Tobramycin
Newborn use only

2020

<table>
<tr><td>Alert</td><td>Aminoglycosides can be inactivated by penicillin and cephalosporin antibiotics. As commonly co-prescribed, where feasible, give at separate sites or separate the administration time of the antibiotics.</td></tr>
<tr><td>Indication</td><td>Treatment of gram-negative infections, including susceptible Pseudomonas aeruginosa</td></tr>
<tr><td>Action</td><td>Aminoglycoside</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>5 mg/kg/dose with dosing interval as follows (1)

<table>
<tr><td>Current Bodyweight</td><td colspan="3"><1200 g</td><td colspan="2">≥1200 g</td></tr>
<tr><td>Postnatal Age</td><td>≤7 days</td><td>8-30 days</td><td>>30 days</td><td>≤7 days</td><td>>7 days</td></tr>
<tr><td>Dose interval*</td><td>48 hourly</td><td>36 hourly</td><td>24 hourly</td><td>36 hourly</td><td>24 hourly</td></tr>
</table>

*Extend dose interval by 12 hours in
1. Perinatal asphyxia and therapeutic hypothermia (2,3,4).
2. Concurrent cyclo-oxygenase inhibitors (indometacin or ibuprofen) (4,5)</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia – Extend the dosing interval by 12 hours. Measure trough concentration before every dose. (2,6-8)
ECMO - Measure trough concentration before 2nd dose. (9)
Renal impairment – Measure trough concentration before every dose. (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</td></tr>
<tr><td>Preparation</td><td>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.</td></tr>
<tr><td>Administration</td><td>Infusion over 30 minutes (20-60 minutes) (1,10,11)</td></tr>
<tr><td>Monitoring</td><td>Urine output, urine analysis, blood urea, nitrogen and creatinine
Anaphylaxis
Trough concentrations – Targeted <2 mg/L (1,10).
Trough concentrations are not required routinely unless:
1. duration of therapy is longer than 5 days –prior to dose on day 5 (10),
2. renal impairment or perinatal hypoxia with Apgar <5 at 5 minutes and/or concomitant use of nephrotoxic agents (10) or therapeutic hypothermia (10) - prior to every dose.
If trough concentration ≥2 mg/L (µg/mL), withhold the dose, repeat trough concentrations before the subsequent dosing and discuss with infectious disease specialist/clinical microbiologist for either extended dosing interval or alternate antibiotic.

Peak concentrations – Not required routinely. Target peak concentrations: 5-12 mg/L, to be measured 2 hours after the end of transfusion. (1)</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to aminoglycosides.</td></tr>
<tr><td>Precautions</td><td>Renal impairment
Auditory impairment
Myasthenia gravis (maternal) and other conditions with neurotransmission depression – May cause or prolong neuromuscular blockade and respiratory paralysis</td></tr>
<tr><td>Drug interactions</td><td>Muscle relaxants and anaesthesia: May exacerbate neuromuscular blockade and respiratory paralysis.
Potent diuretics: Do not give 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: Avoid concurrent or sequential use of neurotoxic and/or nephrotoxic antibiotics, particularly other aminoglycosides, amphotericin B, vancomycin, ibuprofen.</td></tr>
</table>

