

# Sulfamethoxazole and Trimethoprim

## Newborn Use Only

2017

<b>Alert</b>	Not be used in infants < 4 weeks of age. Dose is expressed as trimethoprim (TMP) component. The Antimicrobial Stewardship Team recommends this drug is listed under the following category: Neonates: Restricted; Infants > 4 weeks of age: Oral — unrestricted and IV — restricted.						
<b>Indication</b>	Prophylaxis of urinary tract infections (UTI). Treatment of mild–severe infections including UTI and acute otitis media. Prophylaxis in HIV-exposed infants						
<b>Action</b>	Sulfamethoxazole is a sulfonamide that prevents the formation of dihydrofolic acid, a bacterial compound necessary for survival. Trimethoprim is a synthetic antibiotic that interferes with the production of folic acid by dihydrofolate reductase.						
<b>Drug Type</b>	Sulfonamide with antifolate						
<b>Trade Name</b>	Oral: Bactrim Oral Suspension [Roche]; Septrin Sugar Free Suspension [Aspen] IV: DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP [Hospira]						
<b>Presentation</b>	Oral liquid: Trimethoprim 8 mg/mL and sulfamethoxazole 40 mg/mL, 100 mL IV ampoule: Trimethoprim 16 mg/mL and sulfamethoxazole 80 mg/mL 5mL ampoule						
<b>Dosage / Interval</b>	<b>Dosage recommendations are based on trimethoprim component.</b> <b>UTI prophylaxis</b> PO: 2 mg TMP/kg/dose daily or 5 mg TMP/kg/dose twice weekly. <b>Prophylaxis in HIV-exposed infants &lt; 6 months of age</b> To commence from 4–6 weeks of age at a dose of 20 mg trimethoprim once daily (not per kg basis) (equates to 2.5 mL oral liquid daily) <b>Treatment of mild–severe infections (e.g. UTI, acute otitis media)</b> Mild to moderate infections PO: 3–6 mg TMP/kg/dose 12 hourly (AAP Guidelines 2011). Severe infections IV: 2–3 mg TMP/kg/dose 6 hourly.						
<b>Maximum daily dose</b>							
<b>Route</b>	PO, IV						
<b>Preparation/Dilution</b>	PO: Oral liquid does not require preparation  IV: Draw up 2 mL (32 mg trimethoprim and 80 mg sulfamethoxazole) and add 48 mL of sodium chloride 0.9%, glucose 5% or glucose 10% to make a final volume of 50mL with a concentration of 0.64 mg/mL of TMP.  For severely fluid restricted neonates: Draw up 2 mL (32 mg trimethoprim and 80 mg sulfamethoxazole) and add 18 mL of glucose 5% to make a final volume of 20mL with a final concentration of 3.2 mg/mL of TMP and infuse ONLY VIA A CENTRAL LINE as it is an alkaline solution. Also, follow up with a flush of up to 20 mL.						
<b>Administration</b>	PO: Administer with feeds. Shake well before measuring dose. IV: Infuse over 60–90 minutes. Follow-up with a flush of up to 20 mL.						
<b>Monitoring</b>	Watch for skin reactions and blood dyscrasias. Monitor renal function and full blood count.						
<b>Contraindications</b>	Hypersensitivity to sulfonamides or trimethoprim. Infants < 4 weeks of age (manufacturer says < 8 weeks).						
<b>Precautions</b>	Use with caution in renal impairment. Dosage adjustment is required in renal impairment. Suggested adjustment(Product Info) is as follows (MIMS): <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th colspan="2">Renal Impairment Dose Adjustments</th> </tr> <tr> <th>CrCl (mL/min)</th> <th>Dosage</th> </tr> </thead> <tbody> <tr> <td>Above 25</td> <td>Standard regimen</td> </tr> </tbody> </table>	Renal Impairment Dose Adjustments		CrCl (mL/min)	Dosage	Above 25	Standard regimen
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	<table border="1" style="width: 100%;"> <tr> <td style="width: 30%;">15 to 25</td> <td>One-half the standard regimen</td> </tr> <tr> <td>Below 15</td> <td>Not recommended</td> </tr> </table> <p>Concomitant use of potassium sparing diuretics can lead to hyperkalaemia. In individuals with glucose-6-phosphate dehydrogenase deficiency, haemolysis may occur.</p>	15 to 25	One-half the standard regimen	Below 15	Not recommended
