ONCE DAILY GENTAMICIN - SCH

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Aminoglycosides should be used sparingly in children because of the concerns about toxicity.
- When used, their use should be limited to less than 3 doses (within 48 hours) wherever possible.
- Once daily administration is standard.
- These guidelines provide recommendations for appropriate indications, dose, and monitoring of once daily dosing regimens in children.
- When therapeutic drug monitoring is indicated, trough level is recommended, with an aim for a trough level of < 1 mg/L
- Refer to Appendix 1 for the Gentamicin Flowchart

CHANGE SUMMARY

- Trough level has replaced the Hartford Nomogram for therapeutic drug monitoring.
- This document has had changes made throughout – recommend re-reading the entire document.

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.

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1 Background

Gentamicin is indicated in the management of suspected or proven gram negative bacterial infections. Due to concerns about nephrotoxicity and ototoxicity, its use should be limited to 3 doses (within 48 hours duration) wherever possible, e.g. for empirical treatment of sepsis.

The pharmacodynamic properties of aminoglycosides make once daily administration of doses (once daily dosing) preferable to the traditional divided doses-approach of giving aminoglycosides two or three times daily (three times daily dosing). Clinical evidence supports the sparing use of aminoglycosides, and the use of once daily dosing rather than three times daily dosing regimens for most paediatric patients in whom aminoglycoside use cannot be avoided. These guidelines provide recommendations for appropriate indications, dose, and monitoring of once daily dosing regimens in children.

1.1 What is the appropriate dose in children?

(see section 2.3 for the recommended doses in this guideline)

Clinical trials among children have used single daily doses ranging from 5 – 10.5 mg/kg/day. Neonatal studies have used single daily doses of 4-5 mg/kg/day.[1] Higher doses of gentamicin may be required in the setting of febrile neutropenia, particularly in younger patients, due to higher volumes of distribution.[2-4] Minor elevations in creatinine are common with high doses but significant nephrotoxicity is limited mainly to patients concurrently receiving other nephrotoxins.[3] Once daily dosing gentamicin has also been shown to be effective in critically unwell children, e.g. in ICU.[5]

In obese children (BMI ≥ 95th percentile for age) dose reduction is recommended due to decreased volume of distribution.[6] Doses should be calculated based on the Calculated Dosing Weight (CDW) using Ideal Body Weight (IBW) and Total Body Weight (TBW) measures.[7-9]

CDW = (0.4 X [TBW-IBW]) + IBW

To estimate the IBW in obese children Moore method may be used.[10] It can be calculated by using the corresponding weight for the height percentile on the growth chart. The patient's height-for-age percentile is determined, and the IBW is the weight that corresponds to that weight percentile (e.g., a patient in the 50th percentile height-for-age and gender would have an IBW that corresponds to the 50th percentile weight-for-age and gender).

The following are links for the growth charts according to the age and gender:

- Boys from birth to 36 months: http://www.cdc.gov/growthcharts/data/set1clinical/cj41l017.pdf
- Girls from birth to 36 months: http://www.cdc.gov/growthcharts/data/set1clinical/cj41l018.pdf
- Boys: 2-20 years: http://www.cdc.gov/growthcharts/data/set1clinical/cj41l021.pdf
- Girls: 2-20 years: http://www.cdc.gov/growthcharts/data/set1clinical/cj41l022.pdf

1.2 What is the appropriate method of therapeutic drug monitoring (TDM) and its indications?

When TDM is indicated gentamicin **TROUGH LEVEL** is recommended for neonates, infants and children.

Due to pharmacokinetic variations in volume of distribution and renal clearance, **TDM is indicated for:**

- Neonate (age < 1 month)
- Expected treatment course greater than 3 doses (within 48 hours)
- Haematology / oncology patient
- Critically unwell / ICU patient
- Cystic fibrosis patient
- Obese patient (>95th centile BMI)
- Other risk factors for toxicity (**see** **section 2.2**).

No TDM is necessary:

- in an otherwise healthy child (age ≥ 1 month), if treatment course is up to 3 doses (within 48 hours); *and*
- renal function is normal at baseline and during therapy; *and*
- no concurrent nephro- or ototoxic drugs are used.

1.3 How should gentamicin be administered?

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. There is extensive adult and paediatric experience with slow push administration, which has not been associated with increases in the rates of ototoxicity or nephrotoxicity.[11-15] No neuromuscular toxicity has been seen in patients without underlying neuromuscular disorders, such as myasthenia gravis.[14,15] **Gentamicin may be administered as a slow push over 3 to 5 minutes, except in patients with pre-existing neuromuscular disorders where it may be given as a 30 minute infusion**.

In summary, despite monitoring and maintaining gentamicin levels within an accepted range, it is possible (although uncommon) for toxicity to occur. The most reliable way to prevent aminoglycoside toxicity is to minimise its use. 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.

2 Recommendations

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

2.1 Target Population

- **These guidelines are intended for children being treated for suspected or confirmed gram negative sepsis where gentamicin is indicated**.

