Tobramycin
Newborn use only

2024

<table>
<tr><td>Alert</td><td>Some tobramycin preparations contain metabisulfites.</td></tr>
<tr><td>Indication</td><td>Treatment of gram-negative infections, including susceptible Pseudomonas aeruginosa</td></tr>
<tr><td>Action</td><td>Aminoglycoside. It inhibits protein synthesis by binding to the 30S bacterial ribosome subunit, causing mistranslation of bacterial proteins.[1]</td></tr>
<tr><td>Drug type</td><td>Antibiotic</td></tr>
<tr><td>Trade name</td><td>Tobramycin-PF Injection (Pfizer – preservative free), DBL Tobramycin, Tobra-Day, Tobramycin Injection (Pfizer), Tobramycin Mylan</td></tr>
<tr><td>Presentation</td><td>80mg/2mL ampoule</td></tr>
<tr><td>Dose</td><td><u>ANMF consensus</u>
4 mg/kg/dose. Dose interval as below[2]

Note: Dose is based on both GA at birth and the postnatal age.

<table>
<tr><th>Gestation at birth</th><th>Postnatal age (PNA)</th><th>Frequency</th></tr>
<tr><td><32^{+0} weeks at birth</td><td><7 days of life</td><td>48 hourly</td></tr>
<tr><td></td><td>≥7 days of life</td><td>24 hourly</td></tr>
<tr><td>32^{+0}-36^{+6} weeks at birth</td><td><7 days of life</td><td>36 hourly</td></tr>
<tr><td></td><td>≥7 days of life</td><td>24 hourly</td></tr>
<tr><td>≥37^{+0} weeks at birth</td><td>0-28 days of life</td><td>24 hourly</td></tr>
<tr><td></td><td>>28 days of life</td><td>5-7 mg/kg, 24 hourly</td></tr>
</table>

Monitor trough concentrations (refer to monitoring section)</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia –Measure trough concentration before every dose.[3-5]
ECMO - Measure trough concentration before every dose.[6]
Renal impairment – Measure trough concentration before every dose.[7,10]
Hepatic impairment – No specific dose adjustment.</td></tr>
<tr><td>Maximum dose</td><td>No information.</td></tr>
<tr><td>Total cumulative dose</td><td>No information.</td></tr>
<tr><td>Route</td><td>IV/IM</td></tr>
<tr><td>Preparation</td><td>IV
Draw up 1 mL (40 mg of tobramycin) and add to 19 mL sodium chloride 0.9% or glucose 5% to make a final volume of 20 mL with a final concentration of 2 mg/mL.
IM
Administer undiluted.</td></tr>
<tr><td>Administration</td><td>Infusion over 30 minutes (20-60 minutes)[2], but can be given over 5 minutes in emergency situations.[8]</td></tr>
<tr><td>Monitoring</td><td>Urine output, urine analysis, blood urea, nitrogen and creatinine
Trough concentrations (level) should be measured before the 2nd dose – Targeted <1 mg/L[2]
<u>If trough level ≤1 mg/L:</u>
Continue the same dose and recheck trough level after 2-3 days
<u>If trough concentration >1 mg/L:</u>
Withhold further doses
Repeat the tobramycin concentration every 12-24 hours
Discuss with an infectious disease specialist/AMS pharmacist to adjust the dose or an alternate antibiotic. Tobramycin Model Informed precision dosing (MIPD) is recommended if available. Contact your Antimicrobial Stewardship (AMS) pharmacist</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to aminoglycosides.</td></tr>
<tr><td>Precautions</td><td>Renal impairment
Known or suspected sensorineural hearing loss
Family history of deafness or hearing loss
Myasthenia gravis (maternal) and other conditions with neurotransmission depression – May cause or prolong neuromuscular blockade and respiratory paralysis</td></tr>
</table>

