

Alert	<p>The administration of antibiotics within 1 hour of the identification of sepsis is recommended.(1) The Antimicrobial Stewardship Team has listed this drug under the following categories : Unrestricted – duration up to 48 hours and restricted for duration > 48 hours 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. Unregistered products from overseas available during shortages may contain preservatives.</p>																																				
Indication	Treatment of gram-negative infections.																																				
Action	Bactericidal agent that acts by inhibiting protein synthesis in susceptible bacteria.																																				
Drug type	Aminoglycoside antibiotic																																				
Trade name	DBL gentamicin, Gentamicin BP (Pfizer)																																				
Presentation	10 mg/mL ampoule – paediatric strength 80 mg/2 mL ampoule – adult strength NOTE: SAS product may be considered in the event of a shortage. Consult the local pharmacy.																																				
Dose	<p>Dose: 5 mg/kg as follows: (2-5)</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Corrected Gestational Age/Postmenstrual Age*</th> <th style="text-align: center;">Route</th> <th style="text-align: center;">Dosing interval</th> <th style="text-align: center;">Drug concentration to be performed at:</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">< 30⁺⁰ weeks*</td> <td style="text-align: center;">IV/IM</td> <td style="text-align: center;">48 hourly</td> <td style="text-align: center;">22 hours after the 2nd dose</td> </tr> <tr> <td style="text-align: center;">30⁺⁰–34⁺⁶ weeks*</td> <td style="text-align: center;">IV/IM</td> <td style="text-align: center;">36 hourly</td> <td style="text-align: center;">22 hours after the 2nd dose</td> </tr> <tr> <td style="text-align: center;">≥ 35⁺⁰ weeks*</td> <td style="text-align: center;">IV/IM</td> <td style="text-align: center;">24 hourly</td> <td style="text-align: center;">22 hours after the 2nd dose</td> </tr> <tr> <td style="text-align: center;">*Concurrent cyclo-oxygenase inhibitors (indomethacin or ibuprofen) (6-8)</td> <td style="text-align: center;">IV/IM</td> <td style="text-align: center;">Extend dosing interval by 12 hours Example: 48 hourly to 60 hourly</td> <td></td> </tr> <tr> <td style="text-align: center;">Therapeutic hypothermia (9-13)</td> <td style="text-align: center;">IV/IM</td> <td style="text-align: center;">36 hourly</td> <td style="text-align: center;">Trough concentrations prior to every dose</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.(3, 4)</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">22-hour Gentamicin concentration*</th> <th style="text-align: center;">Interval</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">≤ 1.2 mg/L</td> <td style="text-align: center;">Every 24 hours after previous dose</td> </tr> <tr> <td style="text-align: center;">1.3 mg/L – 2.6 mg/L</td> <td style="text-align: center;">Every 36 hours after previous dose</td> </tr> <tr> <td style="text-align: center;">2.7 mg/L – 3.5 mg/L</td> <td style="text-align: center;">Every 48 hours after previous dose</td> </tr> <tr> <td style="text-align: center;">≥ 3.6 mg/L</td> <td style="text-align: center;">Hold dose, repeat concentration 24 hours later</td> </tr> </tbody> </table> <p>*Different to trough concentration performed prior to next dose – Refer to dose adjustment section.</p> <p>Gentamicin monitoring is required ONCE only, except the duration of gentamicin therapy is greater than 7 days or with the conditions described in dose adjustment and monitoring section.</p>			Corrected Gestational Age/Postmenstrual Age*	Route	Dosing interval	Drug concentration to be performed at:	< 30 ⁺⁰ weeks*	IV/IM	48 hourly	22 hours after the 2 nd dose	30 ⁺⁰ –34 ⁺⁶ weeks*	IV/IM	36 hourly	22 hours after the 2 nd dose	≥ 35 ⁺⁰ weeks*	IV/IM	24 hourly	22 hours after the 2 nd dose	*Concurrent cyclo-oxygenase inhibitors (indomethacin or ibuprofen) (6-8)	IV/IM	Extend dosing interval by 12 hours Example: 48 hourly to 60 hourly		Therapeutic hypothermia (9-13)	IV/IM	36 hourly	Trough concentrations prior to every dose	22-hour Gentamicin concentration*	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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Dose adjustment	<p>Therapeutic hypothermia –36 hourly interval.(9-13). Measure trough concentrations before every dose. ECMO - Renal dysfunction is the main determinant. Measure trough concentration before 2nd dose.(14) Renal impairment – Measure trough concentration before every dose. Hepatic impairment – No specific dose adjustment.</p>																																				
Maximum dose																																					
Total cumulative dose																																					

Route	IV IM – only if IV access is not available.
