Whittington Health NHS

Guideline for Gentamicin Dosing in Adults

Subject:	Gentamicin Dosing in Adults
Policy Number	IPC/Micro 24
Ratified By:	Clinical Guidelines Committee
Date Ratified:	May 2008
Version:	3
Policy Executive Owners:	Dr Julie Andrews/Dr Michael Kelsey Consultant Microbiologists
Designation of Author:	Ai-Nee Lim, Lead Antimicrobial Pharmacist
Name of Assurance Committee:	Infection Prevention & Control Committee
Date Issued:	October 2015
Review Date:	October 2018
Target Audience:	All clinical staff involved in prescribing, dispensing and administering antibiotics. Doctors, Nurses and Pharmacists.
Key Words:	Gentamicin, dosing, treatment, therapeutic dose monitoring

Version Control Sheet

Version	Date	Author	Status	Comment
2.2	October 2010	Ai-Nee Lim (Lead Pharmacist, Antimicrobials) Dr M Kelsey (Consultant Microbiologist) Dr Julie Andrews (Consultant Microbiologist)	In-active	Update
3	October 2015		Active	Three-yearly review of guideline. • Guideline template updated, which now includes 'Criteria for use'. • Extra prescribing information been added to the 'Background' section. • Reference list updated.

➢ Criteria for use

This guideline provides guidance on gentamicin prescribing, therapeutic drug monitoring and administration for adult patients.

➢ Background

IMPORTANT: Careful selection of empiric dosing regimes and serum level monitoring are needed to ensure the safety and efficacy of this drug.

There are 3 different approaches to dosing Gentamicin:

(i) **Once daily dosing**: 7 mg/kg

(ii) **Conventional multiple daily dosing**: 1 – 1.5 mg/kg 8 hourly

(iii) **Endocarditis**: 1 mg/kg 8 hourly

Duration of treatment:

Gentamicin treatment should **not usually exceed 7 days** [4]. Seek Microbiology advice.

Patient monitoring

The main side effects (i.e. ototoxicity and nephrotoxicity) are dose-related [4].

- **Serum-gentamicin concentration** must be monitored in all patients.
- All patients should have the **renal function** (i.e. urea, creatinine and electrolytes) assessed before starting gentamicin therapy and throughout the treatment course.

Renal impairment

In patients with renal impairment, **dosing interval** may need to be increased according to the level of renal impairment and the gentamicin level.

Obesity

In obese patients, gentamicin dose should be calculated according to the **corrected body weight (CBW)** [7]. For all other patients, actual body weight (ABW) should be used to calculate the dose.

Interactions

Risk of ototoxicity and nephrotoxicity is increased with concurrent use of **vancomycin, ciclosporin**, **cisplatin**, loop diuretics (e.g. **frusemide, bumetanide**), **amphotericin, capreomycin** and **colistimethate** [4, 6]. In such cases consider monitoring Gentamicin levels more closely.

Gentamicin can enhance effects of **neuromuscular blocker** (e.g atracurium, vecuronium, rocuronium suxamethonium – which can lead to prolonged and in some cases fatal respiratory depression. Appropriate measures should be taken to accommodate the increased neuromuscular blockade [6].

Contra-indication

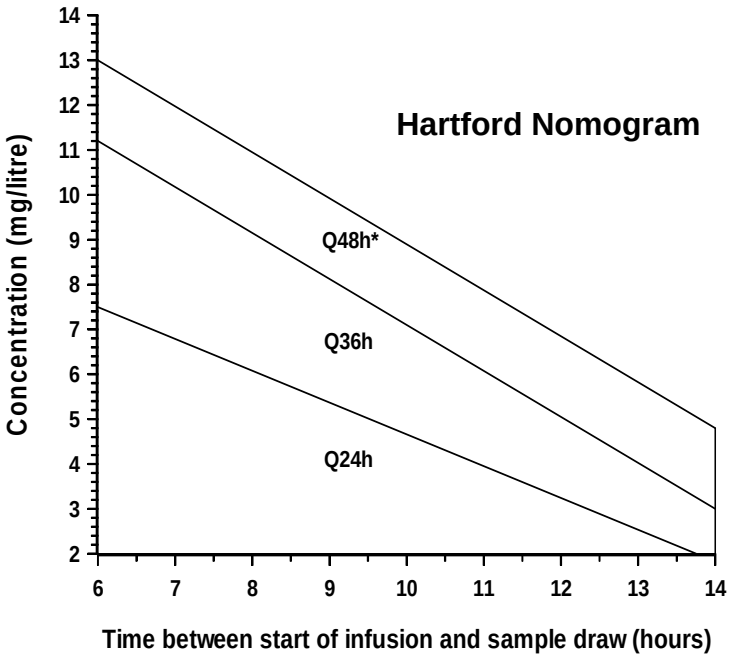
AVOID gentamicin in patients with **myasthenia gravis** – can impair neuromuscular transmission [6].

