

Benzylpenicillin

Newborn use only

2021

Alert	High risk medicine. The Antimicrobial Stewardship Team has listed this drug under the following categories: Unrestricted. 60 mg = 100 000 Units of penicillin.																																																									
Indication	Empiric treatment of early onset sepsis in combination with an aminoglycoside. Directed treatment of infection due to a susceptible bacterium. Treatment of meningitis due to a susceptible bacterium, including Group B <i>Streptococcus</i> (GBS). Treatment of congenital syphilis.																																																									
Action	Bactericidal agent which inhibits cell wall synthesis.																																																									
Drug type	Antibacterial - Penicillin																																																									
Trade name	BenPen																																																									
Presentation	600 mg, 1.2 g and 3 g vial. Each 600 mg dose contains 41.4 mg (1.8 mmol) sodium.																																																									
Dose	<p>Sepsis: (excluding meningitis and congenital syphilis): 60 mg/kg/dose. Dosing interval as per table below</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Corrected Gestational Age/Postmenstrual Age</th> <th>Postnatal Age</th> <th>Interval</th> </tr> </thead> <tbody> <tr> <td>< 30⁺⁰ weeks</td> <td>0–28 days</td> <td>12 hourly</td> </tr> <tr> <td>< 30⁺⁰ weeks</td> <td>29+ days</td> <td>8 hourly</td> </tr> <tr> <td>30⁺⁰–36⁺⁶ weeks</td> <td>0–14 days</td> <td>12 hourly</td> </tr> <tr> <td>30⁺⁰–36⁺⁶ weeks</td> <td>15+ days</td> <td>8 hourly</td> </tr> <tr> <td>37⁺⁰–44⁺⁶ weeks</td> <td>0–7 days</td> <td>12 hourly</td> </tr> <tr> <td>37⁺⁰–44⁺⁶ weeks</td> <td>8+ days</td> <td>8 hourly</td> </tr> <tr> <td>≥45 weeks</td> <td></td> <td>6 hourly</td> </tr> </tbody> </table> <p>Meningitis: 90 mg/kg/dose. Dosing interval as per table below</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Corrected Gestational Age/Postmenstrual Age</th> <th>Postnatal Age</th> <th>Interval</th> </tr> </thead> <tbody> <tr> <td>< 37⁺⁰ weeks</td> <td>0–7 days</td> <td>12 hourly</td> </tr> <tr> <td>< 37⁺⁰ weeks</td> <td>8+ days</td> <td>8 hourly</td> </tr> <tr> <td>≥ 37⁺⁰ weeks</td> <td>0+ days</td> <td>8 hourly</td> </tr> </tbody> </table> <p>Congenital syphilis: 30 mg/kg/dose. Dosing interval as per table below</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Corrected Gestational Age/Postmenstrual Age</th> <th>Postnatal Age</th> <th>Interval</th> </tr> </thead> <tbody> <tr> <td>< 30⁺⁰ weeks</td> <td>0–28 days</td> <td>12 hourly</td> </tr> <tr> <td>< 30⁺⁰ weeks</td> <td>29+ days</td> <td>8 hourly</td> </tr> <tr> <td>30⁺⁰–36⁺⁶ weeks</td> <td>0–14 days</td> <td>12 hourly</td> </tr> <tr> <td>30⁺⁰–36⁺⁶ weeks</td> <td>15+ days</td> <td>8 hourly</td> </tr> <tr> <td>37⁺⁰–44⁺⁶ weeks</td> <td>0–7 days</td> <td>12 hourly</td> </tr> <tr> <td>37⁺⁰–44⁺⁶ weeks</td> <td>8+ days</td> <td>8 hourly</td> </tr> </tbody> </table>	Corrected Gestational Age/Postmenstrual Age	Postnatal Age	Interval	< 30 ⁺⁰ weeks	0–28 days	12 hourly	< 30 ⁺⁰ weeks	29+ days	8 hourly	30 ⁺⁰ –36 ⁺⁶ weeks	0–14 days	12 hourly	30 ⁺⁰ –36 ⁺⁶ weeks	15+ days	8 hourly	37 ⁺⁰ –44 ⁺⁶ weeks	0–7 days	12 hourly	37 ⁺⁰ –44 ⁺⁶ weeks	8+ days	8 hourly	≥45 weeks		6 hourly	Corrected Gestational Age/Postmenstrual Age	Postnatal Age	Interval	< 37 ⁺⁰ weeks	0–7 days	12 hourly	< 37 ⁺⁰ weeks	8+ days	8 hourly	≥ 37 ⁺⁰ weeks	0+ days	8 hourly	Corrected Gestational Age/Postmenstrual Age	Postnatal Age	Interval	< 30 ⁺⁰ weeks	0–28 days	12 hourly	< 30 ⁺⁰ weeks	29+ days	8 hourly	30 ⁺⁰ –36 ⁺⁶ weeks	0–14 days	12 hourly	30 ⁺⁰ –36 ⁺⁶ weeks	15+ days	8 hourly	37 ⁺⁰ –44 ⁺⁶ weeks	0–7 days	12 hourly	37 ⁺⁰ –44 ⁺⁶ weeks	8+ days	8 hourly
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Maximum dose	300 mg/kg/day																																																									
Total cumulative dose																																																										
Route	IV IM (only if IV route not available).																																																									
Preparation	<p>IV</p> <p>Add 3.6 mL of water for injection to the 600 mg vial to make a 150 mg/mL solution. Add 3.2 mL of water for injection to the 1.2 g vial to make a 300mg/mL solution Add 8 mL of water for injection to the 3 g vial to make 300mg/mL</p> <p>FURTHER DILUTE</p> <p>From the 600 mg vial draw up 4 mL (600 mg of penicillin) of solution and add 16 mL of sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 30 mg/mL.</p> <p>From the 1.2 g and 3 g vial draw up 2 mL (600 mg of penicillin) and add 18 mL of sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 30 mg/mL.</p>																																																									