Preparation	10mg/mL – paediatric strength Draw up 1mL (10mg) gentamicin and add to 4mL of sodium chloride 0.9% to make a final volume of 5mL with a concentration of 2mg/mL solution. 80mg/2 mL – adult strength Draw up 1mL (40mg) gentamicin and add to 19mL of sodium chloride 0.9% to make a final volume of 20mL with a concentration of 2mg/mL solution.
Administration	IV - Inject slowly over 5 minutes as an IV injection.(15) IM- only given when IV route is not available as the IM absorption is variable. Administer required dose undiluted, deeply into anterolateral thigh muscle.
Monitoring	Urine output, urine analysis, blood urea, nitrogen and creatinine Monitor for anaphylaxis Trough concentrations – Target trough concentration: <2 mg/L. Repeat trough concentrations are not required routinely unless: (4) (1) duration of therapy is ≥ 7 days – In this scenario, prior to dose on day 7 and then weekly thereafter. (2) renal impairment or perinatal hypoxia with Apgar <5 at 5 minutes and/or concomitant use of other nephrotoxic agents or therapeutic hypothermia In these scenarios, perform trough concentration prior to every dose. If trough concentration ≥ 2 mg/L, 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. Peak concentration should be drawn at 30 minutes post dose.
Contraindications	Hypersensitivity to aminoglycosides
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 or cephalosporins as inactivation occurs.(15) Ensure line is adequately flushed between antibiotics and if possible, stagger the time of administration of each drug so that they are separated by several hours. Avoid use with other potent diuretics, neurotoxic, nephrotoxic and neuromuscular blocking agents.(16)
Adverse reactions	Toxicity is rare in the newborn but can include: 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. Nephrotoxicity and ototoxicity are more pronounced with addition of other nephrotoxic/ototoxic agents such as furosemide and vancomycin.
Compatibility	Fluids: Glucose 5% , glucose 10%, Hartmann’s, sodium chloride 0.9%, Ringer’s (15) Y-Site: Amino acid solutions, amifostine, amiodarone, anidulafungin, atracurium, aztreonam, bivalirudin, calcium chloride, calcium gluconate, caspofungin, ciprofloxacin, cisatracurium,

	clindamycin, dexmedetomidine, digoxin, dobutamine, esmolol, fentanyl, fluconazole, foscarnet, granisetron, hydromorphone, labetalol, linezolid, magnesium sulfate, meropenem, methylprednisolone, metronidazole, midazolam, morphine sulfate, , pancuronium, pethidine, phenobarbital sodium, potassium chloride, remifentanyl, rocuronium, suxamethonium, tigecycline, vancomycin, vecuronium, zidovudine.
Incompatibility	Fluids: Fat emulsions. Y-site: Azathioprine, azithromycin, chloramphenicol, dexamethasone, flucloxacillin, folic acid, frusemide, ganciclovir, heparin sodium, indomethacin, pentamidine, propofol, teicoplanin. Note: Do not mix together with penicillins or cephalosporins.
Stability	Administer immediately, discard unused portion.
Storage	Protect from light. Store below 25°C
Excipients	DBL Gentamicin: Disodium edetate Pfizer Gentamicin: Disodium edetate, sodium hydroxide, sulfuric acid.
