Once Daily Intravenous Tobramycin: Administration and Monitoring in Adults Policy

(excludes patients receiving renal replacement therapy)

April 2025

Gloucestershire Hospitals NHS Foundation Trust

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Objective:

Policy for the administration and monitoring of once-daily intravenous (iv) tobramycin at Gloucestershire Hospitals NHS Foundation Trust (GHNHSFT). This policy is for the use of tobramycin for the treatment of infection only in adults.

Background/policy statement:

Tobramycin is an aminoglycoside antibiotic and is normally reserved for treatment of Gram-negative bacterial infections that are resistant to gentamicin but which remain tobramycin sensitive, or on the advice of a Consultant Microbiologist. Tobramycin is the preferred aminoglycoside for the treatment of respiratory tract *Pseudomonas aeruginosa* infections.

Aminoglycoside antibiotics such as tobramycin must be administered parenterally as they are poorly absorbed from the gastro-intestinal (GI) tract. Once daily administration is now recommended in most clinical situations; this has been the standard accepted regimen for use of iv tobramycin for the last two decades.
Once daily tobramycin is:

- As effective as multiple dosing regimes
- Less toxic (less nephrotoxicity & ototoxicity)
- More convenient to administer and monitor
- More economical

Wherever possible, parenteral therapy should not exceed 7 days

Cautions and contraindications:

Once daily dosing is inappropriate and should **not** be used in:

- Major Burns (>20% total body surface area)
- Ascites
- Patients treated in Renal units or receiving haemodialysis or haemofiltration – (see The Renal Handbook for dosage information in renal replacement therapies or contact Nephrologist or Renal Pharmacist)
- Age less than 18 years (contact Paediatrician or Paediatric Pharmacist for advice)
- Cystic fibrosis (CF) – if used in the context of cystic fibrosis higher doses of aminoglycosides are normally required – it is rare for an adult patient with CF to be managed as an inpatient in GHNHSFT as we are not a Regional Centre for CF.

Contraindications

- Myeloma patients
- Myasthenia gravis
- Patients allergic (hypersensitive) to tobramycin or other aminoglycoside

Cautions

Chronic Kidney Disease (CKD) Stage G4 or more, known or suspected acute kidney injury (AKI) in the previous 48 hours (50% increase in baseline serum creatinine or oliguria > 6 hours). Aminoglycosides are associated with an increased risk of renal failure. If tobramycin is clinically indicated, give one dose as per guidance and check with ward pharmacist or nephrologist before giving a second dose. Tobramycin should be used with caution in patients with **renal impairment and avoid in CrCl less than 20ml/min**. See page 4 for dosage recommendations in renal impairment.

- **Auditory or vestibular dysfunction** - Ototoxicity secondary to tobramycin is independent of drug concentration. Likely signs and symptoms may include: new tinnitus, dizziness, poor balance, hearing loss or oscillating vision (nystagmus). Toxicity is associated with prolonged aminoglycoside use (usually > 10 days but may be > 72 hours) and is secondary to drug accumulation within the inner ear.
  There have also been observed cases of an increased risk of ototoxicity with aminoglycosides administered to patients with mitochondrial mutations, particularly the m.1555A>G mutation, including cases where the patient's aminoglycoside serum levels were within the recommended range. Some cases were associated with a maternal history of deafness and/or mitochondrial mutation. Mitochondrial mutations are rare, and the penetrance of this observed effect is unknown.

  Stop treatment if ototoxicity is suspected and refer to microbiologist or antimicrobial pharmacist for advice on alternative therapy. If tobramycin continues for >7 days, consider referring to Audiology for assessment.

- **Concurrent administration of neurotoxic and / or nephrotoxic agents increases the risk of tobramycin toxicity.** Review therapy and consider amending or withholding nephrotoxic drugs during tobramycin treatment. Avoid co-administration with the following where possible:
  neuromuscular blockers
  other potentially nephrotoxic (e.g. NSAIDs and ACE Inhibitors) or ototoxic drugs
  potent diuretics
  other aminoglycosides
  This list is not exhaustive – consult the Summary of Product Characteristics (SPC) for a full list https://www.medicines.org.uk/emc

- **Conditions characterised by muscular weakness** (aminoglycosides may impair neuromuscular transmission).

