gentamicin, have good activity against gram negative organisms causing serious infections but also have potential for toxicity.
- When used, their use should be limited to less than 3 doses (within 48 hours) wherever possible.
- Amikacin use and monitoring should be discussed with the Infectious Diseases Team.
- Once daily administration is standard for most indications.
- These guidelines provide recommendations for appropriate dose, and monitoring of once daily dosing regimens for most children.
- When therapeutic drug monitoring is indicated for gentamicin and tobramycin, aim for a trough level of < 1 mg/L
- Appendix 1 contains a flowchart with summary advice

CHANGE SUMMARY

- This document has had changes made throughout – recommend re-reading the entire document
- Addition of advice for tobramycin and amikacin.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
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Team Leader:	Staff Specialist	**Area/Dept:** Infectious Diseases SCH

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READ ACKNOWLEDGEMENT

- All SCH staff involved in the provision of antimicrobial agents, who prescribe or who administer gentamicin to SCH patients are to read and acknowledge they understand the contents of this document.
- Department Heads and Nursing Unit Managers at SCH should be aware of the document.

TABLE OF CONTENTS

1 Background

Aminoglycosides are used for suspected or proven serious gram negative bacterial infections. Due to potential for nephrotoxicity and ototoxicity, which are more common with increasing duration of use, use should generally be limited to <=3 doses (within 48 hours duration), e.g. for empirical treatment of sepsis.

The pharmacodynamic properties of aminoglycosides make once daily administration of doses (once daily dosing) ideal for most cases. These guidelines provide recommendations for dose, and monitoring of once daily dosing regimens in most children.

As gentamicin is the most commonly used aminoglycoside, most information here is presented for gentamicin prescription. Generally tobramycin can be substituted for gentamicin at the same dose and with the same monitoring parameters. Amikacin dosing is different and this is given in Section 5.

1.1 What is the appropriate gentamicin dose in children?

(see section 4 for the recommended doses in this guideline)

The recommended dose of gentamicin varies by age and clinical condition from 5 - 7.5 mg/kg/day (See section 4). The pharmacokinetics of aminoglycosides support adjusted body weight as the most appropriate weight parameter to use for dose calculation. This is most important in case of obesity.

In obese children (BMI ≥ 95th percentile for age) dose reduction is recommended due to decreased relative volume of distribution.[6] Doses should be calculated based on the Adjusted body weight formula using both the Ideal Body Weight (IBW) and Measured Weight measures.[7-9]

Adjusted body weight = IBW + 0.4 X (Measured Weight - IBW)

Also refer to Appendix 1 for the ***Gentamicin Flowchart****.*

2 Target Population

- **These guidelines are intended for children being treated for suspected or confirmed gram negative infections where intravenous aminoglycosides are indicated**.

These guidelines do NOT provide recommendations for use in:

- Endocarditis (In the synergistic treatment of enterococcal bacterial endocarditis with ampicillin, three-times daily dosing of gentamicin is recommended).[16]
- Cystic fibrosis: seek advice from the Respiratory Team
- Patients with impaired renal function (creatinine clearance [CrCl] less than 50 mL/min/1.73 m^2) – seek advice from the Renal or Infectious Diseases teams
- Surgical prophylaxis: refer to the SCHN Surgical Antimicrobial Prophylaxis Guideline

3 Pre-treatment Assessment & Clinical Monitoring

1. Assess for ***contraindications*** for aminoglycoside therapy ***and risk factors*** for toxicity

   Contraindications

   - Family or personal history of deafness caused by aminoglycosides, as gentamicin may cause immediate and profound deafness in people with a specific mitochondrial mutation.[17]
   - Previous anaphylaxis or allergy to aminoglycosides.
   - Myasthenia gravis (due to risk of neuromuscular blockade).

