aziTHROMYCIN

Newborn use only

2018

Alert	Azithromycin in the newborn period increases the risk of developing pyloric stenosis.[14-15]
Indication	1. Pertussis – post-exposure prophylaxis and treatment 2. Neonatal chlamydial conjunctivitis and pneumonia 3. Chlamydial and *Mycoplasma* pneumonia >3 months of age 4. Eradication of *Ureaplasma* in preterm infants 5. Prevention of BPD in preterm neonates – routine use is not recommended.
Action	Azithromycin inhibits protein synthesis by attaching to the 50S subunit of the bacterial ribosome in susceptible organisms. It exhibits bacteriostatic activity with higher potency than erythromycin against *Ureaplasma* isolates in vitro. Azithromycin inhibits neutrophil influx and chemoattractant/cytokine release in murine lung non-infectious, as well as pneumonia, injury models. It is preferentially concentrated in pulmonary epithelial lining fluid and alveolar macrophages.[14]
Drug Type	Macrolide antibiotic (subclass Azalide)
Trade Name	Azith, Azithromycin Alphapharm, Azithromycin DBL, Zithromax
Presentation	Oral: 200 mg/5 mL (15 mL) suspension, 500 mg tablet IV: 500 mg vial
Dosage/Interval	<u>Pertussis (post-exposure prophylaxis or treatment)</u> 10 mg/kg/dose daily orally or IV[2] for 5 days. <u>Treatment of neonatal chlamydial conjunctivitis and pneumonitis</u> 20 mg/kg/dose daily orally for 3 days. <u>Eradication of *Ureaplasma* in preterm infants</u> 20 mg/kg/dose daily IV for 3 days. <u>Pneumonia due to *Chlamydia* or *Mycoplasma pneumoniae* >3 months of age</u> Initial therapy or therapy for serious infection: 10 mg/kg/dose **IV** once a day on days 1 and 2, followed by oral therapy if needed. Step-down or Mild therapy: 10 mg/kg **ORALLY** on day 1, followed by 5 mg/kg once daily on days 2–5.
Route	Oral IV
Maximum Daily Dose	20 mg/kg
Preparation/Dilution	**Oral:** Add 9 mL of sterile water. Cap and shake well to produce 15 mL of suspension. Suspension expires 10 days after reconstitution. Write expiry date on bottle. **IV:** Add 4.8 mL of water for injection to the vial to make a concentration of 100 mg/mL solution. Shake until dissolved. Add 1 mL of reconstituted solution to 49 mL of sodium chloride 0.9% to make a concentration of 2 mg/mL and infuse over 1–3 hours. Maximum concentration for infusion is 2 mg/mL.
Administration	**Oral:** Shake well before use. May be given with or without feed. **IV:** Infuse over at least 1 hour.
Monitoring	During infusion – heart rate and blood pressure. IV site for signs of phlebitis. Liver function.
Contraindications	Hepatic dysfunction with prior azithromycin therapy. Concomitant therapy with QT interval prolonging drugs (e.g. cisapride)
Precautions	Hepatic dysfunction. IV solutions of a concentration greater than 2 mg/mL may cause local infusion-site reactions.
Drug Interactions	Drugs that can prolong QT interval. Digoxin – may result in digoxin toxicity.