Special comments	
Evidence	<p>Efficacy Extended interval dosing for gentamicin in neonates provides a superior pharmacokinetic profile compared to multiple doses a day dosing. However, there is insufficient evidence to conclude whether a 'once a day' or a 'multiple doses a day' regimen of gentamicin is clinically superior in treating proven neonatal sepsis. (17, 18) (Rao SC 2016, Nestaas E 2005)</p> <p>Current dosing recommendations are based on 4 prospective observational studies using extended-interval dosing interval with a single drug concentration at 22 hours after the first dose.(2-5) Three of them were consecutive Canadian studies. First of the studies evaluated the extended interval dosing (EID) regimen in neonates \leq28-week gestation. The dosing interval was based on a 22 h level after the first dose of 5mg/kg. All neonates, except one, achieved therapeutic peak and trough levels. Based on the 22 h level, dosing interval was 36 h in 61% of neonates and 48 h in 39% of neonates. In their second prospective, observational study, similar findings were noted in 104 neonates \leq7 days of life, gestational age 23 weeks to full term. Appropriate peak and trough concentrations were attained in all neonates. A third prospective observational study by the group assessed extended-interval dosing of gentamicin in neonates >7 days old and found appropriate peak and trough concentrations in all neonates.(2-4) Fourth observational study by Matinkova et al, in which 4 mg/kg/dose was given at various intervals based on gestational age groups (<34 weeks-48 hourly; 34-38 weeks – 36 hourly; >38 weeks – 24 hourly). The initial dose of gentamicin 4mg/kg during the first week of life was high enough to reach bactericidal C_{max} within 6–10mg/L. However, C_{max} <6 mg/L occurred in 13% of neonates. The inter-dose interval modified according to the recommendation resulted in C_{trough} values within the target range of 0.5–2.0mg/L in all but 2 neonates.(5)</p> <p>Patients who have early (1-hr post-infusion) peak plasma aminoglycoside levels that are >5 ug/mL for gentamicin and tobramycin and >20 ug/ml for amikacin are less likely to die from gram-negative bacteraemia. Moore et al reported a 2.4% mortality rate in adults who achieved 1-hour post-infusion gentamicin or tobramycin peak concentrations above 5 μg/mL. Mortality rate increased to 20.9% for patients failing to achieve peak concentrations above 5 μg/mL within 24–48 hours of starting therapy. (19, 20)</p> <p>Therapeutic hypothermia (TH): Gentamicin clearance is decreased in neonates receiving hypothermia treatment. Modified gentamicin dosing regimens are required to avoid potential toxicity related to higher concentrations.(13)</p> <p>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 multifactorial condition during ECMO, can be considered as 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. (14)</p>

	<p>Cyclo-oxygenase inhibitors: Renal drug clearance of aminoglycosides is lower in infants on cyclo-oxygenase inhibitors. (6-8)</p> <p>Safety Ototoxicity: There is no clear association between peak or trough levels and ototoxicity in neonates. (21-23) The chance of gentamicin ototoxicity is reported to be greater in those who receive the drug for a longer duration.(21) Nephrotoxicity: Nephrotoxicity does not seem to be related to peak or trough levels and more related to drug concentration and longer duration.(24) Among neonates with PDA and receiving gentamicin, non-steroid anti-inflammatory drugs (ibuprofen, indomethacin) therapy increases the risk of acute kidney injury.(25) 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.(26, 27) 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 and should be avoided.(28)</p> <p>Pharmacokinetics Aminoglycosides display concentration-dependent killing, suggesting higher peaks provide greater efficacy.(29, 30) While a peak aminoglycoside concentration to minimum inhibitory concentration (MIC) ratio of 8–10:1 is considered ideal, based on the usual MICs of Escherichia coli (range 0.25–1 mg/L) a peak of at least 5 mg/L has a high likelihood of being effective.(4, 30) Aminoglycosides display a post-antibiotic effect whereby bacterial growth is suppressed despite negligible drug concentrations.(31) Aminoglycosides have poor CNS penetration when administered intravenously.(32)</p>