   Risk factors for toxicity

   - Prolonged duration of therapy (i.e. greater than 3 doses).
   - Concurrent (or prior) administration of potentially nephro- or ototoxic medications:
     - Nephrotoxic agents: e.g. furosemide, vancomycin, amphotericin, cisplatin, other aminoglycosides, aciclovir, regular use of NSAIDs
     - Ototoxic agents: e.g. cisplatin and other aminoglycosides
   - Repeated courses of aminoglycosides (e.g. in preceding 6 months)
   - Renal impairment (i.e. creatinine above normal range for age)
   - Previous aminoglycoside-induced toxicity
2. Assess for ***hearing impairment*** by history prior to starting therapy.
3. Assess for clinically significant ***vestibular*** dysfunction by history and by examination if history is suggestive prior to starting therapy. The signs and symptoms of clinically evident vestibular dysfunction include nystagmus, dizziness, ataxia and/or a positive Romberg's sign. Treatment should be stopped as soon as evidence of vestibular dysfunction occurs.
4. Assess baseline renal function with:
   - serum creatinine (age $\leq$ 1 year); or
   - creatinine clearance (CrCl) (children older than 1 year). For the calculation of CrCl See **dosing tables below.**

   NB: If a recent creatinine result is not available, the first dose of gentamicin should NOT be delayed while awaiting a creatinine result.

4 Gentamicin and Tobramycin

4.1 Gentamicin and Tobramycin Dosing Schedule

Initial dosage of gentamicin and tobramycin for treating infection in neonates and children [18]

Age	**Dose** [N1, N2] **gentamicin or tobramycin**	**Dosing frequency**	**Maximum number of empiric doses** [N3]
Neonates younger than 30 weeks postmenstrual age [N4, N5]	5 mg/kg	48-hourly	2 doses (at 0 and 48 hours)
Neonates **30-34 weeks** postmenstrual age [N4, N5]	5 mg/kg	36-hourly	2 doses (at 0 and 36 hours)
Neonates **35 weeks** postmenstrual age or older [N4, N5]	5 mg/kg	24-hourly	3 doses (at 0, 24 and 48 hours)
Infants and children 1 month to younger than 10 years	7.5 mg/kg up to 320 mg [N6, N7]	24-hourly	3 doses (at 0, 24 and 48 hours)
Children 10 years and older	6 mg/kg up to 560 mg Children with septic shock or requiring intensive care support: 7 mg/kg [N6]	24-hourly	3 doses (at 0, 24 and 48 hours)

N1: *For children with cystic fibrosis, seek advice from the respiratory team. For synergistic therapy (e.g., endocarditis) see Therapeutic Guidelines: Antibiotic*

N2: *When TDM is indicated (see section 4.2), dosing intervals should be adjusted according to the trough level (with an aim of < 1 mg/L).*

N3: *For children with impaired renal function (creatinine clearance [CrCl] less than 50 mL/min/1.73 m^2), seek expert advice from Infectious diseases or Nephrology team. Use the modified (bedside) Schwartz formula to for children older than 1 year [19]*

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

N4: *Postmenstrual age is the time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (postnatal age).*

N5 *Preterm infants, especially if small for gestational age, may have altered pharmacokinetics.*

N6: *Obese patients (BMI ≥ 95th centile) require dose adjustment. See section 1.1.*

N7: *The dose cap does not apply to critically ill children with severe sepsis or septic shock.*

4.2 Monitoring During Gentamicin and Tobramycin Therapy

Appropriate monitoring during therapy includes assessment of both:

1. Serum drug levels (TDM) *if indicated*. Monitoring of drug levels should not replace careful clinical monitoring and adjustment of therapy accordingly; and
2. Clinical outcomes for toxicity (renal function, hearing tests, assessment of vestibular function) and efficacy (i.e. resolution of infection)

1. Therapeutic Drug Monitoring (TDM)

When TDM is indicated, a gentamicin or tobramycin **TROUGH LEVEL** is recommended for neonates, infants and children at SCH. The purpose of this monitoring is for safety, to detect accumulation and potential for toxicity. Other methods of therapeutic drug monitoring, such as use of Hartford nomogram or area-under-the-curve (AUC) monitoring are not in general use at SCH and not covered in this document.

