

Alert	The Antimicrobial Stewardship Team has listed this drug under the following categories : Unrestricted – treatment up to 48 hours Obtain approval from the Infectious Diseases Team – treatment > 48 hours																								
Indication	Treatment of suspected or proven gram negative infection. Often used in combination with a beta-lactam antibiotic as empiric therapy for sepsis in the newborn.																								
Action	Bactericidal agent that acts by inhibiting protein synthesis in susceptible bacteria.																								
Drug Type	Aminoglycoside																								
Trade Name	DBL gentamicin, Gentamicin BP (Pfizer)																								
Presentation	10 mg/mL ampoule – paediatric strength 80 mg/2 mL ampoule – adult strength																								
Dosage / Interval	<p>5mg/kg/dose. Dosing interval as per Tables below</p> <table border="1"> <thead> <tr> <th colspan="2">Method (First 2 doses)</th> <th rowspan="2">Interval (hours)</th> </tr> <tr> <th>Corrected Gestational Age/Postmenstrual Age</th> <th>Route</th> </tr> </thead> <tbody> <tr> <td>< 30⁺⁰ weeks</td> <td>IV/IM</td> <td>48 hourly</td> </tr> <tr> <td>30⁺⁰–34⁺⁶ weeks</td> <td>IV/IM</td> <td>36 hourly</td> </tr> <tr> <td>≥ 35⁺⁰ weeks</td> <td>IV/IM</td> <td>24 hourly</td> </tr> </tbody> </table> <p>Subsequent dose interval is based on a gentamicin concentration at 22 hours after the administration of the 2nd dose as indicated in the table below.</p> <table border="1"> <thead> <tr> <th>Gentamicin level</th> <th>Interval</th> </tr> </thead> <tbody> <tr> <td>≤ 1.2 mg/L</td> <td>Every 24 hours after previous dose</td> </tr> <tr> <td>1.3 mg/L – 2.6 mg/L</td> <td>Every 36 hours after previous dose</td> </tr> <tr> <td>2.7 mg/L – 3.5 mg/L</td> <td>Every 48 hours after previous dose</td> </tr> <tr> <td>≥ 3.6 mg/L</td> <td>Hold dose, repeat concentration 24 hours later</td> </tr> </tbody> </table> <p>Gentamicin monitoring is required ONCE only, except when renal function is compromised. Refer to monitoring section below.</p>	Method (First 2 doses)		Interval (hours)	Corrected Gestational Age/Postmenstrual Age	Route	< 30 ⁺⁰ weeks	IV/IM	48 hourly	30 ⁺⁰ –34 ⁺⁶ weeks	IV/IM	36 hourly	≥ 35 ⁺⁰ weeks	IV/IM	24 hourly	Gentamicin level	Interval	≤ 1.2 mg/L	Every 24 hours after previous dose	1.3 mg/L – 2.6 mg/L	Every 36 hours after previous dose	2.7 mg/L – 3.5 mg/L	Every 48 hours after previous dose	≥ 3.6 mg/L	Hold dose, repeat concentration 24 hours later
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Preparation/Dilution	10 mg/mL – paediatric strength: Add 1 mL (10 mg) of gentamicin to 4 mL sodium chloride 0.9% to make a final volume of 5 mL with a concentration of 2 mg/mL. 80 mg/2 mL – adult strength: Add 1 mL (40 mg) of gentamicin to 19 mL sodium chloride 0.9% to make a final volume of 20 mL with a concentration of 2 mg/mL.																								
Administration	IV: Slow infusion over 5 minutes. IM: Variable absorption by the IM route, use only when IV route is not available. Gentamicin is inactivated by penicillins and cephalosporins so should not be mixed in the same solution or administered simultaneously. Ensure the line is adequately flushed if administered consecutively.																								
Monitoring	Routine therapeutic drug monitoring for ≤ 48 hours duration of therapy is not necessary unless renal function is impaired. For therapy > 48 hours, perform gentamicin concentration 22 hours after the 2 nd dose and determine the dose interval as described in the dosage section. Further gentamicin concentrations are not necessary unless renal function is impaired. Renal impairment: Perform gentamicin concentration 22 hours after every dose to determine the dose interval. Peak concentration may be important if an organism has a high minimum inhibitory concentration (MIC) – speak with your microbiologist. Target peak concentration: 5–12 mg/L.																								

	Peak concentration should be drawn at 30 minutes post dose.
Contraindications	Concurrent therapy with other ototoxic or nephrotoxic drugs.
Precautions	CAUTION in patients with pre-existing renal impairment, auditory or vestibular impairment, hypocalcaemia, depressed neuromuscular transmission.