	Penicillins and cephalosporins: Aminoglycosides may be inactivated by solutions containing penicillin and cephalosporin antibiotics. Where feasible, give at separate sites or separate the administration time of the antibiotics. If this is not possible, flush the line well before and after giving each antibiotic. In renal impairment separate the administration of the antibiotics for the longest duration that is practical.
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: Glucose 5%, glucose 10%, Hartmann's, mannitol, Ringer's, sodium chloride 0.9%, glucose in sodium chloride solutions. Y-site: Aciclovir, calcium chloride, calcium gluconate, ciprofloxacin, dobutamine, dopamine, fluconazole, furosemide (frusemide), adrenaline (epinephrine), linezolid, magnesium sulfate, metronidazole, morphine sulfate, noradrenaline (norepinephrine), sodium bicarbonate, vecuronium, zidovudine
Incompatibility	Penicillins and cephalosporins, allopurinol, amphotericin (all formulations), azathioprine, azithromycin, clindamycin, dexamethasone, diazepam, diazoxide, folic acid, heparin sodium, indomethacin, lansoprazole, pantoprazole, pentamidine, phenytoin, piperacillin/tazobactam, propofol, 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	**Efficacy** Avent et al. (1) compared once daily dosage regimens with the more traditional multiple daily dosing regimens in 120 neonates. The new dosing regimen was 5 mg/kg once daily dosing for infants with bodyweight <1200 g who are >30 days of age and for infants with bodyweight ≥1200 g who are >7 days of age. Multiple daily regimen was 2.5 mg/kg 8-24 hourly based on the gestational and postnatal age. Drug concentrations were more likely to be within therapeutic range with increasing the dose and extending the dosing intervals. Dehoog et al. (10) studied extended dosing regimen restricted to neonates within the first week of life. Neonates received tobramycin, 4 mg/kg per dose, with a gestational age–related initial interval of 48 hours (<32 weeks), 36 hours (32-36 weeks), and 24 hours (≥37 weeks). The target serum peak and trough serum concentrations were 5 to 10 mg/L and 0.5 mg/L, respectively. Peak serum concentrations were above 5 mg/L in 91% of cases, and trough serum concentrations were above 1 mg/L in 25.5% of cases. In their study, routine early therapeutic drug monitoring did not improve the model-based prediction of initial tobramycin dosing intervals. **Safety** Ototoxicity is usually irreversible. (14). Reports about ototoxicity in neonates are contradictory. Some studies report no relation, (15-17) whereas others reported a higher incidence. (18-20) Ototoxicity usually occurs in patients who have received either long or repeated courses of aminoglycosides. (21) Trials evaluating extended dosing regimens did not find any nephrotoxicity as determined by serum creatinine, blood urea nitrogen, urine output, and B2 microglobulin. (1,10) However sample size in these studies were not powered to detect any significant adverse renal outcomes. 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. Ototoxic medication was not the most probable risk factor in any of the patients with serum concentrations outside the therapeutic range. The routine therapeutic drug monitoring of vancomycin and tobramycin was not helpful in detecting neonates at risk for clinically important hearing loss. (22) 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. (23,24) Tobramycin share similar drug behaviour as gentamicin and this caution can therefore be extended to tobramycin. Intraventricular antibiotics: In infants with meningitis and ventriculitis, intraventricular antibiotics in combination resulted in a three-fold increase in mortality compared to standard treatment with intravenous antibiotics alone. (25) **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. (26) Avent et al. using the dose regimen recommended in this formulary found only 3% had a subtherapeutic level <5 µg/mL and only 3% exceeded upper therapeutic range of 12 µg/mL. (1) de Hoog et al. 2002 administered 4 mg/kg tobramycin to neonates within 7 days of life with dosing interval of 48 h (<32 weeks), 36 h (32-36 weeks) and 24 h (≥37 weeks). Using these dosages, the majority of infants had tobramycin peak concentrations from 5 to 10 µg/mL and trough concentrations from 0.5 to 1 µg/mL. (10) Central nervous system (CNS): Intravenous aminoglycosides have poor CNS penetration. (27) Data are limited on the CSF penetration of tobramycin in neonates and children. In neonates with septicaemia or meningitis, CSF concentrations were below 0.5 mg/L in 13 of 17 neonates after intravenous tobramycin despite measurable serum concentrations. (28) There is a case report of post-shunt revision Pseudomonas meningitis/ ventriculitis that was treated by intraventricular tobramycin (1-5 mg daily intrathecally with a target trough CSF concentration of 5-10 µg/L) in conjunction with intravenous tobramycin and ceftazidime (29). However, possible toxicities associated with administering aminoglycosides directly into the CSF and the relationship between CSF concentration and toxicity have not been studied. 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. (2,6,7,8,30) 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. (9). Same principle can be applied to tobramycin. Aminoglycosides and cyclo-oxygenase inhibitors: Renal drug clearance of aminoglycosides is lower in infants on cyclo-oxygenase inhibitors. (4,5)
Practice points	**Dose** Recommended dose regimen is based on Avent et al. 2002 in view of generalisability across all gestational and postnatal age groups. (1) (LOE III-3, GOR B) **Dose adjustment** An increased dosing interval is recommended in therapeutic hypothermia. (2,6,7,8,30) (LOE IV, GOR C) An increased dosing interval is recommended in infants on cyclo-oxygenase inhibitors. (4,5) (LOE IV, GOR B) **Monitoring** Trough and peak concentrations are not required routinely. (1) (LOE III-3, GOR B) Duration of therapy >5 days – Perform trough concentration prior to dose on day 5. (10) (LOE IV, GOR B) Perinatal hypoxia – Perform trough concentrations prior to every dose. (10) (LOE IV, GOR B) Renal impairment – Perform trough concentrations prior to every dose. (10) (LOE IV, GOR B) Concomitant use of other nephrotoxic agents – Perform trough concentrations prior to every dose. (10) (LOE IV, GOR B) ECMO – Perform trough concentration before 2nd dose. (9) (LOE IV, GOR C)