	<p>Meningitis IV Dilute the dose to a maximum concentration of 60 mg/mL.</p> <p>IM Add 1.6 mL water for injection to the 600 mg vial to make a 300 mg/mL solution. Add 3.2 mL water for injection to the 1.2 g vial to make a 300 mg/mL solution. Add 8 mL water for injection to the 3 g vial to make a 300 mg/mL solution.</p>
Administration	IV infusion over 15–30 minutes. Longer infusion time (30–60 minutes) is recommended for large doses Separate from aminoglycoside administration by clearing the line with a flush as penicillins inactivate aminoglycosides. IM injection.
Monitoring	Not routinely required Plasma concentrations may be useful for infections with a high Minimum Inhibitory Concentration (MIC).
Contraindications	Hypersensitivity to penicillin.
Precautions	Hypersensitivity to cephalosporins. Significant CNS toxicity including seizures may occur with high doses and rapid infusions. Consider sodium load, especially in renal failure – a dose of 300 mg/kg/day provides 0.90 mmol/kg/day of sodium. Dose reduction is recommended in significant renal insufficiency.
Drug interactions	Aminoglycosides including gentamicin should not be mixed with penicillin when both drugs are given parenterally as inactivation occurs. Ensure line is adequately flushed between antibiotics.
Adverse reactions	Allergy. Note hypersensitivity to penicillin has not been reported in neonates. Bone marrow suppression, granulocytopenia and hepatitis are rare. Significant CNS toxicity including seizures may occur with high doses and rapid infusions.
Compatibility	Fluids: Glucose 5%, Glucose 10% and sodium chloride 0.9% Y site: Amino acid solutions and fat emulsions.
Incompatibility	Y-site: Aminoglycosides – amikacin, gentamicin, tobramycin; aminophylline, dobutamine, erythromycin, ganciclovir, haloperidol lactate, heparin sodium, labetalol, metaraminol, noradrenaline, pentamidine, phenobarbitone, phentolamine, prochlorperazine, potassium chloride, promethazine, protamine sulfate, suxamethonium, thiopentone, tranexamic acid.
Stability	Administer immediately. Discard unused portion of reconstituted solution.
Storage	Store at room temperature. Protect from light.
Excipients	
Special comments	CSF penetration is poor even when meninges are inflamed, hence the larger dose in meningitis. Prescribe in terms of mg rather than units. 60 mg = 100 000 Units of penicillin.
Evidence	<p>Efficacy: Group B streptococcus (GBS) continues to be a significant global cause of early [1,2] and late onset neonatal sepsis [1]. Isolates remain largely sensitive to benzylpenicillin. [2,3] Benzylpenicillin is usually used in combination with gram negative bacterial cover most commonly an aminoglycoside. WHO recommends penicillin/ampicillin and gentamicin as treatment for neonatal sepsis.[4] In developing countries, among community-acquired neonatal bacteraemia, resistance or reduced susceptibility to the combination of penicillin and gentamicin and to third-generation cephalosporins occurs in more than 40% of cases.[5]</p> <p>Treatment of early onset sepsis: A RCT in 55 infants <48 hours old with suspected sepsis compared penicillin [30 mg/kg/day in two doses] and gentamicin at 6 mg/kg/day in two doses] versus ceftazidime [100 mg/kg/day in two divided doses]. No treatment failure or infant death was reported in either group [6]. [LOE II] A randomised two centre cluster crossover trial in Estonia compared penicillin [15mg/kg 8–12 hourly] + gentamicin [4–5 mg/kg 24–48 hourly] versus ampicillin [25 mg/kg 8–12 hourly] + gentamicin in neonates at risk of early onset sepsis showed similar effectiveness with no difference in change of antibiotics at 72 hours and/or 7 day all-cause mortality. Subgroup analysis reported increased NEC stage III in ELBW infants allocated NEC, but increased mortality in infants born <26 weeks gestation allocated penicillin [7,8]. [LOE III- 2] Guidelines: For early onset neonatal sepsis, guidelines recommend</p>