Adverse Reactions	Common: Nausea, vomiting, abdominal pain and diarrhoea (all less than erythromycin). Rare: Hypertrophic pyloric stenosis, thrombophlebitis (after IV administration), ventricular dysrhythmias (after IV administration). In general, the risk of dysrhythmias is increased when these agents are administered in combination with other drugs that prolong the QT interval. Increased liver enzymes, hepatitis, hepatic necrosis, hypersensitivity reactions.
Compatibility	Fluids: Glucose 5%, glucose 5% in sodium chloride solutions, Hartmann's, sodium chloride 0.9%, sodium chloride 0.45% Y-site : Bivalirudin, ceftaroline fosamil, dexmedetomidine, tigecycline
Incompatibility	Fluids: No information Drugs: Amikacin, amiodarone, aztreonam, cefotaxime, ceftazidime, ceftriaxone, chlorpromazine, ciprofloxacin, clindamycin, fentanyl, furosemide (frusemide), gentamicin, imipenem-cilastatin, ketorolac, midazolam, morphine sulfate, mycophenolate mofetil, pentamidine, piperacillin-tazobactam (EDTA-free), potassium chloride, thiopental sodium, ticarcillin-clavulanate, tobramycin.
Stability	Oral suspension: After reconstitution, the suspension should be stored below 30 °C and any remaining suspension discarded after 10 days. Reconstituted IV solution: Stable for 24 hours at ≤30 °C.
Storage	Oral/IV store below 25 °C. Protect from light.
Special Comments	
Evidence summary	**Efficacy** <u>Pertussis – post-exposure prophylaxis and treatment</u> Systematic review of eradicating *B. pertussis* from the nasopharynx found short-term antibiotics (azithromycin for three to five days, or clarithromycin or erythromycin for seven days) were as effective as long-term (erythromycin for 10 to 14 days) (risk ratio (RR) 1.01; 95% CI 0.98 to 1.04), but had fewer side effects (RR 0.66; 95% CI 0.52 to 0.83). Effective treatment regimens included 3 days azithromycin (10 mg/kg as a single dose) (2 trials); and 5 days azithromycin (10 mg/kg on the first day and 5 mg/kg once daily on day two to five) (2 trials).[1] The Centers for Disease Control and Prevention recommend oral azithromycin as the preferred agent for post-exposure prophylaxis (PEP) and treatment in infants younger than 1 month of age.[2] Azithromycin has the advantage of once daily dosing and shorter duration of therapy. In infants 1 month of age and older, CDC recommends erythromycin, clarithromycin and azithromycin as preferred agents for the treatment of pertussis. For infants 2 months of age and older, an alternative to macrolides is trimethoprim-sulfamethoxazole. Recommended azithromycin dose for both treatment and PEP is the same for infants <6 months of age: 10 mg/kg/day once a day for 5 days (only limited safety data are available)[2] <u>Treatment of chlamydial conjunctivitis and pneumonia</u> *C. trachomatis* infection in neonates is most frequently recognised by conjunctivitis that develops 5–12 days after birth. *C. trachomatis* also can cause a subacute, afebrile pneumonia with onset at ages 1–3 months. There are limited data on the efficacy of azithromycin regimens in newborns. Hammerschlag 1998 reported oral azithromycin 20 mg/kg/day single dose resulted in 2 of 5 treatment failures and oral azithromycin 20 mg/kg/day single dose for 3 days resulted in 1 of 6 treatment failures.[3] However, azithromycin has been extensively trialled for eradication of *C. trachomatis* in populations including infants and children.[4-6] Use of azithromycin for prevention of bronchopulmonary dysplasia provides some safety data in premature infants (see below). Recommendation: The Centers for Disease Control and Prevention (CDC) recommend oral erythromycin 50 mg/kg per day given orally in four divided doses for 14 days for either chlamydial conjunctivitis or pneumonia. An alternative regimen is azithromycin 20 mg/kg/day once daily for 3 days. Topical antibiotic therapy alone is inadequate and is unnecessary when systemic treatment is administered.[7] <u>Pneumonia due to *Chlamydia trachomatis* or *Mycoplasma pneumoniae* in infants >3 months of age</u> A systematic review of antibiotics for community-acquired lower respiratory tract infections secondary to *Mycoplasma pneumoniae* in children found no difference in clinical response between

children randomised to a macrolide antibiotic and children randomised to a non-macrolide antibiotic for infants in whom a diagnosis of mycoplasma or chlamydia pneumonia was not made. In one controlled study of children with recurrent respiratory infections, whose acute LRTI was associated with *Mycoplasma*, *Chlamydia* or both, by polymerase chain reaction and/or paired sera, 100% of children treated with azithromycin had clinical resolution of their illness compared to 77% not treated with azithromycin at one month.[8]
Recommendation of the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: Parenteral: Intravenous azithromycin 10 mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible. Enteral: Azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5.[9]

