Document Control

Title

Gentamicin in Adults, including Extended Interval Gentamicin (5mg/kg) and Multiple Daily Dosing Guidance Guideline

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Version	Date Issued	Status	Comment / Changes / Approval
1.5	Sept 2013	Revision	Review of literature (section 10). Review of audit data (Section 9.1). Addition of KPIs (appendix A). Change to comment on renal replacement therapy (section 4.1). Addition of guidance on dosing of gentamicin after surgical prophylaxis (section 6)
1.6	Oct 2013	Revision	After discussion with surgical doctors.
2.0	Oct 2013	Revision	After discussion with AWG. Addition section 4.4 – no need to monitor levels if eGFR>60. Addition of Listeria as contraindication. Addition of section 5.3 – management of multiple daily dosing
2.1	Nov 2013	Revision	After nursing review by Glossop ward staff. Switch to using height rather than body weight as primary determinant of dose. Other changes to section formatting and wording.
2.2	Dec 2013	Revision	Minor changes after discussion with respiratory consultant
3.0	Mar 2014	Final	Published on BOB
3.1	Mar 2014	Revision	Minor changes to time of laboratory assays and quick reference guide
3.2	Jan 2016	Revision	Change to dose banding, from previous 40mg to 80mg banding, based on audit and pilot study. Submitted to AWG and approved for submission to DTC. Rejected by DTC pending changes.
4.0	Jan 2016	Final	Addition to exclusion criteria limb amputees and cachectic patients, ulna length formula inserted into step 2, ideal body weight formula inserted into step 8. Resubmitted and approved by DTC chair 29th January.
4.1	Feb 2016	Revision	Exclusion conditions added in appendix 1.
5.0	Apr 2019	Final	References reviewed and updated. Addition to sentence on mode of administration for Nurses.

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Approval and Review Process • Drug and Therapeutics Committee		
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CONTENTS

1. Purpose

1.1. This document sets out Northern Devon Healthcare NHS Trust's best practice guidelines for appropriate antimicrobial prescribing and monitoring in adult patients who are treated with gentamicin.

1.2. This guideline applies to all adults and must be adhered to. Special considerations exist for pregnant and breastfeeding patients; liaise with specialist clinicians as appropriate in these cases. See separate guidance for paediatric patients.

1.3. Non-compliance with this guideline may be for valid clinical reasons only. The reason(s) for non-compliance must be documented clearly in the patient's notes.

1.4. This guideline is primarily aimed at all prescribing teams but other staff (e.g. nursing staff, pharmacists) may need to familiarise themselves with some aspects of the guideline.

1.5. Implementation of this guideline will ensure that:

- Adult patients treated with gentamicin are managed according to current evidence and standards of practice in the wider healthcare community.
- A standard of care is specified to facilitate a consistent approach between all disciplines and pharmacy in terms of patient management, specimen processing and drug availability.

2. Definitions

Gentamicin

Gentamicin is an antibiotic used for the treatment of a variety of infections caused by Gram-negative organisms. It can also be used in combination with other antibiotics for the treatment of Gram-positive or mixed infections.

Gentamicin toxicity is serious and can lead to long-term sequelae. Renal damage and ototoxicity are two commonly described complications from sub-optimal dosing and monitoring of gentamicin therapy. Toxicity is more common when gentamicin accumulates and if serum trough levels are higher than recommended. The risk of toxicity developing increases with course length. For this reason, accurate dosing and close monitoring of the patient are recommended.

Gentamicin is usually prescribed using an 'extended interval regime'. A large dose is given, to achieve high peak levels and exert a bactericidal therapeutic effect. Further doses are given after serum gentamicin levels have reduced to low levels (below 1mg/L). In a healthy patient, this typically takes around 24 hours, however the exact duration between doses will depend on renal function. This strategy maximises the 'post antibiotic effect', and reduces the potential for toxicity.

Alternatively, in specific instances, gentamicin may be given as multiple daily doses (see below).

There are contra-indications to the use of gentamicin, including myasthenia gravis, and these can be found in the British National Formulary.

See separate guidance for managing gentamicin in children and neonates.