No TDM is necessary:

- in an otherwise healthy child (age ≥ 1 month), if treatment course is <= 3 doses (within 48 hours); *and*
- renal function is normal at baseline and during therapy; *and*
- no concurrent nephro- or ototoxic drugs are used; and
- Child not obese, critically unwell, or under the care of the Haematology/Oncology team; and
- Child has no other risk factors for toxicity (see section 3)

- **TDM is indicated for all other children in whom gentamicin is used**

When TDM is indicated:

- Monitoring using the trough level is recommended.
- **Children with normal renal function**: The first trough level should be done **before the 4th dose** (if therapy will be ongoing beyond this dose). Trough levels should remain below 1 mg/L. Subsequent monitoring is usually every 3 days, but more frequently if renal function is changing rapidly or substantially (e.g., critically ill patients with severe sepsis or suspected acute renal failure).[18]
- **Neonates**: TDM is recommended for therapy > 48 hours. The first trough level should be taken at 22 hours after the second dose. Subsequent dose interval is based on the 22 hour gentamicin concentration as indicated in the table below:

Gentamicin level (22 hours post–dose)	Interval
≤ 1.2 mg/L	Every 24 hours after previous dose
1.3 mg/L — 2.6 mg/L	Every 36 hours after previous dose
2.7 mg/L — 3.5 mg/L	Every 48 hours after previous dose
≥ 3.6 mg/L	Hold dose, repeat concentration at 24 hours

- In **renal impairment**, TDM should be done **prior to each dose** whilst renal function is impaired

- For any patient, **if the gentamicin trough level is high**, discuss need for ongoing therapy with the Infectious Diseases team and check renal function.

2. Monitoring of clinical outcomes for toxicity

Monitoring is recommended in patients with risk factors for gentamicin toxicity.

a) Renal Function

- Serum creatinine or creatinine clearance should be determined:
  - at baseline;
  - with serum gentamicin levels after day 3 and then every 3 days during therapy (or more frequently if renal impairment is detected at any time).
- Worsening renal function may be an early indicator of impending clinical toxicity.

If nephrotoxicity occurs at any time, consider alternative antimicrobial therapy.

b) Hearing and vestibular function

Ototoxicity and vestibular toxicity is often irreversible. Testing for hearing and vestibular function should be done for patients receiving gentamicin for **longer than 5 days** and repeated periodically if therapy is continued for more than 14 days**.** See section 3, point 3.

In summary, despite monitoring and maintaining gentamicin levels within an accepted range, it is possible for toxicity to occur. The most reliable way to prevent aminoglycoside toxicity is to minimise its use to recommended indications only. Monitoring of drug levels should not replace careful evaluation of risk factors for toxicity prior to commencing aminoglycosides and subsequent clinical monitoring of the patient with respect to efficacy, toxicity and adjustment of therapy accordingly.

4.3 Administration of gentamicin and tobramycin

Gentamicin and tobramycin prescribed according to these guidelines may be administered IV as a slow push over 3 to 5 minutes, or a 30 minute infusion. *For further information regarding infusion rates, dilution, compatibility refer to local injectable guidelines.*

Slow push administration of gentamicin over 3 to 5 minutes has advantages over infusion as it is easier and faster to administer and may achieve higher peak levels. Slow push administration has not been associated with increases in the rates of ototoxicity or nephrotoxicity.[11-15]

5 Amikacin

Note: Amikacin is a highly restricted antimicrobial.

Initial amikacin dosage for treating infection in children [18]

Age	**Amikacin Dose** [N1, N2, N3]	**Dosing frequency** [N2]
Infants and children 1 month to younger than 10 years	30 mg/kg up to 1.25 g [N4, N5, N6]	24-hourly
Children 10 years and older	24 mg/kg up to 2.25 g Children with septic shock or requiring intensive care support: 28 mg/kg [N4,N6]	24-hourly

N1: *Do not use the dosages in this table for Mycobacterial infections; consult ID for dose and TDM.*