to use benzylpenicillin or ampicillin in combination with an aminoglycoside [4, 9-12]. Dosage recommendations range from benzylpenicillin 50 mg/kg/day (divided doses) [10], 100 mg/kg/day in neonates under 7 days age (divided 12 hourly) [12], to 150 mg/kg/day in neonates aged 7–28 days (divided 8 hourly) [12], Conclusion: Benzylpenicillin has similar efficacy to ampicillin in empirical treatment of early onset sepsis in neonates when combined with an aminoglycoside. [Level II, GOR B]

Treatment of late onset sepsis: A RCT in Malawi in 348 infants <60 days age with possible severe infection reported similar efficacy for benzylpenicillin [30 mg/kg 8 hourly IV or 60 mg/kg 8 hourly IV for bacterial meningitis] and gentamicin [6 mg/kg IV daily] versus ceftriaxone [50–100 mg/kg IV once daily depending on age] for 5–14 days as first-line treatment. Mortality and sequelae were similar in both groups [13]. [LOE II] For infants <60 days age with signs of clinical severe infection but without signs of critical illness, several RCTs in developing countries have assessed the efficacy of the WHO recommendations of penicillin or ampicillin in combination with gentamicin for 7 days to other simplified antibiotic regimens requiring fewer days of injections - mostly incorporating a change to oral amoxicillin after 2 days. In all the trials, the simplified regimens were as effective as injectable benzylpenicillin–gentamicin for 7 days on an outpatient basis in young infants with clinical signs of severe infection, without signs of critical illness [14,16]. Another trial in Pakistan in 434 infants < 60 days age with possible serious bacterial infection reported procaine penicillin-gentamicin (both IM) was superior to oral trimethoprim-sulfamethoxazole-IM gentamicin [17]. [LOE II] For infants <60 days without critical illness but with fast breathing, an RCT in Pakistan reported use of a placebo resulted in worse outcomes compared to oral amoxicillin [18]. A large RCT in 3 African countries reported that oral amoxicillin was as effective as injectable procaine benzylpenicillin plus gentamicin for treatment infants <60 days age with fast breathing when referral is not possible.[19] [LOE II] **Guidelines:** WHO guidelines recommend that neonates with signs of sepsis should be treated with ampicillin or penicillin and gentamicin as the first line antibiotic treatment for at least 10 days.[4] Current guidelines in developed countries do not recommend use of benzylpenicillin for late onset sepsis. [9-12]