3. Responsibilities

3.1. Responsibility for education and training lies with the Lead Consultant Microbiologist for Antibiotic Stewardship. It will be provided through formal study days and informal training on the ward.

3.2. The author will be responsible for ensuring the guidelines are reviewed and revisions approved by the Drug and Therapeutics Group in accordance with the Document Control Report.

3.3. All versions of these guidelines will be archived in electronic format by the author within the Antibiotic Stewardship policy archive.

3.4. Any revisions to the final document will be recorded on the Document Control Report.

3.5. To obtain a copy of the archived guidelines, contact should be made with the author.

3.6. Monitoring of implementation, effectiveness and compliance with these guidelines will be the responsibility of the Lead Clinician for Antibiotic Stewardship. Where non-compliance is found, the reasons for this must have been documented in the patient's medical notes.

Role of Antibiotic Working Group (AWG)

3.7. The AWG is responsible for:

- Leading antibiotic guideline development and review within Northern Devon Healthcare Trust
- Involving all relevant stakeholders in guideline development and review

4. Contacts

4.1. Contact numbers:

- Microbiologist — Bleep 193. Via switchboard out of hours.
- Antibiotic Pharmacist — Bleep 029 (Mon-Fri only)

5. General Principles of Height- (Ideal Body Weight-) Based Dosing for Adult Extended Interval Gentamicin 5mg/kg

Step 1: Is the patient suitable?

Exclusion criteria: contraindications to using gentamicin, conditions where extended interval regime is unsuitable (see section 6 for management of gentamicin in the following patient groups: infective endocarditis, *Listeria* infection, other infections when gentamicin is being given for its synergistic activity, ascites, major burns, pregnancy, cystic fibrosis, limb amputees, cachexia).

Patients with renal failure: Dose reduction in not required in patients with renal failure, and may result in reduced efficacy.

Step 2: Selecting the initial gentamicin dose

Initial dose is determined by the patient's **height**, which is used to dose patients on their **ideal body weight**.

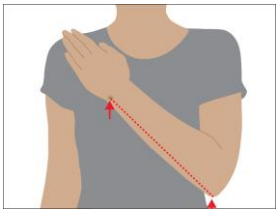
Table 1: Gentamicin Prescribing According to Height (dose banding to achieve 4-6mg/kg IBW)

	Small	Medium	Large
Gentamicin Dose (mg)	**240**	**320**	**400**
Male Height (cm)	<145 (<4'9")	≤ 170 (≤ 5'7")	≥171 (≥5'8")
Female Height (cm)	≤160 (≤5'3")	161-175 (5'4" – 5'8")	≥176 (≥5'9")

If the patient does not know their height, they can be measured standing if able to stand straight. Alternatively, for supine patients a tape measure may be used to measure entire body length or the following measurement gives an approximate height:

Estimating height from ulna length: instructions and tables (BAPEN MUST report, 2012)

If whole-body height cannot be obtained, measure length of forearm (ulna) (cm) as described below, and choose corresponding gentamicin dose from the table.



Measure between the point of the elbow (olecranon process) and the midpoint of the prominent bone of the wrist (styloid process), on the left side if possible.

Table 1: Gentamicin Prescribing According to Ulna length

	Small	Medium	Large
Gentamicin Dose (mg)	**240**	**320**	**400**
Male Ulna Length (cm)	<18.5	18.5 - 26	>26
Female Ulna Length (cm)	<23	23 – 29	>29

Step 3: How to administer gentamicin

Initial dose to be administered as undiluted slow intravenous bolus over 5 minutes. An infusion may be considered for subsequent doses at the Nurse's discretion if the patient complains of persistent discomfort / pain at the injection site after the first dose.

Step 4: How to decide if monitoring of levels is required

Monitoring of levels is not required if eGFR is greater than 60 ml/min/1.73m^2, duration of treatment is expected to be for less than 5 days, AND no significant change in renal function (classed as an increase in serum creatinine of more than 150% over baseline at the time of initiation). In these patients give the calculated dose every 24 hours.

In all other patients, monitor levels as in step 5. Note that gentamicin levels are only usually measured in the laboratory between 10am and 10pm.

