

Benzylpenicillin (Penicillin G)

Newborn use only

2018

Alert	The Antimicrobial Stewardship Team has listed this drug under the following categories: Unrestricted.																																																															
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 vial. Contains Benzylpenicillin sodium powder for reconstitution. Contains 3 mmol/g of sodium.																																																															
Maximum Daily Dose	300 mg/kg/day Adjust meningitis doses to comply with maximum daily dose.																																																															
Dosage/Interval	<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; margin-bottom: 10px;"> <thead> <tr> <th colspan="2">Method</th> <th rowspan="2">Interval</th> </tr> <tr> <th>Corrected Gestational Age/Postmenstrual Age</th> <th>Postnatal Age</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; margin-bottom: 10px;"> <thead> <tr> <th colspan="2">Method</th> <th rowspan="2">Interval</th> </tr> <tr> <th>Corrected Gestational Age/Postmenstrual Age</th> <th>Postnatal Age</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 colspan="2">Method</th> <th rowspan="2">Interval</th> </tr> <tr> <th>Corrected Gestational Age/Postmenstrual Age</th> <th>Postnatal Age</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>	Method		Interval	Corrected Gestational Age/Postmenstrual Age	Postnatal Age	< 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	Method		Interval	Corrected Gestational Age/Postmenstrual Age	Postnatal Age	< 37 ⁺⁰ weeks	0–7 days	12 hourly	< 37 ⁺⁰ weeks	8+ days	8 hourly	≥ 37 ⁺⁰ weeks	0+ days	8 hourly	Method		Interval	Corrected Gestational Age/Postmenstrual Age	Postnatal Age	< 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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Route	IV IM (only if IV route not possible. IM route can be painful).																																																															

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Preparation/Dilution	<p>IV Add 3.6 mL of water for injection to the 600 mg vial to make a 150 mg/mL solution. FURTHER DILUTE Draw up 1 mL (150 mg of penicillin) of solution and add 4 mL of sodium chloride 0.9% to make a final volume of 5mL with a concentration of 30 mg/mL solution.</p> <p>IM Add 1.6 mL water for injection to the 600 mg vial to make a 300 mg/mL solution.</p>
Administration	<p>IV infusion over 15–30 minutes. IV infusion over 30–60 minutes recommended for larger doses (e.g., for meningitis). Separate from aminoglycoside administration by clearing the line with a flush as penicillins inactivate aminoglycosides. IM injection: Only if IV route is not possible.</p>
Monitoring	<p>Plasma concentrations are not usually required. They may be useful for infections with a high Minimum Inhibitory Concentration (MIC).</p>
Contraindications	<p>Hypersensitivity to penicillin.</p>
Precautions	<p>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.</p>
Drug Interactions	<p>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.</p>
Adverse Reactions	<p>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.</p>
Compatibility	<p>Fluids: Glucose 5%, Glucose 10% and sodium chloride 0.9%</p> <p>Y site: Amino acid solutions and fat emulsions.</p>
Incompatibility	<p>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.</p>
Stability	<p>Administer immediately. Discard unused portion of reconstituted solution.</p>
Storage	<p>Store at room temperature. Protect from light.</p>
Special Comments	<p>CSF penetration is poor even when meninges are inflamed, hence larger doses in meningitis. Prescribe in terms of mg rather than units. 60 mg = 100 000 Units of penicillin. 60 mg vial contains 0.18 mmol sodium.</p>
Evidence summary	<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</p>

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 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 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].

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