- **Dehydration** should be corrected before starting an aminoglycoside.

Dosage:

The dose will be dependent on:

- weight (ideal body weight or obese dose body weight) * - see below
- age
- renal function – see **appendix 1** for calculating Creatinine clearance (CrCl calculator)
- For maternity patients – use pregnancy booking weight to calculate the dose if tobramycin is thought to be a suitable treatment choice.

	CrCl above 50ml/min	**CrCl of 20-50ml/min**	**CrCl less than 20ml/min**
Age 65 and over	3mg/kg* IV OD	2mg/kg* IV OD	Do not give Tobramycin
Age under 65 years	5mg/kg* IV OD	3mg/kg* IV OD	Do not give Tobramycin

Which body weight to use?

*In **non-obese patients**, (BMI 30 or less, or actual body weight lower than 120% of ideal body weight) use ideal body weight (IBW) rather than actual body weight (ABW) to calculate the dose, because tobramycin distributes poorly in fat.

To calculate **ideal body weight**, use the following equation or see IBW table in **appendix 2**:

Ideal body weight (Male) = 50kg + (2.3kg x height in inches over 5 feet)
Ideal body weight (Female) = 45.5kg + (2.3kg x height in inches over 5 feet)

For obese patients (BMI greater than 30 or more than 120% of ideal body weight) it is recommended that the dose is calculated using the patient's **obese dose body weight**.
Obese dose body weight is also known as adjusted body weight.

To calculate **adjusted/obese dose body weight**, use the following equation or use the Ideal Body Weight and Obese dose Body Weight calculator (appendix 2)
(NOTE: Do not use calculator if patient is under 5ft or 152.5cm in height.

Adjusted/Obese dose body weight (ODBW) = IBW + 0.4 x (ABW - IBW)

Round dose up or down to the nearest 20mg.

Minimum doses – If after dose re-calculation the revised dose is less than 2mg/kg, strongly consider using an alternative antibiotic with good Gram-negative cover. See Antibiotic Guidelines for advice on choices, and review recent / current Microbiology results, including culture and sensitivity results for Gram negative organisms (eg "coliforms"/Enterobacterales and Pseudomonas).

Maximum doses – if a dose is calculated as being greater than 500mg, check that the dose has been calculated correctly based on ideal body weight, or adjusted/obese dose body weight, depending on whichever of these is applicable.

When to give the dose
The first dose of tobramycin may be given at any time of day (i.e. as soon as it is needed). Subsequent doses should be moved to a time that is convenient for the patient (i.e. not overnight) and to avoid routine therapeutic dose monitoring (tobramycin levels) being required between midnight and 6am. **Evening dosing at 18:00 is preferred.** To facilitate this, the second dose may be given 18 to 36 hours after the first dose provided that the first tobramycin level is within the recommended range (see monitoring/interpretation below) and the patient's renal function has not changed significantly.

Therapeutic Dose Monitoring (TDM):

A 12–18-hour post-dose level is required for TDM purposes. Obtain a single serum sample 12 or 18 hours after the dose and send to CHEMICAL PATHOLOGY. As there is flexibility about the timing of the sampling, a time which is convenient for the patient and the laboratory should be chosen. Preferably, samples should not be collected or sent for testing between midnight and 6am.

Electronic requests for serum tobramycin levels should include the following information:

- Date and time of last dose
- Date and time sample taken
- Dose given and frequency (e.g. once daily)

Take tobramycin level 12-18 hours after the first dose.

If tobramycin levels are within the recommended range with normal renal function, then monitor levels and U&Es twice weekly