	Route Intraventricular antibiotics are associated with increased mortality and should be avoided. (LOE II, GOR B)
References	1. Avent ML, Kinney JS, Istre GR, Whitfield JM. Gentamicin and tobramycin in neonates: comparison of a new extended dosing interval regimen with a traditional multiple daily dosing regimen. American journal of perinatology. 2002;19(08):413-20. 2. Cristea S, Smits A, Kulo A, Knibbe CA, Van Weissenbruch M, Krekels EH, Allegaert K. Amikacin pharmacokinetics to optimize dosing in neonates with perinatal asphyxia treated with hypothermia. Antimicrobial agents and chemotherapy. 2017;61(12):e01282-17. 3. Smits A, Kulo A, van den Anker J, Allegaert K. The amikacin research program: a stepwise approach to validate dosing regimens in neonates. Expert Opin Drug Metab Toxicol 2017;13:157-66. 4. Smits A, De Cock RF, Allegaert K, Vanhaesebrouck S, Danhof M, Knibbe CA. Prospective Evaluation of a Model-Based Dosing Regimen for Amikacin in Preterm and Term Neonates in Clinical Practice. Antimicrob Agents Chemother 2015;59:6344-51. 5. 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. 6. Lutz IC, Allegaert K, de Hoon JN, Marynissen H. Pharmacokinetics during therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy: a literature review. BMJ paediatrics open 2020;4(1). 7. Frymoyer A, Lee S, Bonifacio SL, Meng L, Lucas SS, Guglielmo BJ, Sun Y, Verotta D. Every 36-h gentamicin dosing in neonates with hypoxic–ischemic encephalopathy receiving hypothermia. Journal of Perinatology. 2013;33(10):778-82. 8. Bijleveld YA, De Haan TR, Van Der Lee HJ, Groenendaal F, Dijk PH, Van Heijst A, De Jonge RC, Dijkman KP, Van Straaten HL, Rijken M, Zonnenberg IA. Altered gentamicin pharmacokinetics in term neonates undergoing controlled hypothermia. British journal of clinical pharmacology. 2016;81(6):1067-77. 9. Raffaeli G, Pokorna P, Allegaert K, Mosca F, Cavallaro G, Wildschut E, Tibboel D. Drug disposition and pharmacotherapy in neonatal ECMO: from fragmented data to integrated knowledge. Frontiers in pediatrics. 2019;7:360. 10. 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. 11. Tobramycin. Australian Injectable Drugs Handbook 8th edition. Accessed on 8 September 2020. 12. MIMS online. Tobramycin. Accessed on 26 August 2020. 13. Micromedex online. Tobramycin. Accessed on 25th August 2020. 14. de Hoog M, Schoemaker RC, Mouton JW, van den Anker JN. Tobramycin population pharmacokinetics in neonates. Clinical Pharmacology & Therapeutics 1997;62(4):392-9. 15. McCracken GH Jr. Aminoglycoside toxicity in infants and children. Am J Med 1986;8O(suppl 6B):172-8. 16. Colding H, Andersen EA, Prytz S, Wulffsberg H, Andersen GE. Auditory function after continuous infusion of gentamicin to high-risk newborns. Acta Paediatr Stand 1989;78:840-3. 17. Adelman C, Linder N, Levi H. Auditory nerve and brain stem evoked response thresholds in infants treated with gentamicin as neonates. Ann Otol Rhinol Laryngol 1989;98(4 pt 1):283-6. 18. Kohelet D, Usher M, Arbel E, Arlazoroff A, Goldberg M. Effect of gentamicin on the auditory brainstem evoked response in term infants: a preliminary report. Pediatr Res 1990;28:232-4. 19. Salamy A, Eldredge L, Tooley WI-I. Neonatal status and hearing loss in high-risk infants [see omments]. J Pediatr 1989;114:847-52. 20. Tsai CH, Tsai FJ. Auditory brainstem responses in term neonates treated with gentamicin. Acta Paediatr Sin 1992;33:417-22. 21. McCormack JP, Jewesson PJ. A critical reevaluation of the “therapeutic range” of aminoglycosides. Clinical infectious diseases 1992;14(1):320-39. 22. 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. 23. Wang, X., Hong, Y., Cai, P., Tang, N., Chen, Y., Yan, T., Liu, Y., Huang, Q., Li, Q., 2017. Rapid and Reliable Detection of Nonsyndromic Hearing Loss Mutations by Multicolor Melting Curve Analysis. Scientific Reports.. doi:10.1038/srep42894

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