They are NOT for use in:

- children with endocarditis (In the synergistic treatment of enterococcal bacterial endocarditis with ampicillin, traditional three times daily dosing of gentamicin remains standard practice).[16]
- children with cystic fibrosis: seek advice from the respiratory team
- children with impaired renal function (estimated glomerular filtration rate [eGFR] less than 50 mL/min/1.73 m^2)

2.2 Pre-treatment Assessment & Clinical Monitoring

1. Assess for ***contraindications*** for gentamicin 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.

   Risk factors

   - Prolonged duration of therapy (i.e. greater than 3 doses).
   - Concurrent (or prior) administration of potentially nephro- or ototoxic medications:
     - Nephrotoxic agents: eg frusemide, vancomycin, amphotericin, cisplatin, other aminoglycosides, aciclovir, regular use of NSAIDs
     - Ototoxic agents: eg 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. Absence of ***hearing impairment*** should be assessed by history at the start of therapy.
3. Absence of clinically significant ***vestibular*** dysfunction should be assessed by history at the start of 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. Baseline renal assessment should include:
   - serum creatinine (age $\leq$ 2yrs); or
   - estimated glomerular filtration rate eGFR (age > 2yrs). For the calculation of eGFR See below **(Table 1, NB7)**

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

2.3 Dosing Schedule

TABLE 1: DAILY GENTAMICIN DOSES[18]				
Preterm Neonate: <38 weeks postmenstrual age (NB1)				
Age		**Dose**	**Dosing frequency (NB5)**	**Maximum number of empiric doses**
Neonates younger than 30 weeks	Postnatal age 0 to 7 days	5 mg/kg	48-hourly	2 doses (at 0 and 48 hours)
	Postnatal age 8 to 28 days	4 mg/kg	36-hourly	2 doses (at 0 and 36 hours)
	Postnatal age 29 days or older	4 mg/kg	24-hourly	3 doses (at 0, 24 and 48 hours)
Neonates 30-34 weeks	Postnatal age 0 to 7 days	4.5 mg/kg	36-hourly	2 doses (at 0 and 36 hours)
	Postnatal age 8 days or older	4 mg/kg	24-hourly	3 doses (at 0, 24 and 48 hours)
Neonates 35 to 37 weeks		4 mg/kg	24-hourly	3 doses (at 0, 24 and 48 hours)
Neonates 38 weeks postmenstrual age and older, infants and children (NB1)				
Neonate: ≥38 weeks gestation, 0-7 days of life		4 mg/kg	24-hourly	3 doses (at 0, 24 and 48 hours)
Neonate: ≥38 weeks gestation, 8-28 days of life		5 mg/kg	24-hourly	3 doses (at 0, 24 and 48 hours)
Infants and Children				
Infants and children		7.5 mg/kg (max:320 mg per day) **NB 2-7**	24-hourly	3 doses (at 0, 24 and 48 hours)

NB1*: 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).*

NB2*: The dose cap does not apply to critically ill children with severe sepsis or septic shock.*

NB3*: Obese patients (BMI ≥ 95th centile) require dose adjustment. Initial gentamicin dose should be based on the IBW.* ***See section 1.1 for the method of calculating IBW****.*

NB4*: Higher doses may be required in critically unwell patients or patients with febrile neutropenia. Consult ID for advice.*

NB5*: When TDM is indicated, dosing intervals should be adjusted according to the trough level (with an aim of < 1 mg/L).*

NB6: *For use of aminoglycoside in children with cystic fibrosis, seek advice from the respiratory team.*

NB7*: For children with impaired renal function (estimated glomerular filtration rate [eGFR] less than 50 ml/min/1.73 m^2), seek expert advice from Infectious diseases or Nephrology team. Use the modified Schwartz formula to calculate (eGFR) for children 2 years or older*[19]

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

2.4 Monitoring During Gentamicin 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:

- Monitoring using the trough level is recommended.
- If gentamicin is to be used for > 48 hours (so, "targeted therapy") TDM should be done. The first trough level therefore should be done **before the 4th dose** (*which is the first dose of directed therapy*). Subsequent monitoring is usually every 48 hours, but more frequently if renal function is changing rapidly or substantially (eg: critically ill patients with severe sepsis or suspected acute renal failure).[18]
- In preterms and neonates: TDM is recommended **before the second dose** of gentamicin. Further trough levels should be considered before every subsequent third dose (i.e. before 5th dose, 8th dose etc.).[21]
- In **renal impairment**, TDM should be done **prior to each dose** whilst renal function is impaired
- If trough level is high, discuss with infectious diseases team for extending dosing interval.

2. Monitoring of clinical outcomes for toxicity

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

a) Renal Function

- Serum creatinine or estimated GFR 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. Because ototoxicity and vestibular toxicity is often irreversible, treatment should usually be stopped.

b) Hearing and vestibular function

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 2.2, point 3.

3 References

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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 72 hours), unless guided by culture results or clinical deterioration;
- 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;
- 'Traditional' / multi-daily dosing may be indicated in endocarditis: *consult ID*;
- Assess co-morbidities, including obesity.

Dose

Dose 24-hour
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 ≥ 72 hours; *or*
- Haematology / oncology patient; *or*
- Critically unwell / ICU patient; *or*
- Cystic fibrosis patient; *or*
- Obese patient (>95th centile BMI); *or*
- Other risk factors for toxicity *(see section 2.2 above)*.

Clinical toxicity:

- Renal function;
- Hearing & vestibular function.

Therapeutic Drug Monitoring (TDM)

TDM for once daily dosing:

- Before the 4th dose (which is the first dose of directed therapy), then every 48 hr. More frequently if renal function deteriorating.
- Before second dose in neonates.
- Prior to each dose in renal impairment.