<p>Practice points</p>	<p>Dose There is insufficient evidence whether a 'once a day' regimen of gentamicin is optimal in treating proven neonatal sepsis, however, pharmacokinetic data suggests 'once a day' gentamicin regimens are superior to a 'multiple doses a day' regimens.(17) (LOE I, GOR B) The recommended dose regimen in this formulary is a pragmatic adaptation of the dosing used in 4 prospective observational studies.(2-5) (LOE III-3, GOR B)</p> <p>Dose adjustment An increased dosing interval is recommended in therapeutic hypothermia.(9-13) (LOE IV, GOR B) An increased dosing interval is recommended in infants on cyclo-oxygenase inhibitors.(6) (LOE IV, GOR B)</p> <p>Monitoring The evidence suggests a serum gentamicin concentration performed 22 hours after the 1st dose is useful to guide dosing intervals. (2-4)(LOE III-3, GOR B). However, in daily practice, gentamicin is most often discontinued within 36-48 hours of commencement (once the neonate is deemed no longer at risk of sepsis and septic screen remain negative). Therefore, measurement of drug concentrations is recommended only after the 2nd dose to limit the burden of blood sampling. (ANMF consensus recommendation). Subsequent concentrations are not routinely required. (2-4) (LOE III-3, GOR B) 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 (2-4, 17, 18) (LOE III-3, GOR B) Consider performing peak concentrations if there is poor clinical response in gram negative infections, oedema or macrosomia.(5) (LOE IV, GOR C). A peak concentration, if required, can be performed after the 2nd or 3rd dose. (29) Target peak concentrations of 5–12 mg/L. (17-19, 29) (LOE IV, GOR C) Target trough concentrations of < 2 mg/L to reduce risk of ototoxicity and nephrotoxicity. (33, 34) (LOE IV, GOR C - adult)</p>

	<p>Duration of therapy ≥ 7 days – Perform trough concentration prior to dose on day 7 and then weekly thereafter. (4, 35) (LOE IV, GOR B)</p> <p>Perinatal hypoxia – Perform trough concentrations prior to every dose. (4, 35) (LOE IV, GOR B)</p> <p>Renal impairment – Perform trough concentrations prior to every dose. (4, 35) (LOE IV, GOR B)</p> <p>Concomitant use of other nephrotoxic agents – Perform trough concentrations prior to every dose. (4, 35) (LOE IV, GOR B)</p> <p>ECMO – Perform trough concentration before 2nd dose.(14) (LOE IV, GOR B)</p> <p>Route</p> <p>Intraventricular antibiotics are associated with increased mortality and should be avoided.(28) (LOE II, GOR B)</p> <p>General</p> <p>Aim to minimise aminoglycoside toxicity by (1) avoiding gentamicin to patients at elevated risk (i.e. on indomethacin, history of hypoxia and/or significant renal dysfunction), (2) minimising the duration of treatment and (3) prescribing a dose in a way that minimizes risk (i.e. EID with dose adjustment as necessary). (ANMF consensus recommendations)</p>
<p>References</p>	<ol style="list-style-type: none"> 1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. <i>Intensive care medicine.</i> 2017;43(3):304-77. 2. Alshaikh B, Dersch-Mills D, Taylor R, Akierman AR, Yusuf K. Extended interval dosing of gentamicin in premature neonates ≤ 28-week gestation. <i>Acta Paediatrica.</i> 2012;101(11):1134-9. 3. Dersch-Mills D, Akierman A, Alshaikh B, Yusuf K. Validation of a Dosage Individualization Table for Extended-Interval Gentamicin in Neonates. <i>Annals of Pharmacotherapy.</i> 2012;46(7-8):935-42. 4. Dersch-Mills D, Akierman A, Alshaikh B, Sundaram A, Yusuf K. Performance of a dosage individualization table for extended interval gentamicin in neonates beyond the first week of life. <i>The Journal of Maternal-Fetal & Neonatal Medicine.</i> 2016;29(9):1451-6. 5. Martínková J, Pokorná P, Záhora J, Chládek J, Vobruba V, Selke-Krulichová I, et al. 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>Clinical therapeutics.</i> 2010;32(14):2400-14. 6. Allegaert K. The impact of ibuprofen or indomethacin on renal drug clearance in neonates. <i>The Journal of Maternal-Fetal & Neonatal Medicine.</i> 2009;22(sup3):88-91. 7. Smits A, De Cock RFW, Allegaert K, Vanhaesebrouck S, Danhof M, Knibbe CAJ. Prospective Evaluation of a Model-Based Dosing Regimen for Amikacin in Preterm and Term Neonates in Clinical Practice. <i>Antimicrobial Agents and Chemotherapy.</i> 2015;59(10):6344. 8. Smits A, Kulo A, Van Den Anker J, Allegaert K. The amikacin research program: a stepwise approach to validate dosing regimens in neonates. 2016:1-10. 9. Frymoyer A, Lee S, Bonifacio SL, Meng L, Lucas SS, Guglielmo BJ, et al. Every 36-h gentamicin dosing in neonates with hypoxic–ischemic encephalopathy receiving hypothermia. <i>Journal of Perinatology.</i> 2013;33(10):778-82. 10. Bijleveld YA, De Haan TR, Van Der Lee HJH, Groenendaal F, Dijk PH, Van Heijst A, et al. Altered gentamicin pharmacokinetics in term neonates undergoing controlled hypothermia. <i>British Journal of Clinical Pharmacology.</i> 2016;81(6):1067-77. 11. Lutz IC, Allegaert K, de Hoon JN, Marynissen H. Pharmacokinetics during therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy: a literature review. <i>BMJ Paediatr Open.</i> 2020;4(1):e000685-e. 12. Cristea S, Smits A, Kulo A, Knibbe CAJ, van Weissenbruch M, Krekels EHJ, et al. Amikacin Pharmacokinetics To Optimize Dosing in Neonates with Perinatal Asphyxia Treated with Hypothermia. <i>Antimicrobial Agents and Chemotherapy.</i> 2017;61(12):e01282-17.

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