Step 5: How to take gentamicin levels

Take a level 6-14 hours **after the first dose only**

Routine monitoring of gentamicin levels subsequently is not required (unless changes in renal function measured or suspected)

Place sample (minimum volume 2mL) in a yellow-topped bottle (clotted blood) and document on the microbiology request form the following:

- ⇨ EXACT time and date the last dose was given (see prescription chart);
- ⇨ EXACT time and date the sample was taken.

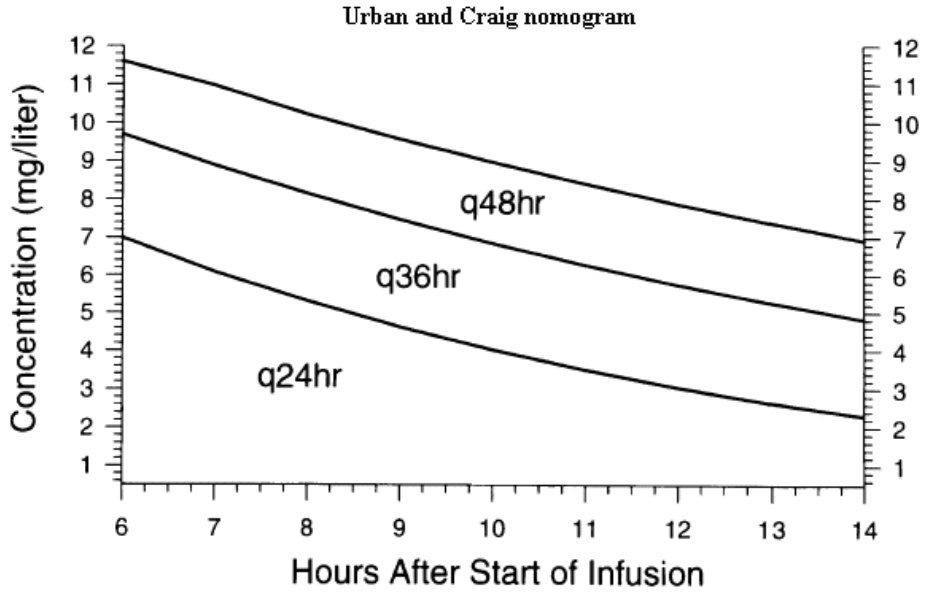
The specimen bottle and form must be labelled according to the Trust Specimen Acceptance Policy.

Do not take the blood sample from the IV line used for gentamicin administration.

Assays will usually be processed between 10am and 10pm. Levels will not be processed outside this window. Assay results will generally be available within one hour of processing. If assay results are required outside this window, then the case must be discussed with the duty Consultant Microbiologist.

Step 6: How to re-dose gentamicin

For subsequent dosing, there should be no change to the initial dose. The interval between doses is adjusted according to the Urban-Craig nomogram below.



Step 7: Duration of treatment and repeated monitoring

Review all prescriptions on a daily basis and contact microbiology for advice on alternative agents in on-going infection. Courses should not exceed 5 days in duration without microbiology input.

Toxicity is very uncommon with short courses (less than 5 days) of gentamicin. Toxicity is more likely to occur in patients receiving other nephrotoxic drugs (e.g. NSAIDs, cyclosporin, glycopeptides).

U&Es need to be checked at least every 48 hours in all patients on once daily gentamicin.

Step 8: Management of extended interval gentamicin (5mg/kg) dosing in patients excluded from the extended dosing protocol (section 4)

Gentamicin is **contraindicated** in patients with myasthenia gravis.

Dosing

Once daily dosing as per step 2 should be used in the following patients, but follow the advice below regarding monitoring:

- Ascites;
- Major burns (more than 20% of surface area);
- Pregnancy;
- Cystic fibrosis.

Amputees should have the following adjustments made to their ideal body weight, which may affect the gentamicin dose given (BAPEN MUST report executive summary 2012):

- **Upper limb 4.9% of total ideal body weight** (comprising the following weights: upper arm 2.7%; forearm 1.6%; hand 0.6%);

- **Lower limb 15.6% of total ideal body weight** (comprising the following weights: thigh 9.7%; lower leg 4.5%; foot 1.4%).

