



Appropriate use of sulfonamide antibiotics

What are sulfonamides and how do they work?

Sulfonamides are a group of synthetic medicines that contain the sulfonamide chemical group. As well as antibiotics,* this group includes thiazide diuretics, furosemide, acetazolamide, sulfonyleureas and some COX-2 inhibitors.

The only antibiotic medicine containing a sulfonamide routinely available, and subsidised, in New Zealand is sulfamethoxazole with trimethoprim (co-trimoxazole). Sulfadiazine (unsubsidised, Section 29 medicine) is occasionally used in a hospital setting.

Sulfonamide antibiotics work by interfering with folic acid synthesis in susceptible organisms, due to their structural similarity to para-aminobenzoic acid (PABA) in bacterial cells. Folic acid is essential for nucleic acid synthesis. When used alone, sulfonamide antibiotics are bacteriostatic to susceptible organisms. However, sulfamethoxazole in combination with trimethoprim (co-trimoxazole), which acts at a different enzyme in the pathway of folic acid synthesis, is thought to be synergistic and may be bactericidal in certain cellular conditions.

Which infections should sulfonamide antibiotics be used for?

There are limited uses for sulfonamide antibiotics due to increasing bacterial resistance, potential for adverse effects and

the availability of more active antibiotics.¹ In most cases, they are used in primary care only when first-line recommended antibiotics have been ineffective or are contraindicated.

First-line indications for sulfonamide antibiotics

Co-trimoxazole is commonly used in general practice, but in most circumstances, it is indicated as a first-line antibiotic in hospital settings only, such as for the treatment of pneumocystis pneumonia and nocardiosis (rare bacterial infection affecting lungs, brain or skin) in immunocompromised people. Toxoplasmosis is usually treated with a combination of sulfadiazine and pyrimethamine (both unapproved Section 29 medicines), also in a specialist setting.

A first-line indication where co-trimoxazole may be considered in a primary care setting would be for the treatment of mild, lower urinary tract infection in a child. However, it is the trimethoprim component, rather than sulfamethoxazole, which is important. Trimethoprim is only available in tablets of 300 mg, therefore unsuitable for use in children. As co-trimoxazole is available in a liquid formulation, and contains trimethoprim, this is an appropriate choice.

 For further information see: "Managing urinary tract infections in children", BPJ 44 (May, 2012).

Second-line indications for sulfonamide antibiotics

Co-trimoxazole is not recommended first-line for the majority of patients in primary care with infections. However, it can be considered when first-line choices have been ineffective,

* By definition sulfonamides are antimicrobials rather than antibiotics, i.e. an antibiotic is a substance produced by bacteria or fungi which have antimicrobial activity, whereas sulfonamides are synthetic.

Co-trimoxazole for MRSA

The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing in New Zealand, and at least half of the cases are now thought to be community acquired.

There is evidence that co-trimoxazole is effective against MRSA, although further clinical trials are needed.²

Patients with a non-healing wound or an infected surgical wound that is not responding to first-line antibiotics should have a wound swab taken to check for the presence of MRSA and to guide antibiotic choice. Depending on susceptibility, appropriate treatments in the community include co-trimoxazole, clindamycin (requires specialist endorsement) and tetracyclines.

are contraindicated, or antibiotic sensitivities indicate that co-trimoxazole is the appropriate choice. Antibiotics are not always indicated in the first instance for some of these infections, e.g. otitis media, sinusitis, salmonellosis, and other second-line antibiotics may be preferable to co-trimoxazole (Table 1).

N.B. Second-line antibiotics usually have less predictable susceptibility against the likely pathogens causing a clinical syndrome, e.g. *Streptococcus pneumoniae* susceptibility to co-trimoxazole is unpredictable; in 2011 resistance was 29% across New Zealand.⁴

Prescribing co-trimoxazole

Co-trimoxazole (trimethoprim and sulfamethoxazole in fixed ratio 1:5) is available as:

- Tablets – 80/400 mg (trimethoprim 80 mg + sulfamethoxazole 400 mg)
- Oral liquid – 40/200 mg/5 mL (trimethoprim 40 mg + sulfamethoxazole 200 mg in 5 mL)
- Injection (not subsidised) – 80/400 mg/5 mL (trimethoprim 80 mg + sulfamethoxazole 400 mg in 5 mL)