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Below 15	Not recommended				
<b>Drug Interactions</b>	Risk of prolonged QT interval with concurrent use of chloral hydrate, erythromycin and fluconazole.				
<b>Adverse Reactions</b>	Gastrointestinal upset (vomiting, diarrhoea). Severe dermatologic reactions, blood dyscrasias, hepatotoxicity. Prolonged use may result in fungal or bacterial superinfection. Prolonged QT interval, torsades de pointes, ventricular tachycardias have been reported in adults.				
<b>Compatibility</b>	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9%, sodium chloride 0.45%  Y site: Aciclovir, amino acid solutions, amphotericin B liposomal, lipid emulsions, metronidazole, milrinone, morphine, pancuronium, piperacillin-tazobactam, vecuronium, zidovudine.				
<b>Incompatibility</b>	Y site: Amikacin, aminophylline, amiodarone, amphotericin b lipid complex, ampicillin, atropine, calcium chloride, calcium gluconate, cefazolin, cefotaxime, ceftazidime, ceftriaxone, chloramphenicol, clindamycin, dexamethasone, diazepam, diazoxide, digoxin, dobutamine, dopamine, adrenaline (epinephrine), erythromycin, fentanyl, fluconazole, folic acid, furosemide, ganciclovir, gentamicin, heparin, hydralazine, hydrocortisone, indometacin, insulin, isoprenaline, ketamine, lactated ringer's, lidocaine (lignocaine), methylprednisolone, midazolam, multiple vitamins injection, noradrenaline (norepinephrine), benzylpenicillin, phenobarbital (phenobarbitone), phenytoin, piperacillin, potassium chloride, propranolol, pyridoxine, ranitidine, sodium bicarbonate, tobramycin, urokinase, vancomycin.				
<b>Stability</b>	IV: Start infusion immediately after diluting – infusion must be completed within 2 hours of preparation. Monitor for precipitation, particularly with concentrated infusions.				
<b>Storage</b>	Store IV and oral preparations below 30°C. Do not refrigerate. Protect from light.				
<b>Special Comments</b>					
<b>Evidence summary</b>	<p><b><u>Prophylaxis in vesicoureteric reflux</u></b> The proportion of infants with high grade vesicoureteric reflux (VUR) among all infants with febrile UTIs is small. There is no statistically significant benefit of prophylaxis in preventing recurrence of febrile UTI/pyelonephritis in infants without reflux.<sup>1</sup> There is benefit of prophylaxis in reducing the recurrence of infections in children with VUR but no change in renal scarring and concerns regarding multi-resistant strains among treated children.<sup>2,3</sup></p> <p><b><u>Treatment duration of infections</u></b> McMullan et al reviewed the evidence for minimum intravenous and total antibiotic duration in children younger than 18 years with bacterial infections, comparing shorter courses with traditionally longer durations. In many infections, especially when clinical improvement is rapid, emerging data suggest that traditional long durations of intravenous antibiotics might be unnecessary and that intravenous to oral switch can occur earlier. In most of the other infections, evidence for routine longer courses is sparse.<sup>4</sup> In a Cochrane review of childhood lower urinary tract infection, no difference in persistent bacteriuria or recurrence was noted between 2–4 days and 7–14 days of oral antibiotics. Results from a subsequent Cochrane review showed that a single-dose antibiotic was associated with more persistent bacteriuria than was 10 days of antibiotics, although there was no difference in symptom duration or recurrence. A large retrospective study of infants younger than 6 months found no difference in treatment</p>				