Drug interactions	Muscle relaxants and anaesthesia - May exacerbate neuromuscular blockade and respiratory paralysis. Potent diuretics - Avoid where possible tobramycin in conjunction with ethacrynic acid, furosemide or other potent diuretics, which may themselves cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Other neurotoxic and/or nephrotoxic agents - Minimise concurrent or sequential use of neurotoxic and/or nephrotoxic antibiotics, particularly other aminoglycosides, amphotericin B, vancomycin, ibuprofen.
Adverse reactions	Renal: Increased blood urea nitrogen, increased serum creatinine, oliguria, nephrotoxicity Ototoxicity: Auditory and vestibular impairment, hearing loss. Endocrine: Decreased serum calcium, magnesium, potassium and sodium Dermatologic: Dermatitis, rash, urticarial Central nervous system: Lethargy Haematologic: Anaemia, leucocytosis, leukocytopenia, thrombocytopenia Gastrointestinal: Diarrhoea, vomiting Local: Pain at injection site.
Compatibility	Fluids:[8] Glucose 5%, glucose 10%, sodium chloride 0.9%, sodium chloride 0.45%, Ringer's, glucose 5% in sodium chloride 0.9%. Y-site:[8] Aciclovir, adrenaline (epinephrine), alfentanil, alprostadil, amino acid solution, amifostine, amikacin sulfate, aminophylline, amiodarone, benzylpenicillin, calcium chloride, calcium gluconate, caspofungin, cefamandole, cefepime, cefotaxime, cefoxitine, ceftazidime, ceftizoxime, ciprofloxacin, clindamycin phosphate, dexmedetomidine, digoxin, diltiazem, dobutamine, dopamine, doxycycline, enalaprilat, epinephrine, epoetin alfa, esmolol, fentanyl citrate, filgrastim, fluconazole, fluorouracil, fosphenytoin, furosemide (frusemide), gentamicin sulfate, glycopyrrolate, isoproterenol, ketamine, labetolol, lidocaine, linezolid, lorazepam, magnesium sulfate, meropenem, metronidazole, meropenem, meropenem/vaborbactam, methadone, methylprednisolone sodium succinate, metaprolol, metronidazole, midazolam hydrochloride, milrinone lactate, morphine sulfate, multivitamin, naloxone hydrochloride, nicardipine, nitroglycerin, noradrenaline (norepinephrine), octreotide, ondansetron hydrochloride, pamidronate, pancuronium, papaverine, penicillin G potassium, penicillin G sodium, phenobarbital, phentolamine, piperacillin, potassium acetate, potassium chloride, propranolol, protamine, pyridoxine, remifentanil, rocuronium bromide, sodium acetate, sodium bicarbonate, sodium nitroprusside, streptokinase, succinylcholine, tacrolimus, thiamine, ticarcillin, ticarcillin disoium/clavulanate potassium, tolazoline, urokinase, vancomycin hydrochloride, vasopressin, vecuronium, voriconazole, zidovudine.
Incompatibility	Fluids:[8] No information Y-site:[8] Allopurinol, amphotericin (all formulations), ampicillin (refer to micormedex[8]), azathioprine, azithromycin, cefazolin, cefoperazone, ceftriaxone, cloxacillin, dexamethasone sodium phosphate, diazepam, diazoxide, folic acid, ganciclovir, heparin sodium, hydralazine (refer to Micromedex[8]), hydrocortisone sodium succinate (refer to micromedex[8]), indomethacin, insulin (refer to micromedex[8]), lansoprazole, pantoprazole (refer to micromedex[8]), pentamidine, pentobarbital, phenytoin, piperacillin/tazobactam (tazocin), propofol, SMOFlipid, sulfamethoxazole/trimethoprim.
Stability	Administer immediately, discard unused portion.
Storage	Tobramycin-PF and Tobra-Day: Refrigerate at 2-8°C. Protect from light. All other brands: Store at room temperature below 25°C. Protect from light.
Excipients	Tobramycin-PF: Disodium edetate. DBL: Sodium metabisulfite, disodium edetate, sulfuric acid and/or sodium hydroxide. Pfizer: Sodium metabisulfite, disodium edetate, sulfuric acid and/or sodium hydroxide, phenol. Tobra-Day: Sulfuric acid and sodium hydroxide.
Special comments	
Evidence	**Background** Tobramycin is a naturally occurring aminoglycoside isolated from Streptomyces tenebrarius.[1] Tobramycin is a later-generation aminoglycoside with in-vitro activity against bacteria resistant to first generation aminoglycoside e.g. gentamicin.[1] It has a spectrum of activity against Gram-negative bacteria, including P aeruginosa. It also has activity against staphylococci but are largely ineffective against other Gram-positive bacteria as monotherapy. Anaerobic bacteria are also intrinsically resistant.[1]