If the patient is cachectic, then use actual body weight to guide dosing.

Formula for calculating ideal body weight (using **whole body height** pre-amputation*):

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet

*If the patient is a double lower-limb amputee and does not remember their previous whole-body height, it may be helpful to refer to the ulna formula in section step 2.

Choose the nearest whole vial dose (240mg, 320mg, 400mg) which provides a dose in the range 4-6mg/kg of **amputation-adjusted ideal body weight** for the patient.

Cachectic patients may also require dose adjustment in addition to monitoring, as below:

Calculate dose based on actual body weight, if less than the ideal body weight formula states.

Choose the nearest whole-vial dose (240mg, 320mg, 400mg) which provides a dose in the range 4-6mg/kg of **actual body weight** for the patient.

Monitoring

Patients receiving 5mg/kg gentamicin who are excluded from normal monitoring protocols (section 4) and with normal renal function (calculated creatinine clearance greater than 30 mL / min / 1.73m^2)

- Give the initial dose as calculated in section step 2.
- Take a level 24 hours after the initial dose (pre-dose).
- Give the second dose of gentamicin immediately after taking the blood for the level.
- If the pre-dose gentamicin level is found to have been greater than 1mg/L then contact the Antibiotic Pharmacist (bleep 029) if within weekday working hours, or contact the duty Consultant Microbiologist (bleep 193, or via switchboard if out of hours), for advice before giving a third dose.
- A post-dose level is not required.

Patients receiving 5mg/kg gentamicin who are excluded from normal monitoring protocols (section 4) and with reduced renal function (calculated creatinine clearance less than 30 mL / min / 1.73m^2)

- Give the initial dose as calculated in step 2.
- Take a level 24 hours after the initial dose (pre-dose).
- **Wait** for the result of the gentamicin assay before re-dosing.
- If, after clinical assessment, it is felt that any delay in administration of gentamicin would compromise management, then phone a microbiologist for advice.
- If the gentamicin level is less than 1mg/L then give the second dose, otherwise phone for advice using the contact details as above. This assay will not be done outside the normal laboratory window, and will need to be discussed with the duty Consultant Microbiologist if felt to be clinically indicated.
- A post-dose level is not required.

6. Dosing of gentamicin when given as a multiple daily dose

Multiple daily dosing may be used in specific infections (e.g. endocarditis caused by *Streptococci, Listeria* infections). In endocarditis caused by *Streptococci*, gentamicin (if indicated) is usually given two to three times a day, at a dose of 1mg/kg.

This guidance also applies to other infections in which gentamicin is being used for its synergistic action (e.g. *Listeria* infections).

Levels should be taken before the 3rd dose, and this dose should then be given without awaiting the result.

- The pre-dose level should be below 1mg/L.
- A post-dose level is not routinely recommended.
- These cases should usually be discussed with the duty Consultant Microbiologist, and / or Antibiotic Pharmacist.

7. Dosing of gentamicin after surgical prophylaxis

If patients have received a dose of gentamicin for surgical prophylaxis and it is decided that they require a treatment dose of gentamicin to treat infection then it is safe to give the usual treatment dose on top of the prophylactic dose, as this will not significantly exceed a treatment dose that is known to be safe from experience with the 'Hartford nomogram'.

- Give the standard dose (step 2) as soon as it is decided the patient should receive a treatment dose.
- Determine dosing frequency using the standard approach (step 6).
- If in doubt, discuss with the Antibiotic Pharmacist, or duty Consultant Microbiologist.

8. Monitoring Compliance with and the Effectiveness of the Guideline

Standards/ Key Performance Indicators

8.1. Key performance indicators comprise:

KPI	Reason	How will be monitoring be carried out
% consistent with dose banding (i.e. small, medium, large)	*monitor guideline compliance and safe prescribing*	Annual audit based on drug charts
% with height / weight recorded in notes	*monitor guideline compliance and safe prescribing*	Annual audit based on end of bed notes
% with assay between 6 and 14 hours after initial dose, with time of dose and time of blood draw recorded on request form	*monitor guideline compliance and safe prescribing*	Patients identified from annual audit based on drug charts; data from pathology system
% on gent for more than 5 days	*monitor antibiotic protocol compliance and safe prescribing*	Annual audit based on drug charts
% with trough creatinine rise of >150% (over trough in preceding year)	*monitors for adverse renal outcomes*	Patients identified from annual audit based on drug charts; data from pathology system
% with trough creatinine rise of >150% (over creatinine before starting)	*monitors for adverse renal outcomes*	Patients identified from annual audit based on drug charts; data from pathology system