Treatment of meningitis: In developed country settings, current guidelines [9-11] do not recommend benzylpenicillin as empiric treatment of meningitis due to relatively poor CSF penetration of benzylpenicillin [20] and the high incidence of resistance to benzylpenicillin / gentamicin combinations [5]. Where used, higher dosages of benzylpenicillin [60 mg/kg 8 hourly IV] have been given [13]. For infants in whom GBS has been isolated from CSF, high dose benzylpenicillin [21] or cefotaxime [9,10,21] may be used. [LOE II GOR B]

Treatment of congenital syphilis: Azimi et al compared penicillin concentrations in CSF in infants undergoing therapy for congenital syphilis receiving aqueous penicillin G 60 mg/kg/day IV 12 hourly (23 infants), 120 mg/kg/day (40 infants), or procaine penicillin G 30 mg/kg/day IM (100 infants). Mean CSF penicillin levels were 0.416, 0.493 and 0.077 µg/mL respectively. All patients who received aqueous penicillin G, but only 82% of those from patients who received procaine penicillin G, had treponemicidal concentrations >0.018 µg/mL, and 33.3% of those who received procaine penicillin G had CSF penicillin concentrations <0.018 µg/mL 18 and 24 hours after a dose. [20] Two RCTs have reported use of benzathine benzylpenicillin 30 mg/kg IM as treatment of asymptomatic newborns at high risk of congenital syphilis. No treatment failures were reported [22,23]. [LOE II GOR D] **Guidelines:** ASID 2014 guidelines recommend benzylpenicillin 50 mg/kg 12 hourly IV for 10 days or procaine penicillin 50 mg/kg IM for 10 days for infants with or at high risk of congenital syphilis [11]. Centres for disease control and prevention 2015 guidelines recommend aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose (30 mg/kg/dose) IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days [31]. [LOE IV GOR B]

Safety: Trials have generally reported uncommon adverse events attributable to benzyl penicillin [14,15,19] with diarrhoea occurring in 0.4% of infants treated with a penicillin / gentamicin combination [15]. No cases of Stevens-Johnson syndrome, anaphylaxis or acute renal failure were reported in infants. An intramuscular injection abscess has been reported after procaine benzylpenicillin–gentamicin [14]. Seizures after high doses and rapid infusion have been reported in other patient populations.

Pharmacokinetics: Metsvaht et al in infants born gestational ages < 28 weeks and birth weights < 1,200 g reported the median peak and trough concentrations of were 147 µg/ and 7 µg/ml after