Prevention of bronchopulmonary dysplasia in preterm infants
Nair et al conducted a systematic review of azithromycin and other macrolides on the incidence of bronchopulmonary dysplasia (BPD) in preterm infants. Macrolides when used prophylactically, did not show significant reduction in BPD (risk ratio, RR, 0.88, 95% CI, 0.75–1.03), death (RR 0.89, 95% CI 0.79–1.01) or in the composite outcome of BPD/death. Similarly, there was no significant reduction in BPD (RR 0.64, 95% CI 0.31–1.31) or the composite outcome of BPD/death (RR 0.41, 95% CI 0.05–3.13), when macrolides were used in *Ureaplasma*-positive infants. However, prophylactic azithromycin therapy (3 studies) was associated with significant reduction in BPD (RR 0.83, 95% CI 0.71–0.97; number needed to treat, 10) and of BPD or death (RR 0.86, 95% CI 0.77–0.97; NNT 10). Dose regimens were 10 mg/kg/day for 7 days (2 studies) and 10 mg/kg/day for 7 days followed by 5 mg/kg/day for further 7 days (one study).
Conclusion: Although prophylactic azithromycin therapy was associated with a reduction in BPD and BPD/death in preterm infants, there is limited information on pharmacokinetics and potential harmful effects; further studies should be done before routine use of azithromycin in the neonatal population.[11]

Eradication of *Ureaplasma* in preterm infants
A 3-day course of 20 mg/kg/day IV azithromycin commencing treatment within 72 hours of life in 24–28 weeks GA infants showed efficacy in eradicating *Ureaplasma spp.* from the preterm respiratory tract.[12] All post-treatment cultures were negative. Side effects reported in this study were related to prematurity. However, systematic review found no significant reduction in BPD (RR 0.64, 95% CI 0.31–1.31) or the composite outcome of BPD/death (RR 0.41, 95% CI 0.05–3.13), when macrolides were used in *Ureaplasma*-positive infants. Conclusion: The efficacy and safety of using macrolide antibiotics for eradication of *Ureaplasma* is unproven.[11]

Bioavailability
Bioavailability of oral azithromycin is 38%.[13]

Safety
Eberly et al[14] reviewed 2466 children who developed infantile hypertrophic pyloric stenosis. Azithromycin exposure in the first 14 days had an odds ratio (OR) of 8.26 and, at 15–42 days, an OR of 2.98. No association was identified between day 43 and day 90. A systematic review of 11 articles involving 473 neonates found no significant difference in the incidence of elevated liver enzymes between the azithromycin and placebo group and reported 4 cases of infantile hypertrophic pyloric stenosis (<1%).[15]

Pharmacokinetics
Preterm neonates have reduced azithromycin clearance and increased volume of distribution compared to older children. The estimated half-life is approximately 58 hours for a typical 1 kg neonate. Once administered, very little of azithromycin resides in the plasma and the vast majority of azithromycin accumulates intracellularly leading to a prolonged elimination $t_{1/2}$ and extended mean residence time (MRT). These characteristics favour administering higher dosage regimens of azithromycin. For effective *Ureaplasma* eradication, the plasma concentration of free unbound azithromycin must be maintained above the minimum inhibitory concentration that is required to

	inhibit 50% (MIC_{50}) of *Ureaplasma*. Multiple dose administration of 10 mg/kg/day for 3 days azithromycin is inadequate to maintain azithromycin plasma concentrations above the MIC_{50}. On the other hand, a dosage regimen of 20 mg/kg/day for 3 days would be sufficient to maintain azithromycin plasma concentration above the MIC_{50}.[16] Azithromycin (AZM) in fine granules was studied by Tajima T, et al 1997, for its pharmacokinetics and clinical efficacy in eight child patients with ages between 1 month and 8 years. AZM was administered to the patients once a day at a dose of 10 mg/kg for 3 days. The clinical efficacy of AZM in 8 patients with microbial infections (pneumonia in one, *Mycoplasma* pneumonia in two, acute tonsillitis in one, pertussis in one, *Campylobacter* enteritis in one, infectious enteritis in one, *Salmonella* enteritis in one) were evaluated as "excellent" in five cases, "good" in two and "not evaluable" in one. As for the microbial efficacy, isolated strains were eradicated in 2 out of 3 patients. No adverse reaction was found except for one case with abnormal laboratory change, a mildly increased ALT value. Plasma samples were collected from 3 cases. The elimination half-life of AZM was 45.8 hours. $AUC_{0-\infty}$was 12.6 microgram.h/mL. Urine sample was collected from one. AZM concentration in urine was 35.0 microgram/mL during a period between 48 and 72 hours after the start of treatment.[18]
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