Process for Implementation and Monitoring Compliance and Effectiveness

8.2. This guideline will be published on BOB and cascaded via the intranet.

8.3. Incidents involving gentamicin should be reported according to the Trust's Incident Reporting Policy. Critical incident reports relating to gentamicin will be collated by the Antibiotic Pharmacist. Results will be reported on an annual basis to the Drug and Therapeutics Group.

9. References

References for earlier guidelines

- Freeman CD et al. *Once-daily dosing of aminoglycosides: review and recommendations for clinical practice*. JAC 1997, 39, 677-86

  Peak concentration: MIC ration of 8:1 optimises bactericidal effect and avoids bacterial regrowth. Peak:MIC ratio of 10:1 reduces acquired resistance. Once daily dosing should maximize concentration and also post-antibiotic effect which lasts 0.5 to 10 hours. Patient studies support high doses for reducing morbidity and mortality. Studies of renal toxicity show no difference between once daily and multiple daily dose regimes. Nephrotoxicity may be related to long treatment durations and high trough concentrations. Little data on ototoxicity. Theoretically, less frequent dosing may allow elution of gentamicin from renal and cochlear cells. Three meta-analyses of once daily dosing essentially show trends to improved outcomes and reduced toxicity for once daily dosing. Note that eGFR<20ml/min is not an exclusion for extended interval dosing – redose when level below 1mg/l.

- Nicolau DP et al. *Experience with a Once-Daily Aminoglycoside Program administered to 2,184 Adult Patients*. AAC. 1995, p. 650–655 Vol. 39, No. 3

  Basis of Hartford nomogram with 7mg/kg dosing. Excluded dialysis. Toxicity related due to duration. No long term nephrotoxicity. Do not need to monitor gentamicin levels if simple (<60 yrs, not on ITU, not amputee, no other nephrotoxic agents, 24h dosing; Cr measured every 2-3 days). In obese patients, dosing altered by formula = ideal body weight + 0.4 x (actual body weight - ideal body weight).

- Scottish Medicines Consortium (2017). *Intravenous Gentamicin Use in Adults (HARTFORD Guidance).* https://www.sapg.scot/media/2934/sapg_intravenous_gentamicin_adults_hartford.pdf Last accessed 12th Feb 2019

  Uses Hartford nomogram. Suggests altering doses and time interval for renal failure. Not particularly relevant to the NDDH guidelines.

- Urban AW and Craig WA. 1997. *Daily dosage of aminoglycosides*. Current clinical Topic in Infectious Diseases. Vol 17. 236-255

  Describes 5mg/kg nomogram. PAE may be less in neutropenia. Bacteria may become less sensitive after first exposure – extended interval maximizes first dose effect. Targets resistant sub-populations. Use of 5mg/kg advocated in this paper partly as this was maximum daily dose approved by FDA. Do not need to monitor levels in low risk patients (eGFR>60 and expected duration less than 5 days).

- Pubmed Literature review September 2013 using “Gentamicin Extended Interval” and “Gentamicin toxicity” (humans). Plus ‘Related articles’ search for all listed references.

- Spanggaard MH, Hønge BL, Schønheyder HC, Nielsen H. *Short-term gentamicin therapy and risk of renal toxicity in patients with bacteraemia.* Scand J Infect Dis. 2011 Dec;43(11-12):953-6.

Describes experiences in Danish hospital. Recommend amox / gent as first line for urinary sepsis, although clinicians have final say on choice and so there are gent exposed and gent not exposed cohorts. Matched 315 pts – 165 gent exposed. Fairly well matched groups, although non-exposed groups had higher baseline creatinine. NB excluded patients with 'pre-existing kidney disease'. If less than 5 days gent, then no difference in nephrotoxicity, mortality, dialysis, ICU admission. In 26 patients with >40umol rise in Cr – little difference in long term creatinine between groups. Conclude that short courses of gentamicin are not associated with long term nephrotoxicity.