	Efficacy The dose recommendation in this formulary was adapted from the Dutch Pediatric Formulary cohort study.[2] The Dutch study evaluated the target attainment of tobramycin following nationwide implementation of tobramycin formulary. Target trough concentration was defined as ≤1 mg/L. The study included 221 neonates in tobramycin group. The 221 neonates in the tobramycin cohort were mostly preterm infants (65.6%). Median tobramycin trough concentrations were 0.6 mg/L, with 23.1% of samples showing toxic concentrations (>1 mg/L). Toxic tobramycin trough concentrations were most prevalent in patients dosed every 24 h (term patients [36.8%] and preterm patients ≥ 7 days PNA [25.4%]) and least prevalent in preterm neonates < 7 days of PNA who are dosed every 36–48 hours (2.2% for < 32 weeks and 14.3% for 32–37 weeks of gestation). In a subgroup of 71 extreme preterm infants, the prevalence of toxic trough concentrations (18.3%) was comparable to the prevalence found in 42 preterm infants with a higher GA of 28–32 weeks (14.3%). **Safety** Two main toxicities associated with aminoglycosides are (1) non-oliguric renal impairment[9] and (2) ototoxicity.[10] Non-oliguric renal impairment is reversible and due to accumulation of drug in proximal tubular epithelial cells, leading to tubular necrosis.[9] Shift of multiple daily dosing to extended dosing (e.g. once daily regimen) reduced this toxicity in adults.[11] There are no comparable data in neonates but similar extended dosing principles have been adopted for neonates. Ototoxicity is usually irreversible.[10] Ototoxicity is caused via damage to the sensory hair cells of the inner ear and may result in irreversible cochlear function impairment. Vestibular impairment can also occur, but this is reversible on cessation of the drug. The exact mechanism is not understood; the dose–effect relationship seems to be idiosyncratic and possibly associated with certain mitochondrial genetic variations.[12] Dehoog et al. 2003 studied automated auditory brainstem response (A-ABR) in neonates in relation to exposure to tobramycin and vancomycin. Exposure to vancomycin, tobramycin, or furosemide or a combination, was not related to failure to pass A-ABR screening. Exposure to vancomycin and tobramycin in terms of treatment duration and total dose was not significantly different between neonates passing and failing hearing screening. There was no increased risk of failed hearing screening with either peak or trough serum concentration of vancomycin or tobramycin. This study suggested that routine therapeutic drug monitoring of vancomycin and tobramycin was not useful in detecting neonates at risk for clinically important hearing loss.[13] **MT-RNR1 genotype:** MT-RNR1 gene mutation is one of the common causes of hereditary hearing loss, particularly in Asian population. In individuals who carry mutations in MT-RNR1 gene, a single dose of gentamicin can result in hearing loss.[14,15] This is presumed to be shared by all aminoglycosides. **Metabisulfites as excipients:** Some tobramycin preparations have metabisulfites as excipients, which has been reported to cause anaphylaxis.[16] European Commission on guidelines for labelling of excipients recommend a package labelling to indicate metabisulfites may rarely cause severe hypersensitivity reactions and bronchospasm.[17] **Pharmacokinetics** Tobramycin and gentamicin share similar drug behaviour in terms of volume distribution and clearance. Main differences are that tobramycin clearance and volume of distribution are higher than the respective pharmacokinetic parameters for gentamicin in neonates.[18] Aminoglycosides and therapeutic hypothermia (TH): Pharmacokinetic data for aminoglycosides in TH are available for gentamicin and amikacin. Same principle can be applied to tobramycin. Aminoglycoside clearance is significantly lower in TH.[3-5,19] Aminoglycosides and ECMO: During ECMO, gentamicin has an increased volume of distribution (Vd), and decreased clearance (Cl), leading to a prolonged elimination half-life. The renal dysfunction, which is a common condition during ECMO, is probably the main determinant of the prolonged elimination half-life of gentamicin. Given the concentration dependent antimicrobial activity of aminoglycosides, it is recommended to perform therapeutic drug monitoring (TDM) to ensure adequate antimicrobial exposure and avoid toxicity.[6] Aminoglycosides and cyclo-oxygenase inhibitors: Renal drug clearance of aminoglycosides is lower in infants on cyclo-oxygenase inhibitors.[20,21]
Practice points	

