Amoxicillin (Amoxycillin)

Newborn Use Only

2017

<table>
<tr><td>Alert</td><td>The Antimicrobial Stewardship Team recommends this drug is listed under the following category: Unrestricted</td></tr>
<tr><td>Indication</td><td>Directed treatment of infections caused by susceptible gram positive (including Streptococcus species, Enterococcus faecalis and Listeria monocytogenes) and susceptible gram negative bacteria (some strains of Escherichia coli, non-beta-lactamase-producing Haemophilus influenzae, Neisseria meningitidis, non-penicillinase-producing strains of Proteus and Salmonellae).
Empiric treatment of suspected early onset sepsis including meningitis, with an aminoglycoside.</td></tr>
<tr><td>Action</td><td>Bactericidal – inhibits synthesis of the bacterial cell wall. Amoxicillin is hydrolysed by beta-lactamases and therefore not effective against penicillinase-producing bacteria.</td></tr>
<tr><td>Drug Type</td><td>Antibacterial – semi-synthetic, bactericidal aminopenicillin</td></tr>
<tr><td>Trade Name</td><td>Alphamox Suspension [Alphapharm], Amoxil Paediatric Drops [Aspen], Amoxil Parenteral [Aspen], Amoxil Syrup Forte Sugar Free [Aspen], Amoxil Syrup Sugar Free [Aspen], Amoxycillin Sandoz [Sandoz], APO-Amoxycillin [Apotex], Bgramin [Ascent Pharma], Chemmart Amoxycillin [Apotex], Cilamox Sugar Free Syrup [Aspen Pharma], Fisamox [Aspen], Ibiamox [Willow], Maxamox [Sandoz], Ranmoxy Granules [Ranbaxy], Terry White Chemists Amoxycillin [Apotex]</td></tr>
<tr><td>Presentation</td><td>IV: Amoxicillin sodium 500 mg and 1 g vials
PO: Syrup 125 mg/5 mL and 250 mg/5 mL; Paediatric drops 100 mg/mL</td></tr>
<tr><td>Dosage / Interval</td><td>IV
Treatment of standard infections: 50 mg/kg/dose.
Treatment of meningitis: 100 mg/kg/dose.
Dosing interval as per table below
<table>
<tr><th>Corrected Gestational Age/Postmenstrual Age</th><th>Postnatal Age</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>
</table>
PO
Treatment: 25–50 mg/kg/dose. Dose interval as follows:
<table>
<tr><th>Corrected Gestational Age/Postmenstrual Age</th><th>Postnatal Age</th><th>Interval</th></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>
</table>
Prophylaxis (e.g. UTI): 10–15 mg/kg/dose once a day</td></tr>
<tr><td>Maximum Daily Dose</td><td>300 mg/kg/day</td></tr>
<tr><td>Route</td><td>IV
IM (only if IV route not possible as intramuscular route is painful)
PO</td></tr>
<tr><td>Preparation/Dilution</td><td>IV:
Add 4.6 mL of water for injection to the 500 mg vial for reconstitution to make 100 mg/mL solution OR
Add 9.2 mL of water for injection to the 1 g vial for reconstitution to make 100 mg/mL solution.
Further dilution (for 100 mg/kg/dose infusion IV):
Draw up 5 mL (500 mg of amoxicillin) of solution and add 5 mL sodium chloride 0.9% to make a final volume of 10mL with a concentration of 50 mg/mL.
IM:
Add 2.6 mL of water for injection to the 500 mg vial for reconstitution to make 167 mg/mL solution
PO:
1. Syrup 125 mg/5 mL: Add 87 mL water, invert the bottle and shake well. Final reconstituted</td></tr>
</table>