➢ Prescribing

	Once daily 7 (seven) mg/kg dosing	Conventional multiple daily dosing	Endocarditis (synergistic dosing)
Inclusion criteria:	➢ Suspected or documented Gram-negative infections. ➢ Sensitive Gram-positive infections on the advice of microbiology.	➢ Suspected or documented Gram-negative infections but are **NOT eligible for the once daily dosing** regimen (*see under exclusion criteria*).	➢ Endocarditis concomitantly treated with a beta-lactam.
Exclusion criteria:	Patients presenting with one or more of the following should NOT be treated with the once daily dosing regimen: ▪ Severe liver disease / ascites (> 20% actual body weight) ▪ Renal impairment (creatinine clearance < 20ml/minute) ▪ Endocarditis ▪ Prophylaxis ▪ Major burns (> 20% total body surface area) ▪ Pregnancy ▪ Cystic fibrosis	N/A	N/A
Standard dose (rounded to the nearest 20mg)	7 mg/kg* once a day **Level must be checked BEFORE giving the second dose.** Use the Hartford nomogram to guide dosing interval (see below). If serum level is not completed before the next dose, and renal function appears normal and urine output has not fallen, give the second dose to ensure continuity of therapy.	**Loading dose:** 2 mg/kg* stat (*independent of renal function*) **Maintenance dose:** 1 – 1.5 mg/kg* 8 hourly	1 mg/kg* 8 hourly
Dosing in renal impairment	**Level must be checked BEFORE any subsequent doses are given.** Use the Hartford nomogram to guide dosing interval (see below).	In renal impairment, dosing interval will need to be increased as shown below [(1)]: **Renal function** / **CrCl (ml/min)**§ / **Dosing interval** Normal: > 70: 8 hourly Mildly impaired: 30 – 70: 12 hourly Moderately impaired: 10 – 29: 24 hourly Severely impaired: 5 – 9: 48 hourly Continuous Renal Replacement Therapy (CRRT): 24 hourly *Dosing interval may require further adjustments according to levels.*	

* If obese (i.e. BMI ≥ 25 or less than 20% over IBW), use corrected body weight (CBW) instead of actual body weight . See page 5.]

§ See Creatinine Clearance calculation on page 5.

	Once daily 7 (seven) mg/kg dosing	Conventional multiple daily dosing	Endocarditis (synergistic dosing)
Timing of assay	A **single** blood sample, at any time between **6 – 14 hours** after the start of the infusion. *NB: It is advisable to take blood samples nearer the 6-hour timeframe whenever possible.*	**Trough (pre-dose)**: immediately BEFORE giving a dose.	
Assay frequency	After the **first** dose. ***Stable renal function*:** Then twice weekly (unless otherwise advised by Microbiology) ***Unstable or impaired renal function*:** Then daily or as advised by Microbiology	***Stable renal function*:** Before the **3rd** or **4th** dose. Re-check levels twice a week. ***Unstable or impaired renal function*:** Before the **2nd** dose. Then daily or as advised by Microbiology	
Therapeutic range	Interpret results using the Hartford nomogram. 	Aim for: **Trough (pre-dose)**: less than 2 mg/L (*for endocarditis: less than 1 mg/L)* *Dosage should be adjusted by varying the dosing interval rather than the unit dose. The dosing interval will be recommended as 8, 12, 24, 36 or 48 hours, depending on the level measured. Contact Microbiology / Pharmacy for advice.*	

Interpretation of measured level

The Gentamicin level is evaluated via the Hartford nomogram.

- If the level falls in the area designated Q24H, Q36H or Q48H, the dosing interval will be recommended as 24, 36 or 48 hours respectively.
- If the level falls on the line, the longer dosing interval will be recommended.
- If the level falls above Q48H* on the nomogram at the given time, the scheduled therapy should be stopped and serial levels followed to determine the appropriate time of the next dose (when the level falls below 1 mg/L).

