Benzylpenicillin
Newborn use only

2024

<table>
<tr><td>Alert</td><td>New South Wales Antimicrobial Stewardship category: Unrestricted.
60 mg = 100 000 Units of penicillin.
Separate from aminoglycoside administration by clearing the line with a flush as penicillins inactivate aminoglycosides.</td></tr>
<tr><td>Indication</td><td>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 Streptococcus (GBS).
Treatment of congenital syphilis.</td></tr>
<tr><td>Action</td><td>Bactericidal agent which inhibits cell wall synthesis.</td></tr>
<tr><td>Drug type</td><td>Antibacterial - Penicillin</td></tr>
<tr><td>Trade name</td><td>BenPen Powder for injection.</td></tr>
<tr><td>Presentation</td><td>600 mg, 1.2 g and 3 g vial. Each 600 mg dose contains 41.4 mg (1.8 mmol) sodium.</td></tr>
<tr><td>Dose</td><td>Sepsis: (excluding meningitis and congenital syphilis): 60 mg/kg/dose. Dosing interval as per table below
<table>
<tr><th>Corrected Gestational Age/Postmenstrual Age</th><th>Postnatal Age (days of life)</th><th>Interval</th></tr>
<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>
</table>
Meningitis: 90 mg/kg/dose. Dosing interval as per table below
<table>
<tr><th>Corrected Gestational Age/Postmenstrual Age</th><th>Postnatal Age (days of life)</th><th>Interval</th></tr>
<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>
</table>
Congenital syphilis: 30 mg/kg/dose. Dosing interval as per table below
<table>
<tr><th>Corrected Gestational Age/Postmenstrual Age</th><th>Postnatal Age (days of life)</th><th>Interval</th></tr>
<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>
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<tr><td>37^{+0}–44^{+6} weeks</td><td>8+ days</td><td>8 hourly</td></tr>
</table></td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia – Refer to evidence section.
ECMO – Beyond the scope of this formulary.
Renal impairment – No specific dose adjustment.
Hepatic impairment – No specific dose adjustment.</td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV
IM (only if IV route not available).</td></tr>
<tr><td>Preparation</td><td>IV
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.
FURTHER DILUTE</td></tr>
</table>

	From the 600 mg vial draw up 3 mL (450 mg of penicillin) of solution and add 12 mL of glucose 5% or sodium chloride 0.9% to make a final volume of 15 mL with a final concentration of 30 mg/mL. From the 1.2 g and 3 g vial draw up 2 mL (600 mg of penicillin) and add 18 mL of glucose 5% or sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 30 mg/mL. **Meningitis IV** Dilute the dose to a maximum concentration of 60 mg/mL. **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.
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	Hypersensitivity. 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.
Overdose	Encephalopathy can occur with large doses. There is no specific treatment for benzylpenicillin overdosage. Penicillin is removed by haemodialysis in adults. Patients usually recover as the penicillin blood level decreases.[29] For further information, contact the Poisons Information Centre on 131 126 (Australia).
Compatibility	Fluids:[27,29] Glucose 5%, sodium chloride 0.9% Y site:[27] Amino acid solutions; SMOF fat emulsion,[28] Amikacin, atracurium, atropine, azathioprine, aztreonam, calcium chloride, calcium gluconate, cefamandole, cefazolin, cefoperazone, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, clindamycin, cloxacillin, dexamethasone sodium phosphate, digoxin, dopamine, enalaprilat, epinephrine (adrenaline) hydrochloride, epoetin alfa, esmolol, fentanyl, fluconazole, folic acid, furosemide, gentamicin sulfate, glycopyrrolate, heparin sodium, hydrocortisone, indomethacin, imipenem-cilastatin, insulin (regular), ketamine, lidocaine, magnesium sulfate, meropenem, methylprednisolone sodium succinate, metoprolol, midazolam, morphine sulfate, multivitamin, naloxone, nitroglycerin, norephinephrine (noradrenaline) bitartrate, pantoprazole, penicillin G potassium, pentoxifylline, piperacillin, potassium chloride, propranolol, pyridoxine, SMOF lipid emulsion, sodium bicarbonate, sodium nitroprusside, theophylline, thiamine, ticarcillin, ticarcillin-clavulanate, tobramycin, tolazoline, urokinase, vasopressin, verapamil. Variable compatibility: Aminophylline, erythromycin, hydralazine, metaraminol, phenobarbitone (phenobarbital), phentolamine, prochlorperazine, promethazine, suxamethonium (succinylcholine).
Incompatibility	Y-site:[27] Amphotericin B, diazepam, diazoxide, dobutamine, doxycycline, ganciclovir, labetalol, morphine HCL, papaverine, pentamidine, pentobarbital, phenytoin, protamine, sulfamethoxazole/trimethoprim, thiopentone, tranexamic acid.
Stability	Administer immediately. Discard unused portion of reconstituted solution.
Storage	Store at room temperature. Protect from light.
Excipients	None