	suspension volume is 100 mL. 2. Syrup 250 mg/5 mL: Add 87 mL water, invert the bottle and shake well. Final reconstituted suspension volume is 100 mL. 3. Paediatric drops 100 mg/mL: Add 18 mL water, invert the bottle and shake well. Final reconstituted suspension volume is 21 mL.
Administration	IV: **Infuse over 30 minutes into the proximal cannula site.** Separate from aminoglycosides by clearing the lines with a flush as penicillins inactivate them. **Doses of 100 mg/kg should be diluted to 50 mg/mL and infused over 30 minutes**. IM injection: Only if IV route is not possible. PO: The liquid preparation should be shaken well before measuring the dose. The dose may be mixed with the milk. After mixing, administer immediately.
Monitoring	Monitoring is not usually required. Follow infectious disease/microbiology advice in case of poor therapeutic response.
Contraindications	Hypersensitivity to penicillins (unlikely to be an issue in neonates).
Precautions	Hypersensitivity to cephalosporins (unlikely to be an issue in neonates). In renal impairment, the excretion of amoxicillin will be delayed. In infants with severe renal impairment, it may be necessary to reduce the total daily dose.
Drug Interactions	IV: Aminoglycosides, including gentamicin, should not be mixed with amoxicillin when both drugs are given parenterally as inactivation of the aminoglycoside occurs. Ensure line is adequately flushed between antibiotics. PO: No significant drug-drug interaction found for neonates on oral amoxicillin.
Adverse Reactions	Common: Diarrhoea, skin rash (erythematous maculopapular), phlebitis at the injection site, superinfection with resistant organisms during prolonged therapy Uncommon/rare: Neurotoxicity, electrolyte disturbances e.g. hypernatraemia due to the sodium content (3.3 mmol per gram in Amoxil IV and 2.6 mmol per gram in Fisamox IV), erythema multiforme, exfoliative skin lesions, *C. difficile* diarrhoea, pancytopenia, raised liver enzymes. Amoxicillin may result in a false positive for glucose in the urine due to excessive amounts of urinary amoxicillin.
Compatibility	Fluids: Sodium chloride 0.9%, sterile water for injection Y site: No information[9]
Incompatibility	Fluids: Glucose and glucose-containing solutions, fat emulsions Y site: Aminoglycosides, ciprofloxacin, imipenem-cilastatin, midazolam, potassium chloride, sodium bicarbonate[9]
Stability	IV: The reconstituted solution should be administered immediately; discard unused portion of the reconstituted solution. PO: The medication mixed with milk should be administered immediately.
Storage	IV: Store below 25°C. Protect from light. PO: Store unreconstituted powder for oral suspension at 20–25 degrees Celsius. Reconstituted suspension is stable for 14 days at room temperature or if refrigerated. Refrigeration is preferred.
Special Comments	Clearance is primarily by the renal route. Clearance increases with increasing gestational age and postmenstrual age. Serum half-life is longer in premature infants and infants younger than 7 days.
Evidence summary	**Effectiveness:** There are few studies of amoxicillin in the neonatal population to study effectiveness and the majority of the information is derived from studies of ampicillin. A study in two Estonian NICUs comparing ampicillin + gentamicin versus penicillin + gentamicin in the empiric therapy of neonates at risk of early-onset sepsis showed similar effectiveness in need to change antibiotics at 72 hours and/or 7-day all-cause mortality [1]. Subgroup analysis in ELBW neonates showed similar results, though NICU mortality was lower in the ampicillin group in < 26 weeks gestation neonates[2]. In an RCT of amoxicillin prophylaxis for prevention of catheter-related infections in newborn