‡ Peak levels may occasionally be useful but should only be taken on the request of Microbiology. **Peak (post-dose)**: ONE HOUR after giving a dose. Aim for: 5 – 10 mg/L (*for endocarditis: 3 – 5 mg/L)*

	Once daily 7 (seven) mg/kg dosing	Conventional multiple daily dosing	Endocarditis (synergistic dosing)
Sample details MUST be recorded on the microbiology assay request form in order for results to be interpreted	• Time the infusion was STARTED • Time blood sample was taken	• Time the dose was given • Time blood sample was taken e.g. pre-dose 'trough' or 1 hour post-dose 'peak' • Dose and dosing interval	
	Sample should be collected in a **6ml red top vacutainer tube (serum sample)** separate from any other tests. Gentamicin assays are available from 09:00 to 16:00 Monday to Friday. On weekends, samples should arrive in the laboratory no later than 11:00.		
Length of treatment	Whenever possible, do not treat for more than seven days. Prolonged treatment with Gentamicin carries an increased risk of toxicity even when levels are within acceptable limits.		
Administration	Dilute in 100ml glucose 5% or sodium chloride 0.9%. Infuse intravenously over 1 hour.	Give neat. Slow bolus intravenous injection over 2 – 3 minutes.	
Incompatibility	The beta-lactam ring in various penicillins, cephalosporins and other beta-lactam antibiotics, inactivates Gentamicin. DO NOT mix these together in a syringe / infusion bag or administer through the same intravenous line. Give at separate sites or flush line with sodium chloride 0.9% in-between drugs.		

*** Dose calculated using Actual Body Weight unless obese.**

If obese i.e. BMI ≥ 25 or > 20% over Ideal Body Weight (IBW) then dose should be based on Corrected Body Weight (CBW):

- Ideal Body Weight (IBW) / kg

  MALE: IBW = 50kg + (2.3 x every inch over 5 feet)
  OR
  = 50kg + (0.91 x every cm over 152.4cm)

  FEMALE: IBW = 45.5kg + (2.3 x every inch over 5 feet)
  OR
  = 45.5kg + (0.91 x every cm over 152.4cm)

- Excess Body Weight (EBW) / kg

  EBW = Actual Body Weight – Ideal Body Weight

- Corrected Body Weight (CBW) / kg

  CBW = Ideal Body Weight + (0.4 x EBW)

§ Estimate creatinine clearance (CrCl) using the Cockcroft & Gault equation:

MALE: $\text{CrCl (ml/min)} = \frac{1.23 \times (140 - \text{age}) \times \text{Body Weight (kg)}}{\text{Serum Creatinine (micromol/l)}}$

FEMALE: $\text{CrCl (ml/min)} = \frac{1.04 \times (140 - \text{age}) \times \text{Body Weight (kg)}}{\text{Serum Creatinine (micromol/l)}}$

NB: If > 20% overweight, use Ideal Body Weight (IBW) to calculate CrCl.

➢ Contacts

During working hours (Monday to Friday, 09:00 – 17:00)

SpRs in Microbiology	ext. 5085 / 5780, or bleep 3069
Consultant Microbiologist	ext. 5082 / 3894
Lead Pharmacist, Antimicrobials	ext. 3644 or bleep 3138

Out of hours

On-call SpR in Microbiology	Via Whittington switchboard
On-call Pharmacist	Via Whittington switchboard

➢ References

1. Ashley C, Currie A (Ed). The Renal Drug Handbook. 2nd Ed 2004, Radcliffe Medical Press, Oxford.
2. Freeman C, Nicolau D, Belliveau P and Nightingale C. Once-daily dosing of aminoglycosides: review and recommendations for clinical practice. *Journal of Antimicrobial Chemotherapy* 1997; 39:677 – 686
3. Nicolau D. et al. Experience with a once daily aminoglycoside program administered to 2,184 adult patients. *Antimicrobial Agents and Chemotherapy* 1995; 35:650 – 655
4. British Medical Association and Royal Pharmaceutical Society. British National Formulary 68 (September 2014 – March 2015) BMJ Group and Pharmaceutical Press, London.
5. Shulman R, Drayan S, Harries M, Hoare D, Badcott S (Ed). UCL Hospitals Injectable Drug Administration Guide. 1st Ed 1998, Blackwell Science, Oxford.
6. Stockley's Drug interaction (online). Pharmaceutical Press. Accessed on 13/10/2014.
7. Wurtz, R. et al. Antimicrobial dosing in obese patients. *Clinical Infectious Diseases* 1997; 25: 112 – 118

➢ Compliance with this guideline – Tool to develop monitoring arrangements for policies and guidelines

What key element(s) need(s) monitoring as per local approved policy or guidance?	Who will lead on this aspect of monitoring? Name the lead and what is the role of the multidisciplinary team or others if any.	What tool will be used to monitor/check/observe/ Assess/inspect/ authenticate that everything is working according to this key element from the approved policy?	How often is the need to monitor each element? How often is the need complete a report ? How often is the need to share the report?	What committee will the completed report go to?
Element to be monitored	**Lead**	**Tool**	**Frequency**	**Reporting arrangements**
Appropriate dosing and monitoring of gentamicin.	Respective speciality team supported by the Microbiology & Pharmacy Department.	In-house audit tool.	Ad hoc as issues arises.	Respective departmental meeting.