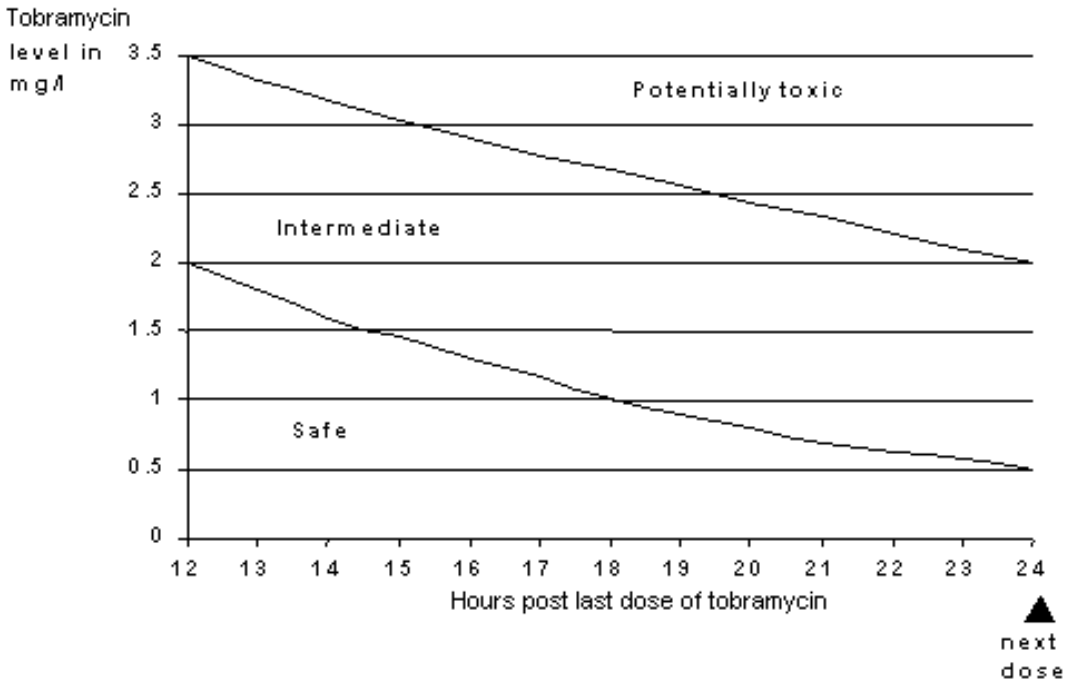
Information on sample requirements for tobramycin levels can be found at:
https://www.gloshospitals.nhs.uk/our-services/services-we-offer/pathology/tests-and-investigations/tobramycin/

Interpretation:

Target serum concentration for once-daily tobramycin:

12 hours post dose = <2mg/L
18 hours post dose = <1mg/l

Take tobramycin level 12-18 hours after the first dose. Plot the result of the level on the graph below to decide if the level is **safe** (recommended range), **intermediate** or **potentially toxic**.



Safe: If the serum tobramycin level is ≤ 2mg/l after 12 hours or ≤1mg/l after 18 hours it is safe to give the next dose on time (same dose).

Intermediate: If the level falls in the intermediate area a dose reduction needs to be made, this reduced dose should be given when the next dose is due. If after dose re-calculation the revised dose is less than 2mg/kg, strongly consider alternative Gram-negative cover. Consult empirical Antibiotic Guidelines for information and review recent/current Microbiology results.

Dose reduction to a new dose will be required as per this equation:

$$\text{New Dose} = \frac{\text{Previous daily dose} \times \text{Target serum value}}{\text{Actual serum value}}$$

The **Target Serum Value** is the intersection of time (hours post last dose of tobramycin) and the line separating the Intermediate and Safe areas on the graph above
Serum tobramycin levels should be rechecked 12 to 18 hours after the new revised dose has been administered.

Example: Patient has a level of 2.5mg/l at 16 hours post 360mg dose

(safe level at 16 hours post-dose is 1.3 or less)

$$\text{New dose} = 360\text{mg} \times \frac{1.3}{2.5} = 187\text{mg rounded to } 180\text{mg}$$

Potentially toxic: Omit the next dose if the level is in the potentially toxic area. Consider whether it is safe to continue ongoing tobramycin during the current treatment episode or whether alternative antibiotic treatment (specifically for Gram negative cover) is required. Discuss with Microbiology if necessary. Generally, it is recommended to stop tobramycin in patients whose levels are genuinely potentially toxic.

If tobramycin levels are within the recommended range with normal renal function, then monitor levels and U&Es twice weekly

Caution must be used when using this graph to interpret levels taken from patients with fluctuating renal dysfunction, as their concentration-time-curve may be different.

NB
A common (and spurious) reason for a patient having high tobramycin levels is if the blood sample for tobramycin level is taken too early. If the patient has a high tobramycin level please check to see if this is the explanation for the level being high. If it is, repeat the tobramycin level at the correct time point (12-18 hours after the last dose) and then interpret the level when it is available before deciding on how to proceed.