- Adams, R; Carter, S; Lewis, T; Shaw, O. 2015. *Gentamicin MAU trial NDDH*.

  Proof of concept trial for new dose banding based on height/ideal body weight

- Kemp, N. 2015. *Audit of gentamicin dosing in NDDH*.

  Data gathering to ascertain the level of compliance with current gentamicin policy v3.1.

- BAPEN MUST report 2012.
  Estimating height from ulna length: instructions and tables. (Ulna length table and diagram in step 2)
  Weight adjustments to ideal body weight for amputees (step 8)

- The "Devine" ideal body weight formula in step 8.

10. Associated Documentation

- Trust incident reporting policy
- Antimicrobial Prescribing Policy

Appendix 1: Gentamicin Extended Interval Dosing Quick Reference Guide

Adult Extended Interval Gentamicin Quick Guide

Step 1: Is the patient suitable?

See quick links on Trust Intranet for full guideline, including dosing in excluded patients (infective endocarditis, Listeria infection, other infections when gentamicin is being given for its synergistic activity, ascites, major burns, pregnancy, cystic fibrosis, limb amputees, cachexia) and renal failure.

Gentamicin Prescribing According to Height			
Gentamicin Dose	Small **240mg**	Medium **320mg**	Large **400mg**
Male Height	≤145cm (≤4'9")	146- 170cm (4'10" – 5'7'')	≥171cm (≥5'8'')
Female Height	≤160cm (≤5'3'')	161-175cm (5'4'' – 5'8'')	≥176cm (≥5'9'')

Step 2: Selecting the initial gentamicin dose

Dose according to height (as a marker of ideal body weight), using the table below.

Step 3: How to administer gentamicin

Give gentamicin dose undiluted as a slow intravenous bolus over 3-5 minutes, unless the patient complains of injection site pain – then it may be given as an infusion (see http://medusa.wales.nhs.uk)

Step 4: How to decide if monitoring of levels is needed

- Monitoring of levels is **not** required **if** eGFR is greater than 60 ml/min/1.73m^2 **and** duration of treatment is expected to be for less than 5 days. In these patients give the calculated dose every 24 hours **unless** there has been a significant change in renal function (see full guideline).
- In all other patients, monitor as in step 5.

Step 5: How to take gentamicin levels

- Take a blood sample between **6 and 14 hours** after dosing and placed in a yellow topped tube (clotted blood)
- Assays will only be run between **10am and 10pm** every day

Note: if gentamicin is given between 3am and 10am, assays must be taken before 10pm if they are to be available within 24 hours.

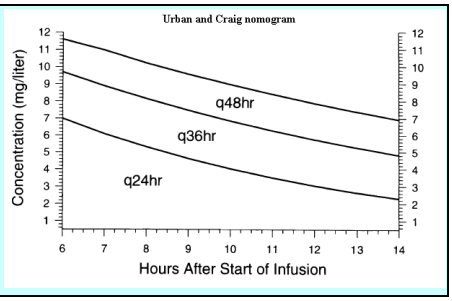
- Samples received after 10pm will be assayed at 10am the following day.
- Results should be available within an hour of processing.

It is the prescriber's responsibility to think about the time of the assay. Document when the level should be taken in the notes and on the medication chart.

If assays are taken between 8pm and 10pm, the laboratory should be informed and urgent portering requested. If these instructions are followed, a result should be available before a subsequent dose is due. The result will usually be available within 30 minutes of the assay being run.

Step 6: How to redose gentamicin

- For subsequent dosing, there should be no change to the initial dose.
- The interval between doses is adjusted according to the assay level, using the Urban-Craig nomogram (see right).
- All patients on gentamicin will be reviewed by a microbiologist, if course length exceeds 5 days.
- There is no need for routine subsequent monitoring of levels without advice.
- Renal function should be checked daily.



For advice please contact: Antibiotic pharmacist # **029 or** Consultant microbiologist # **193** (via switchboard out of hours)