	<p>administration of 30 mg/kg and 59 µg/ml and 3 µg/ml after administration of 15 mg/kg. The half-life averaged 3.9 hours for the lower dose and 4.6 hours for the higher dose group, longer in VLBW neonates than in adults and term infants. Renal clearance correlated with creatinine. 34% of the dose was excreted in urine within 12 hours. A dose of 15 mg/kg 12 hourly was sufficient to achieve serum concentrations above the MIC (90) for group B streptococci for the entire dosing interval. [24] Muller et al in infants born gestational age <32 weeks on day 3 reported a half-life 3.9 hours with increased clearance with increasing birth weight. A dosing regimen of 30 mg/kg every 12 hours was reported as adequate for the treatment of common infections. [25] However, due to relatively poor CSF penetration of penicillin [20], higher doses are required in infants at risk of meningitis [see above]. Six hourly dosing is recommended for infants with postmenstrual age ≥ 45 weeks [26].</p>
<p>Practice points</p>	
<p>References</p>	<ol style="list-style-type: none"> 1. Seale AC, Bianchi-Jassir F, Russell NJ, Kohli-Lynch M, Tann CJ, Hall J, Madrid L, Blencowe H, Cousens S, Baker CJ, Bartlett L, Cutland C, Gravett MG, Heath PT, Ip M, Le Doare K, Madhi SA, Rubens CE, Saha SK, Schrag SJ, Sobanjo-Ter Meulen A, Vekemans J, Lawn JE. Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children. <i>Clin Infect Dis</i>. 2017;65:S200-S19. 2. Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, Bizzarro MJ, Goldberg RN, Frantz ID, 3rd, Hale EC, Shankaran S, Kennedy K, Carlo WA, Watterberg KL, Bell EF, Walsh MC, Schibler K, Laptook AR, Shane AL, Schrag SJ, Das A, Higgins RD, Eunice Kennedy Shriver National Institute of Child H, Human Development Neonatal Research N. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues.[Erratum appears in Pediatrics. 2011 Aug;128(2):390]. <i>Pediatrics</i>. 2011;127:817-26. 3. Capanna F, Emonet SP, Cherkaoui A, Irion O, Schrenzel J, Martinez de Tejada B. Antibiotic resistance patterns among group B Streptococcus isolates: implications for antibiotic prophylaxis for early-onset neonatal sepsis. <i>Swiss Med Wkly</i>. 2013;143:w13778. 4. WHO recommendations on newborn health: guidelines approved by the WHO Guidelines Review Committee. Geneva: World Health Organization; 2017 (WHO/MCA/17.07). Licence: CC BY-NC-SA 3.0 IGO. 5. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics--systematic review and meta-analysis. <i>Arch Dis Child</i>. 2013;98:146-54. 6. Snelling S, Hart CA, Cooke RW. Ceftazidime or gentamicin plus benzylpenicillin in neonates less than forty-eight hours old. <i>J Antimicrob Chemother</i>. 1983;12 Suppl A:353-6. 7. Metsvaht T, Ilmoja ML, Parm U, Maipuu L, Merila M, Lutsar I. Comparison of ampicillin plus gentamicin vs. penicillin plus gentamicin in empiric treatment of neonates at risk of early onset sepsis. <i>Acta Paediatr</i>. 2010;99:665-72. 8. Metsvaht T, Ilmoja ML, Parm U, Merila M, Maipuu L, Muursepp P, Julge K, Sepp E, Lutsar I. Ampicillin versus penicillin in the empiric therapy of extremely low-birthweight neonates at risk of early onset sepsis. <i>Pediatr Int</i>. 2011;53:873-80. 9. Clinical Excellence Commission, 2018, Newborn Antibiotic Guideline for early and late onset sepsis during birth episode of care. Revised June 2018. Sydney: Clinical Excellence Commission. 10. NICE Clinical guideline 2012. Neonatal infection (early onset): antibiotics for prevention and treatment. nice.org.uk/guidance/cg149. 11. Australasian Society for Infectious Diseases. Management of Perinatal Infections guideline. 2014. 12. The British National Formulary for Children. 2018. https://about.medicinescomplete.com/. 13. Molyneux EM, Dube Q, Banda FM, Chiume M, Singini I, Mallewa M, Schwalbe EC, Heyderman RS. The Treatment of Possible Severe Infection in Infants: An Open Randomized Safety Trial of Parenteral Benzylpenicillin and Gentamicin Versus Ceftriaxone in Infants <60 days of Age in Malawi. <i>Pediatr Infect Dis J</i>. 2017;36:e328-e33. 14. African Neonatal Sepsis Trial g, Tshetu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, Gisore P, Ayede AI, Falade AG, Adejuyigbe EA, Anyabolu CH, Wammanda RD, Ejembi CL, Ogala WN, Gram L, Cousens S. Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial. <i>Lancet</i>. 2015;385:1767-76.

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