Appendix 1

Calculating renal function

Cockroft-Gault equation for estimating creatinine clearance:

Creatinine Clearance (GFR) = $\frac{(140 - \text{Age}) \times \text{Weight (Kg)} \times F}{\text{Serum Creatinine (µmol/litre)}}$

Where F = 1.23 (For Men)
1.04 (For Women)

Online calculator (CrCl calculator)

Appendix 2

Calculating ideal body weight and obese dose body weight

Ideal Body Weight and adjusted/obese dose Body Weight calculator

(NOTE: Do not use calculator if patient is under 5ft or 152.5cm in height.

Alternatively, obtain the ideal body weight from the table below and use the following equation to calculate an obese dosing body weight:

Obese dose body weight = IBW + 0.4 x (ABW - IBW)

Males				Females		
Height (ft'in)	Height (cm)	IBW (kg)		Height (ft'in)	Height (cm)	IBW (kg)
4'10	147	45.4		4'8	142	36.3
4'11	150	47.7		4'9	144.5	38.6
5'0	152.5	50.0		4'10	147	40.9
5'1	155	52.3		4'11	150	43.2
5'2	157.5	54.6		5'0	152.5	45.5
5'3	160	56.9		5'1	155	47.8
5'4	162.5	59.2		5'2	157.5	50.1
5'5	165	61.5		5'3	160	52.4
5'6	167.5	63.8		5'4	162.5	54.7
5'7	170	66.1		5'5	165	57.0
5'8	172.5	68.4		5'6	167.5	59.3
5'9	175	70.7		5'7	170	61.6
5'10	177.5	73.0		5'8	172.5	63.9
5'11	180	75.3		5'9	175	66.2
6'0	183	77.6		5'10	177.5	68.5
6'1	185.5	79.9		5'11	180	70.8
6'2	188	82.2		6'0	183	73.1
6'3	190.5	84.5		6'1	185.5	75.4
6'4	193	86.8		6'2	188	77.7
6'5	195.5	89.1				
6'6	198.5	91.4				
6'7	201	93.7				

For further advice or clarification during normal office hours please contact:

☎ Medicines Information:	CGH ext. 3030	GRH ext. 6108
☎ Duty Microbiologist:	CGH ext. 4430	GRH ext. 5054

Out of hours
Please contact the on-call pharmacist or on call consultant microbiologist

Selected References:

1. Begg EJ, Barclay ML, Duffull SB. A suggested approach to once-daily aminoglycoside dosing. *Br J Clin Pharmac* 1995; 39: 605-609.
2. Freeman CD, Nicolau DP, Belliveau PP, Nightingale CH. Once-daily dosing of aminoglycosides: review and recommendation for clinical practice. *J Antimicrob Chemother* 1997; 39: 677-686.
3. The Renal Drug Database. Accessed 23/4/25 https://www.renaldrugdatabase.com/s/article/TOBRAMYCIN
4. Summary of Product Characteristics for Tobramycin 40mg/ml Injection (Hospira UK Ltd). Electronic Medicines Compendium. Tobramycin 40mg/ml Solution for Injection - Summary of Product Characteristics (SmPC) - (emc) | 1425 Date of revision of the text February 2024.
5. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press Tobramycin | Drugs | BNF | NICE [Accessed on 23/04/25]

Authorisation	Name and Position	Date Approved
Responsible Authors	Dr. Robert Jackson Consultant Microbiologist Delyth Ahearne Countywide Antimicrobial Pharmacist	Policy last revised 27/2/25 With minor alterations 3/4/25
Policy Sponsor	Dr. Robert Jackson Consultant Microbiologist Medical Lead for AMS in GHNHSFT	Policy last revised 27/2/25 With minor alterations 3/4/25
Assured by	GHNHSFT Antimicrobial Stewardship Group	**05/03/2025** With post-meeting agreement by the CMMs – April 2025 **07/05/25** and follow up meeting with RJ/DA/Ali on 9/5/25

Consideration at authorised groups (e.g. Board, Board sub committees, Policy Group, Clinical policies Sub Group, Departmental meetings etc)

Name of Group	Date considered
Respiratory unit meeting	13/05/25