References

1. Darlow CA, da Costa RM, Ellis S, Franceschi F, Sharland M, Piddock L, et al. Potential antibiotics for the treatment of neonatal sepsis caused by multidrug-resistant bacteria. Pediatric Drugs. 2021;23:465-84.
2. Hartman SJ, Orriëns LB, Zwaag SM, Poel T, de Hoop M, de Wildt SN. External validation of model-based dosing guidelines for vancomycin, gentamicin, and tobramycin in critically ill neonates and children: a pragmatic two-center study. Pediatric Drugs. 2020;22:433-44.
3. Choi D, Park J, Lee S, An S. Effect of hypothermia treatment on gentamicin pharmacokinetics in neonates with hypoxic-ischaemic encephalopathy: A systematic review and meta-analysis. Journal of Clinical Pharmacy and Therapeutics. 2018;43(4):484-92.
4. Bijleveld YA, De Haan TR, Van Der Lee HJ, Groenendaal F, Dijk PH, Van Heijst A, et al. Altered gentamicin pharmacokinetics in term neonates undergoing controlled hypothermia. British journal of clinical pharmacology. 2016;81(6):1067-77.
5. Lutz IC, Allegaert K, de Hoon JN, Marynissen H. Pharmacokinetics during therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy: a literature review. BMJ Paediatr Open. 2020;4(1).
6. Raffaeli G, Pokorna P, Allegaert K, Mosca F, Cavallaro G, Wildschut ED, et al. Drug disposition and pharmacotherapy in neonatal ECMO: from fragmented data to integrated knowledge. Frontiers in pediatrics. 2019;7:360.
7. de Hoog M, Mouton JW, Schoemaker RC, Verduin CM, van den Anker JN. Extended-interval dosing of tobramycin in neonates: Implications for therapeutic drug monitoring. Clinical Pharmacology & Therapeutics. 2002;71(5):349-58.
8. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: Sep/28/2024).
9. Mingeot-Leclercq M-P, Tulkens PM. Aminoglycosides: nephrotoxicity. Antimicrobial agents and chemotherapy. 1999;43(5):1003-12.
10. Hutchin T, Cortopassi G. Proposed molecular and cellular mechanism for aminoglycoside ototoxicity. Antimicrobial agents and chemotherapy. 1994;38(11):2517-20.
11. Barza M, Ioannidis JP, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. Bmj. 1996;312(7027):338-44.
12. de Hoog M, Van Zanten G, Hoeve L, Blom A, Van Den Anker J. A pilot case control follow-up study on hearing in children treated with tobramycin in the newborn period. Int J Pediatr Otorhinolaryngol. 2002;65(3):225-32.
13. de Hoog M, van Zanten BA, Hop WC, Overbosch E, Weisglas-Kuperus N, van den Anker JN. Newborn hearing screening: tobramycin and vancomycin are not risk factors for hearing loss. The Journal of pediatrics. 2003;142(1):41-6.
14. Dean L. Gentamicin Therapy and MT-RNR1 Genotype. In: Pratt VM, McLeod HL, Rubinstein WS, et al., eds. Medical Genetics Summaries. Bethesda (MD): National Center for Biotechnology Information (US); April 29, 2015.
15. Wang X, Hong Y, Cai P, Tang N, Chen Y, Yan T, et al. Rapid and reliable detection of nonsyndromic hearing loss mutations by multicolor melting curve analysis. Scientific reports. 2017;7(1):42894.
16. Kendigelen P, Sucu A, Kaya G. Anaphylaxis after administration of amikacin containing sodium metabisulfite in a premature newborn. Archivos Argentinos de Pediatria. 2016;114(3):e195-8.
17. European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668). 22 November 2019. EMA/CHMP/302620/2017 Rev. 1. https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-and-package-leaflet-medicinal-products-human-use-sante-2017-11668-revision-1_en.pdf.
18. Valitalo PA, van den Anker JN, Allegaert K, de Cock RF, de Hoog M, Simons SH, et al. Novel model-based dosing guidelines for gentamicin and tobramycin in preterm and term neonates. Journal of Antimicrobial Chemotherapy. 2015;70(7):2074-7.
19. Cristea S, Smits A, Kulo A, Knibbe CA, Van Weissenbruch M, Krekels EH, et al. Amikacin pharmacokinetics to optimize dosing in neonates with perinatal asphyxia treated with hypothermia. Antimicrobial agents and chemotherapy. 2017;61(12):10.1128/aac. 01282-17.
20. Allegaert K. The impact of ibuprofen or indomethacin on renal drug clearance in neonates. The Journal of Maternal-Fetal & Neonatal Medicine. 2009;22(sup3):88-91.

	21. Smits A, De Cock R, Allegaert K, Vanhaesebrouck S, Danhof M, Knibbe C. Prospective evaluation of a model-based dosing regimen for amikacin in preterm and term neonates in clinical practice. Antimicrobial agents and chemotherapy. 2015;59(10):6344-51.

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