N2: *Perform pre-treatment assessment, including renal function as advised in section 3 Consult ID prior to initiation and seek advice regarding TDM if therapy continues beyond a single dose. Peak levels may be required for dose adjustment, dosing interval (frequency) should be adjusted according to the trough level (with an aim of < 4 mg/L).*

N3: *For children with impaired renal function (creatinine clearance [CrCl] less than 50 mL/min/1.73 m^2), seek expert advice from ID or Nephrology team. Use the modified (bedside) Schwartz formula to for children older than 1 year* [19]

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

N4: *Obese patients (BMI ≥ 95th centile for age) require dose adjustment. See section 1.1.*

N5: *The dose cap does not apply to critically ill children with severe sepsis or septic shock.*

N6: *The amikacin doses in this table are recommended in the eTG and derived by multiplying the gentamicin dose by four.*

Initial amikacin dosage for treating infection in neonates[22]

Age	**Postnatal age**	**Amikacin Dose** [N1, N2]	**Dosing frequency** [N3]
Neonates younger than 30 weeks postmenstrual age [N4, N5]	0-7 days	14 mg/kg	48-hourly
	8-28 days	12 mg/kg	36-hourly
	29 days or older	12 mg/kg	24-hourly
Neonates 30-34 weeks postmenstrual age [N4, N5]	0-7days	12 mg/kg	36-hourly
	8 days or older	12 mg/kg	24-hourly
Neonates 35 weeks postmenstrual age or older [N4, N5]	All	12 mg/kg	24-hourly

N1: *The doses in this table have been adapted from the Australasian Neonatal Medicines Formulary (22).*

N2: *Perform pre-treatment assessment, including renal function as advised in section 3. Consult ID prior to initiation and seek advice regarding TDM if therapy continues beyond a single dose. Peak and trough levels may be required for dose adjustment.*

N3: *Dosing interval (frequency) should be adjusted according to the trough level (with an aim of < 4 mg/L).*

N4: *Postmenstrual age is the time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (postnatal age).*

N5: *Preterm infants, especially if small for gestational age, may have altered pharmacokinetics*

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Appendix 1 – Gentamicin flowchart

THIS FLOWCHART SHOULD BE READ IN CONJUNCTION WITH THE 'ONCE DAILY GENTAMICIN' SCH GUIDELINE

Pre-therapy assessment

If treatment with gentamicin is indicated:

- Use should be restricted to up to 3 doses (within 48 hours), unless guided by specific clinical indication and culture results;
- Baseline creatinine should be taken and checked before a second dose of gentamicin is given. If the patient has known abnormal renal function, *consult Renal team for advice;*
- Use should be avoided where possible in patients with abnormal hearing OR abnormal vestibular function.
- Multi-daily dosing may be indicated in endocarditis: *consult ID for advice*;
- Assess risk factors and co-morbidities, including obesity
- **Gentamicin** is **contraindicated in patients with personal or family history of aminoglycoside induced deafness, previous anaphylaxis or allergy to aminoglycosides and myasthenia gravis**

Dose

Dose 24-hourly in term neonates and children
See **Table 1** for dosing.

Monitoring Clinical + TDM

NO drug level monitoring if:

- Age ≥ 1 month; *and*
- Previously well & not critically ill; *and*
- Expected treatment course up to 3 doses (within 48 hours); *and*
- Normal renal function (baseline and during therapy); *and*
- No concurrent nephro- or ototoxic drugs.

Monitoring required if:

- Neonate (age < 1 month); *or*
- Expected treatment course > 48 hours; *or*
- Haematology / oncology patient; *or*
- Critically unwell / ICU patient; *or*
- Cystic fibrosis patient; *or*
- Obese patient (>95th centile BMI for age); *or* Renal impairment or other risk factors for toxicity *(see section 3 above)*.

Clinical toxicity:

- Renal function;
- Hearing & vestibular function.

Therapeutic Drug Monitoring (TDM)

TDM for once daily dosing:

- Before each dose in renal impairment.
- Before the 4th dose (or the first dose of directed therapy), then every 3 days. More frequently if renal function deteriorating.
- Before third dose in neonates.