Drug Interactions	Gentamicin should not be mixed with penicillins parenterally as inactivation occurs. Ensure line is adequately flushed between antibiotics.
Adverse Reactions	<p>Toxicity is rare in the newborn but can include:</p> <ol style="list-style-type: none"> 1. Nephrotoxicity- Associated with excessive accumulation of gentamicin. The initial symptoms may be due to renal tubular concentrating defect. These include excessive losses of sodium, calcium and magnesium. This may progress to proteinuria, increased urea, oliguria, increased serum creatinine. Renal impairment is usually reversible. 2. Ototoxicity. Primarily vestibular but also auditory toxicity. Associated with excessive accumulation of gentamicin and duration of therapy. Effects often irreversible. 3. Neuromuscular blockade- Muscular paralysis and respiratory failure may occur particularly when used with other neuromuscular blockers such as pancuronium. 4. Hypersensitivity- Very rare – rash, urticaria, fever, laryngeal oedema, eosinophilia. <p>NEPHROTOXICITY AND OTOTOXICITY ARE MORE PRONOUNCED WITH ADDITION OF OTHER NEPHROTOXIC/OTOTOXIC AGENTS SUCH AS FRUSEMIDE AND VANCOMYCIN.</p>
Compatibility	<p>Fluids: Glucose 5% , glucose 10%, Hartmann's, mannitol , sodium chloride 0.9%</p> <p>Y-Site: Amino acid solutions, amifostine, amiodarone, anidulafungin, atracurium, aztreonam, bivalirudin, caspofungin, ciprofloxacin, cisatracurium, dexmedetomidine, esmolol, fluconazole, foscarnet, granisetron, hydromorphone, labetalol, linezolid, magnesium sulfate, midazolam, morphine sulfate, palonosetron, pancuronium, pethidine, potassium chloride, remifentanyl, tigecycline, vecuronium, zidovudine.</p>
Incompatibility	<p>Fluids: Fat emulsions.</p> <p>Y-site: Azathioprine, azithromycin, chloramphenicol, dexamethasone, flucloxacillin, folic acid, frusemide, ganciclovir, heparin sodium, indomethacin, pentamidine, propofol, teicoplanin.</p>
Stability	Administer immediately, discard unused portion.
Storage	Protect from light. Store below 25°C
Evidence summary	<p>Dosing: Dosage and intervals Extended interval dosing vs traditional multiple doses a day</p> <ol style="list-style-type: none"> 1. Extended interval dosing for gentamicin in neonates is safe and effective with a superior pharmacokinetic profile when compared to traditional dosing^{3,4,15} (Level I, Grade A). <p>Term infants</p> <ol style="list-style-type: none"> 1. Recommended dosing for term babies is 4–5 mg/kg 24 hourly^{3,4,15} (Level II, Grade B). 2. HIE infants undergoing hypothermic therapy: Longer drug intervals of up to 36 hours may be more appropriate for cooled infants with moderate to severe HIE to avoid toxicity^{5,6,7} (Level III, Grade C). <p>Preterms: High dose versus low dose</p> <ol style="list-style-type: none"> 1. Higher doses of 4–5 mg/kg at extended intervals of 36–48 hours confers a more favourable pharmacokinetic profile than low doses of 2.5 mg/kg 24 hourly^{1,2,8-15} (Level II, Grade B). <p>Monitoring: Target peak and trough concentrations</p> <ol style="list-style-type: none"> 1. Target peak concentrations of 5–12 mg/L for efficacy^{3,4,17,19} (Level II, Grade B). 2. Routine peak concentrations are not necessary as high dose extended interval dosing regimens are able to achieve target peak concentrations in the majority of infants^{1-4,8-15} (Level II, Grade B). 3. Consider performing peak concentrations if there is poor clinical response in gram negative infections, oedema or macrosomia^{16,18} (Level III, Grade C).