To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval

		Yes/No	Comments
1.	**Does the procedural document affect one group less or more favourably than another on the basis of:**		
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
	• Disability - learning disabilities, physical disability, sensory impairment and mental health problems	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	No	
4.	**Is the impact of the procedural document likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the procedural document without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this procedural document, please refer it to the Director of Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact the Director of Human Resources.

Checklist for the Review and Approval of Procedural Document

To be completed and attached to any procedural document when submitted to the relevant committee for consideration and approval.

	Title of document being reviewed:	Yes/No	Comments
1.	**Title**		
	Is the title clear and unambiguous?	Yes	
	Is it clear whether the document is a guideline, policy, protocol or standard?	Yes	
2.	**Rationale**		
	Are reasons for development of the document stated?	Yes	
3.	**Development Process**		
	Is it clear that the relevant people/groups have been involved in the development of the document?	Yes	
	Are people involved in the development?	Yes	
	Is there evidence of consultation with stakeholders and users?	Yes	
4.	**Content**		
	Is the objective of the document clear?	Yes	
	Is the target population clear and unambiguous?	Yes	
	Are the intended outcomes described?	Yes	
5.	**Evidence Base**		
	Are key references cited in full?	N/A	
	Are supporting documents referenced?	N/A	
6.	**Approval**		
	Does the document identify which committee/ group will approve it?	Yes	
7.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	Yes	
8.	**Document Control**		
	Does the document identify where it will be held?	Yes	
9.	**Process to Monitor Compliance and Effectiveness**		
	Are there measurable standards or KPIs to	Yes	

	Title of document being reviewed:	Yes/No	Comments
	support the monitoring of compliance with and effectiveness of the document?		
	Is there a plan to review or audit compliance with the document?	Yes	
10.	**Review Date**		
	Is the review date identified?	Yes	
	Is the frequency of review identified? If so is it acceptable?	Yes	
11.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for co-ordinating the dissemination, implementation and review of the document?	Yes	

Executive Sponsor Approval			
If you approve the document, please sign and date it and forward to the author. Procedural documents will not be forwarded for ratification without Executive Sponsor Approval			
Name		Date	
Signature			
Relevant Committee Approval			
The Director of Nursing and Patient Experience's signature below confirms that this procedural document was ratified by the appropriate Governance Committee.			
Name		Date	
Signature			
Responsible Committee Approval – only applies to reviewed procedural documents with minor changes			
The Committee Chair's signature below confirms that this procedural document was ratified by the responsible Committee			
Name		Date	
Name of Committee		Name & role of Committee Chair	
Signature			

Appendix 1

Rationale for using once daily dosing over conventional multiple daily dosing

- ***Concentration-dependent killing action of Gentamicin is enhanced***. With the once daily dosing regimen, peak serum concentration is maximised to achieve optimal bactericidal activity and to prevent bacterial regrowth.
- ***Once daily dosing regimen takes advantage of the post-antibiotic effect (PAE) of Gentamicin.*** Bacterial growth continues to be suppressed despite Gentamicin concentration falling below the minimum inhibitory concentration (MIC). PAE is prolonged with the higher peak serum concentration of a once daily dosing regimen.
- ***Constant exposure to Gentamicin has been shown to promote adaptive resistance*****, leading to decreased bacterial killing.** The longer dosing interval of the once daily dosing regimen allows for a drug-free period in which bacteria that have developed a relative resistance to Gentamicin are allowed to become sensitive again.
- ***Nephrotoxicity and possibly ototoxicity is less with once daily dosing of Gentamicin***. It is suggested that Gentamicin uptake in the renal cortical and cochlear cells is mediated by a mechanism that is saturable and that drug accumulation is reduced with a less frequent administration of Gentamicin.
- ***Once daily dosing is also more convenient to administer and monitor***.

Situations where once daily dosing is NOT appropriate

- There are insufficient data available for the use of once daily dosing in population of patients with significant alteration in the pharmacokinetic parameters of volume of distribution and/or drug clearance (refer to exclusion criteria below). Conventional multiple daily dosing should be used in these patients.
- Once daily dosing is not advocated for use in antimicrobial surgical prophylaxis therapy and infections where Gentamicin is used for synergism (such as in combination with a beta-lactam agent for the treatment of Gram-positive infection, particularly enterococcus and streptococcus) in which 'sub-therapeutic' level of Gentamicin is adequate to achieve synergy and risk of toxicity may be minimised.

**** PLEASE REFER TO SEPARATE DOCUMENT FOR PROPHYLAXIS DOSE FOR GENTAMICIN AND GENTAMICIN DOSING IN PAEDIATICS AND NEONATALS ****

Please see Whittington Hospital NHS Trust Guidelines:
'Paediatric and Neonatal Gentamicin Guideline'
'Surgical Antimicrobial Prophylaxis Guidelines'