	infants with central venous catheters, bacterial contamination of the catheter tip at removal was significantly reduced in the amoxicillin group. No significant difference was found in the incidence of invasive infection[3]. In a randomised, open-label, equivalence trial in Africa, oral amoxicillin was found to be equivalent to injectable procaine penicillin plus gentamicin in the treatment of neonates and young infants with fast breathing[4]. IV amoxicillin has similar properties to ampicillin and there is little to choose between the two when given by the IV route to treat susceptible organisms[5]. Amoxicillin achieves higher serum and CSF concentrations than ampicillin[6]. Oral amoxicillin has similar properties to ampicillin. Both the antibiotics are well absorbed when given by mouth, widely distributed in body tissues (including bronchial secretions) and rapidly excreted in the urine. Oral amoxicillin has better bioavailability but can be variable in young children[5]. Oral medication can nearly always be used to complete any sustained course of treatment.[13] **Pharmacokinetics:** Study of amoxicillin pharmacokinetics in preterm infants[7] has shown that a q12h schedule in the first week achieves serum concentrations well above the MIC for major micro-organisms in neonatal infections. Another study[8] in neonates older than 1 week showed that amoxicillin clearance was related to post-conceptional age and not to postnatal age with a rapid linear increase in clearance after 34 weeks post-conceptional age. In a study[10], early switching to the oral route in asymptomatic full-term newborns with early onset GBS disease maintained serum amoxicillin concentrations within the therapeutic range. The dose used in that study was 200–300 mg/kg/day in 4 divided doses. All the concentrations were in the therapeutic range with the lower dose. Another pharmacokinetic study in 6–13 days old neonates concluded that amoxicillin should be useful for oral treatment of neonatal infections caused by susceptible micro-organisms in infants who are not critically ill. The dose used was 50 mg/kg twice a day.[11] **Recommendation:** Amoxicillin can be used as a substitute for benzylpenicillin or ampicillin for suspected, early-onset, neonatal sepsis in combination with an aminoglycoside. When amoxicillin is used in combination with an aminoglycoside for the treatment of meningitis, it is recommended that the dose be doubled from 50 to 100 mg/kg/dose.[12] This is in keeping with similar recommendations for benzylpenicillin and ampicillin based on high minimum bactericidal concentration of group B streptococci and high inocula of the organisms in neonatal meningitis. (Level of evidence 5, Grade of recommendation D).
References	1. 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. Acta Paediatr 2010;99:665–72 2. Metsvaht T, Ilmoja ML, Parm U, Merila M, Maipuu L, Muursepp P et al. Ampicillin versus penicillin in the empiric therapy of extremely low-birthweight neonates at risk of early onset sepsis. Pediatr Int 2011;53:873–80 3. Harms K, Herting E, Kron M, Schiffmann H, Schulz-Ehlbeck H. Randomized, controlled trial of amoxicillin prophylaxis for prevention of catheter-related infections in newborn infants with central venous silicone elastomer catheters. J Pediatr 1995; 127: 615-9 4. African Neonatal Sepsis Trial (AFRINEST) group, Tshefu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, Gisore P et al. Oral amoxicillin compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with fast breathing when referral is not possible: a randomised, open-label, equivalence trial. Lancet 2015; 385: 1758-66 5. Neonatal Formulary: Drug use in pregnancy and the first year of life. 7th Ed. 2015: 76-7 6. Fanos V, Dall'Agnola A. Antibiotics in neonatal infections: A Review. Drugs 1999; 58: 405-27 7. Huisman-de Boer J, van den Anker JN, Vogel M, Goessens WHF, Schoemaker RC, de Groot R. Amoxicillin pharmacokinetics in preterm infants with gestational ages of less than 32 weeks. Antimicrob Agents Chemother 1995; 39: 431-4 8. Pullen J, Driessen M, Stolk LML, Degraeuwe PLJ, van Tiel FH, Neef C et al. Amoxicillin

	pharmacokinetics in (preterm) infants aged 10 to 52 days: Effect of postnatal age. Ther Drug Monit 2007; 29: 376-80 9. Australian Injectable Drugs Handbook, 6th Ed accessed on www.aidh.hcn.com.au on 26th July 2016. 10. Gras-Le Guen C, Boscher C, Godon N, Caillon J, Denis C, Nguyen JM et al. Therapeutic amoxicillin levels achieved with oral administration in term neonates. Eur J Clin Pharmacol 2007; 63: 657-62 11. Lonnerholm G, Bengtsson S, Ewald U. Oral pivampicillin and amoxycillin in newborn infants. Scand J Infect Dis 1982; 14: 127-30. 12. McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, Clark JE, Cooper CM, Curtis N, Goeman E, Hazelton B, Haeusler GM, Khatami A, Newcombe JP, Osowicki J, Palasanthiran P, Starr M, Lai T, Nourse C, Francis JR, Isaacs D, Bryant PA, ANZPID-ASAP group. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. Lancet Infect Dis 2016;16(8):e139-52.

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