	<p>4. Target trough concentrations of < 2 mg/L to reduce risk of ototoxicity and nephrotoxicity. Levels of < 1 mg/L may be preferred in prolonged therapy beyond 3 doses^{3,4,18,19} (Level II, Grade B). Timing of sampling:</p> <ol style="list-style-type: none"> 1. A serum gentamicin concentration performed 22 hours after the 1st dose is useful to guide dosing intervals^{1,2} (Level III, Grade C). 2. A trough concentration performed prior to the 3rd dose is useful to check for drug accumulation.¹⁹ 3. A peak concentration, if required, can be performed after the 2nd or 3rd dose.¹⁹
References	<ol style="list-style-type: none"> 1. Alshaikh B, Dersch-Mills D, Taylor R, Akierman AR, Yusuf K. Extended interval dosing of gentamicin in premature neonates < 28-week gestation. <i>Acta Paediatr</i> 2012;101(11):1134–9. 2. Dersch-Mills D, Akierman A, Alshaikh B, Yusuf K. Validation of a dosage individualization table for extended-interval gentamicin in neonates. <i>Ann Pharmacother</i> 2012;46(7-8):935–42. 3. Rao SC, Srinivasjois R, Hagan R, Ahmed M. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. <i>Cochrane Database Syst Rev</i> 2011;(11):CD005091. 4. Nestaas E, Bangstad HJ, Sandvik L, Wathne KO. Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. <i>Arch Dis Child Fetal Neonatal Ed.</i> 2005 Jul;90(4):F294–300. 5. Frymoyer A, Meng L, Bonifacio SL, Verotta D, Guglielmo BJ. Gentamicin pharmacokinetics and dosing in neonates with hypoxic ischemic encephalopathy receiving hypothermia. <i>Pharmacotherapy</i> 2013;33(7):718–26. 6. Smit E, Liu X, Gill H, Sabir H, Jary S, Thoresen M. Factors associated with permanent hearing impairment in infants treated with therapeutic hypothermia. <i>J Pediatr</i> 2013;163(4):995–1000. 7. Mark LF, Solomon A, Northington FJ, Lee CK. Gentamicin pharmacokinetics in neonates undergoing therapeutic hypothermia. <i>Ther Drug Monit.</i> 2013 Apr;35(2):217–22. 8. Rastogi A, Agarwal G, Pyati S, Pildes RS. Comparison of two gentamicin dosing schedules in very low birth weight infants. <i>Pediatr Infect Dis J</i> 2002;21(3):234–40. 9. Mercado MC, Brodsky NL, McGuire MK, Hurt H. Extended interval dosing of gentamicin in preterm infants. <i>Am J Perinatol</i> 2004;21(2):73–7. 10. Stickland MD, Kirkpatrick CM, Begg EJ, Duffull SB, Oddie SJ, Darlow BA. An extended interval dosing method for gentamicin in neonates. <i>J Antimicrob Chemother</i> 2001;48(6):887–93. 11. 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. <i>Am J Perinatol.</i> 2002 Nov;19(8):413–20. 12. Bajaj M, Palmer K. Gentamicin usage in newborns—a simple and practical regime. <i>Pharm World Sci.</i> 2004 Aug;26(4):242–4. 13. Murphy JE. Prediction of gentamicin peak and trough concentrations from six extended-interval dosing protocols for neonates. <i>Am J Health-Syst Pharm</i> 2005;62(8):823–7. 14. Lannigan R, Thomson A. Evaluation of 22 neonatal gentamicin dosage protocols using a Bayesian Approach. <i>Paediatric and Perinatal Drug Therapy</i> 2001;4:92. 15. Darmstadt GL, Miller-Bell M, Batra M, Law P, Law K. Extended-interval dosing of gentamicin for treatment of neonatal sepsis in developed and developing countries. <i>J Health Popul Nutr.</i> 2008 Jun;26(2):163–82. 16. Martinkova J, Pokorna P, Zahora J, Chladek J, Vobruba V, Selke-Krulichova I, Chladkova J. Tolerability and outcomes of kinetically guided therapy with gentamicin in critically ill neonates during the first week of life: an open-label, prospective study. <i>Clin Ther</i> 2010;32(14):2400–14. 17. Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. <i>J Infect Dis.</i> 1984 Mar;149(3):443–8. 18. UK Nice Guidelines August 2012. Antibiotics for early-onset infection: Antibiotics for the prevention and treatment of early onset neonatal infection. 19. Touw DJ, Westerman EM, Sprij AJ. Therapeutic drug monitoring of aminoglycosides in neonates. <i>Clin Pharmacokinet.</i> 2009;48(2):71–88. 20. Australian Injectable Drugs Handbook, Fifth Edition, 2011. 21. Micromedex 2.0 22. Clinical Excellence Commission- Sepsis Neonatal First Dose. Empiric Intravenous Antibiotic Guideline V1. 23. Robinson R, Nahata M. Safety of Intravenous Bolus Administration of Gentamicin in Pediatric

	<p>Patients. The Annals of Pharmacotherapy. 2001; 35:1327–1331.</p> <p>24. Bromiker R, Adelman C, Arad I et al. Safety of Gentamicin in Administered by Intravenous Bolus in the Nursery. Clinical Pediatrics; 1999;38:433–435.</p> <p>25. Australian Injectable Drugs Handbook, 6th Edition, Society of Hospital Pharmacists of Australia 2014.</p> <p>26. Neofax accessed on www.neofax.micromedex.solutions.com on 29th July 2015.</p>
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