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	**Background** Group B streptococcus (GBS) continues to be a significant global cause of early[1,2] and late onset neonatal sepsis.[1] Isolates remain universally susceptible to benzylpenicillin.[2,3] Benzylpenicillin is usually used in combination with an aminoglycoside. WHO recommends penicillin/ampicillin and gentamicin as empiric treatment for neonatal sepsis.[4] Benzylpenicillin is a time dependent antibiotic. The effect of time dependent antibiotics relies on the length of time that the antibiotic is in contact with causative pathogen. This generally refers to fT>MIC; this reflects the percentage of time for which the free fraction of drug concentration remains above the MIC. For b-lactams (penicillins, cephalosporins, carbapenems) it has been proposed that dosing schedules should maintain plasma concentrations above MIC for at least 50% of the dosing interval, but the efficacy of b-lactams is enhanced with longer exposure times. Continuous infusions can potentially improve target attainment for fT>MIC, they may, however, be impractical in many settings. Decreased mortality has been associated with continuous infusion of b-lactam antibiotics in critically ill patients with severe sepsis.[30] **Efficacy** **Treatment of early onset sepsis:** A RCT in 55 infants <48 hours old with suspected sepsis compared penicillin [30 mg/kg/day in 2 doses] and gentamicin at 6 mg/kg/day in 2 doses] versus ceftazidime [100 mg/kg/day in 2 doses]. No treatment failure or infant death was reported in either group.[5] [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.[6] Subgroup analysis of this study showed in-hospital mortality for infants with gestational age <26 weeks was lower in the ampicillin group, but ampicillin treatment was associated with a higher colonization rate by Klebsiella pneumoniae, including ampicillin-resistant strains.[7] [LOE III- 2] For early onset neonatal sepsis, WHO and other major network guidelines recommend to use benzylpenicillin or ampicillin in combination with an aminoglycoside.[4,8-11] 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.[11] [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.[12,13] 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.[14] [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.[15] 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.[16] [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.[8-10] **Treatment of meningitis:** In developed country settings, current guidelines[8-10] do not recommend benzylpenicillin as empiric treatment of meningitis due to relatively poor CSF penetration of benzylpenicillin.[17] Where used, higher dosages of benzylpenicillin [60 mg/kg 8 hourly IV] have been given.[11] For infants in whom GBS has been isolated from CSF, high dose benzylpenicillin[8] or cefotaxime[8,9] 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.[17] Two RCTs reported use of benzathine penicillin 30 mg/kg IM as treatment for asymptomatic newborns at high risk of congenital syphilis. No treatment failures were reported.[18,19] [LOE II GOR D] **Guidelines:** ASID 2022 guidelines recommend benzylpenicillin 30 mg/kg 12 hourly IV in the 1st week of life and then 30 mg/kg IV 8 hourly from day 8 of life to complete a total of 10 days therapy or procaine penicillin 50 mg/kg IM daily for 10 days for infants with or at high risk of congenital syphilis.[20] **Therapeutic hypothermia:** PharmaCool study group[21,22] described the population pharmacokinetics of amoxicillin and benzylpenicillin during therapeutic hypothermia for hypoxic ischaemic encephalopathy. Both amoxicillin and benzylpenicillin had reduced clearance on day 2 of life during TH (0.26 L/h and 0.48 L/h, respectively), in comparison to normal Cl post TH (0.41 L/h and 0.75 L/h, respectively). ANMF consensus: There is currently insufficient evidence to implement the dosing recommendation of pharmacool study group. No specific dose/interval adjustment during therapeutic hypothermia can be provided by ANMF group. Any dose adjustment decision is to be made in consultation with paediatric ID specialist. **Safety** Diarrhoea has been reported in 0.4% of infants treated with a penicillin/gentamicin combination.[23] 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.[12] **Pharmacokinetics** Metsvaht et al[24] in infants born gestational ages < 28 weeks and birth weights <1,200 g reported the median peak and trough concentrations of were 147 µg/mL 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,[17] higher doses are required in infants at risk of meningitis. Six hourly dosing is recommended for infants with postmenstrual age ≥ 45 weeks.[26]
Practice points	In a clinical setting, there is generally no time to wait for the result from microbiologic samples when there is suspected sepsis. Antibiotic treatment can therefore be viewed as having two phases, namely an initial, empirical treatment phase followed by a targeted treatment phase once a causative pathogen is confirmed. Antibiotic dose optimization may focus on either efficacy or safety, respectively. **Empirical Treatment Phase:** In the 1 hours to days of treatment, the primary focus is to deliver effective treatment. During this earliest stage mortality is directly related to the effects of the life-threatening infection and managing toxicity is less central. Initial antibiotic doses should be targeting the "worst-case" minimal inhibitory concentrations, captured by the phrase "go hard and go home". During the empirical treatment phase, the benefits (e.g., high probability that causative pathogens are killed) outweigh the risks (e.g., development of renal toxicity) and therefore a certain trade-off in dosing regimen to achieve relatively high exposures in relation to non-pathogen specific MIC may be acceptable.[30] **Targeted Treatment Phase:** After an initial empirical treatment there are two possible outcomes. Treatment may be discontinued because the clinical picture of sepsis cannot be microbiologically confirmed and an alternative diagnosis emerges. On the other hand, the microbiological cause confirming the diagnosis of sepsis may be identified. In the latter case treatment will be continued and toxicity issues become more important.[30]
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Original 1.2	**8/08/2015**
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Current version

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