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	<p>failure between intravenous antibiotics for 3 days or less and 4 days or more.<sup>4-7</sup></p> <p><b>Prophylaxis in HIV-exposed infants</b></p> <p>All HIV-exposed infants born to mothers living with HIV must receive co-trimoxazole prophylaxis, commencing at 4–6 weeks of age (or at first encounter with the healthcare system) and continued until HIV infection can be excluded.<sup>8</sup></p>
<b>References</b>	<ol style="list-style-type: none"> <li>1. Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. <i>Pediatrics</i> 128(3), 595–610(2011).</li> <li>2. de Bessa J Jr, de Carvalho Mrad FC, Mendes EF, Bessa MC, Paschoalin VP, Tiraboschi RB, Sammour ZM, Gomes CM, Braga LH, Bastos Netto JM. Antibiotic prophylaxis for prevention of febrile urinary tract infections in children with vesicoureteral reflux: a meta-analysis of randomized, controlled trials comparing dilated to nondilated vesicoureteral reflux. <i>J Urol</i> 2015;193(5 Suppl):1772-7.</li> <li>3. Pérez-Gaxiola G. Antibiotic prophylaxis reduced symptomatic urinary tract infection in children with vesicoureteral reflux, but not scarring. <i>Arch Dis Child Educ Pract Ed</i> 2015;100:52.</li> <li>4. 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. <i>Lancet Infect Dis</i> [Internet]. 2016 [cited 2016 Aug];16(8):e139-52.</li> <li>5. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA. Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. <i>Cochrane Database Syst Rev</i> 2003;1: CD003966.</li> <li>6. Fitzgerald A, Mori R, Lakhanpaul M, Tullus K. Antibiotics for treating lower urinary tract infection in children. <i>Cochrane Database Syst Rev</i> 2012; 8: CD006857.</li> <li>7. Brady PW, Conway PH, Goudie A. Length of intravenous antibiotic therapy and treatment failure in infants with urinary tract infections. <i>Pediatrics</i> 2010; 126: 196–203.</li> <li>8. WHO. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. <a href="http://www.who.int/entity/hiv/pub/guidelines/ctxguidelines.pdf">http://www.who.int/entity/hiv/pub/guidelines/ctxguidelines.pdf</a>; 2006. (accessed August 15, 2016) Micromedex solutions. Accessed on 10 August 2016.</li> <li>9. Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America, et al: Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. <i>MMWR Recomm Rep</i> 2009; 58(RR11):1-166.</li> <li>10. Van der Veen EL, Rovers MM, Albers FW, et al: Effectiveness of trimethoprim/sulfamethoxazole for children with chronic active otitis media: a randomized, placebo-controlled trial. <i>Pediatrics</i> 2007; 119(5):897-904.</li> <li>11. DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP Product Information <a href="https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&amp;t=&amp;q=Sulfamethoxazole">https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&amp;t=&amp;q=Sulfamethoxazole</a>. Accessed 16/9/2016.</li> <li>12. Lieberthal AS, Carroll AE, Chonmaitree T, et al: The diagnosis and management of acute otitis media. <i>Pediatrics</i> 2013; 131(3):e964-e999.</li> <li>13. Markowitz N &amp; Saravolatz LD: Use of trimethoprim-sulfamethoxazole in a glucose-6-phosphate dehydrogenase-deficient population. <i>Rev Infect Dis</i> 1987; 9(suppl 2):S218-S225.</li> <li>14. Bell TAL, Foster JN, &amp; Townsend ML: Trimethoprim-sulfamethoxazole-induced hepatotoxicity in a pediatric patient. <i>Pharmacotherapy</i> 2010; 30(5):539.</li> <li>15. Oliver RM, Rickenbach MA, Thomas MR, et al: Intrahepatic cholestasis associated with co-trimoxazole. <i>Br J Clin Pract</i> 1987; 41:975-976.</li> <li>16. Paap CM &amp; Nahata MC: Trimethoprim/sulfamethoxazole dosing during renal dysfunction. <i>Ann Pharmacother</i> 1995; 29:1300.</li> </ol>

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