Table 1: Second-line indications for the use of co-trimoxazole

Infection	First-line antibiotic	Other second-line antibiotics	Notes for using co-trimoxazole
Acute exacerbations of chronic bronchitis	Amoxicillin	Doxycycline	Only if evidence of sensitivity to co-trimoxazole
Pneumonia in adults	Amoxicillin	Erythromycin, roxithromycin, doxycycline	Can be used as monotherapy if a history of penicillin allergy
Otitis media in children	Amoxicillin	Cefaclor, erythromycin	Only if antibiotics are required
Sinusitis	Amoxicillin	Doxycycline, cefaclor	Only if bacterial infection suspected
Cellulitis	Flucloxacillin	Erythromycin, roxithromycin, cefaclor	If a history of penicillin allergy
Diabetic foot complications	Amoxicillin + clavulanic acid	Cefaclor	Use with metronidazole to cover polymicrobial infection
Salmonellosis	Ciprofloxacin	-	Antibiotic treatment usually unnecessary, treat only if severe symptoms
Acute pyelonephritis	Ciprofloxacin	Amoxicillin + clavulanic acid	Refer to hospital if moderate to severe symptoms

For treatment of an infection the following doses are suitable:¹

- Child aged six weeks – five months – 20/100 mg (2.5 mL), twice daily
- Child aged six months – five years – 40/200 mg (5 mL), twice daily
- Child aged six – 12 years – 80/400 mg (10 mL or one tablet), twice daily
- Child aged over 12 years and adults and –160/800 mg (two tablets), twice daily

Alternatively, the co-trimoxazole dose for children can be calculated by body weight:⁵

- Child aged 6 weeks – 12 years – 0.5 mL/kg oral liquid, twice daily

Co-trimoxazole should be avoided in infants aged under six weeks, due to the risk of hyperbilirubinaemia.

Co-trimoxazole is contraindicated in people with a previous hypersensitivity reaction or severe hepatic damage. Severe renal impairment, bone marrow depression and agranulocytosis are also contraindications to use of co-trimoxazole, unless these can be closely monitored for and the clinical need outweighs the risk.

If co-trimoxazole is being taken long-term, a full blood count is recommended monthly, especially in patients who are poorly nourished or who may be folate deficient.⁶

Adverse effects of co-trimoxazole

Adverse effects with sulfonamide antibiotics are relatively common, occurring in approximately 3% of people taking a course of treatment.⁷ Nausea, vomiting, anorexia, diarrhoea and hyperkalaemia are the most commonly reported adverse effects, but co-trimoxazole is also rarely associated with serious hypersensitivity reactions and blood dyscrasias (bone marrow depression and agranulocytosis) especially in elderly people.¹

Hypersensitivity reactions

It is estimated that 0.09% of people experience a hypersensitivity reaction after taking a sulfonamide antibiotic, although the frequency is much higher among people with HIV and AIDS.⁸ Reactions include; anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness-like syndrome, lupus-like syndrome, multi-organ hypersensitivity syndrome, pneumonitis, hepatitis, interstitial nephritis, systemic vasculitis and pancytopenia.⁹

Silver sulfadiazine for burns: no longer recommended

In the past, topical silver sulfadiazine 1% cream was a common treatment for superficial and mid-dermal burns treated in primary care. It is still an effective treatment, however, newer occlusive dressings are associated with faster healing, decreased pain, fewer dressing changes and improved patient satisfaction.³

Double-check and prescribe clearly: is it mg of trimethoprim, or mg of co-trimoxazole?

Dosing recommendations of co-trimoxazole vary, particularly in paediatric references, with some using milligrams of the trimethoprim component alone and other using milligrams of both components combined. Administration errors can easily occur, and most often result in significant under-dosing of co-trimoxazole.

Patients with a hypersensitivity reaction may present with fever, painful macropapular rash, lesions in mucous membranes, cough, sore throat or difficulty breathing. A "hypersensitivity" syndrome characterised by hypotension, fever, rash and pulmonary infiltrates has also been associated with sulfonamides.⁸ Hypersensitivity symptoms usually develop within one to three weeks after starting treatment, and resolve within one to two weeks after ceasing treatment.^{8, 10}

Anaphylaxis typically occurs within thirty minutes of the first dose, but is more common with parenteral administration.⁸ Urticaria or isolated angioedema can occur within minutes to days after the first dose.⁸

Hypersensitivity reactions to sulfonamide antibiotics are not completely understood but are thought to be related to the drugs' sulphur moiety (the sulphur part of the drug molecule) and the presence of an arylamine group.⁸ There is no well-validated diagnostic test for sulfonamide sensitivity.

If a hypersensitivity reaction occurs, sulfonamide antibiotics should be avoided, unless the benefit outweighs the risk. A history of Stevens-Johnson syndrome, toxic epidermal necrolysis or anaphylaxis would be a contraindication to using a sulfonamide antibiotic.⁸

Risk of cross-reactivity with other sulfonamides is low

Other sulfonamide medicines, such as thiazide diuretics, do not contain the arylamine group and are less likely to cause severe hypersensitivity reactions.⁸ Cross-reactivity between sulfonamide antibiotics and other sulfonamide medicines is also unlikely.⁷

Despite this low risk, many practitioners take a cautious approach, and avoid prescribing all sulphur-containing medicines in a patient who has had a reaction after taking a sulfonamide antibiotic. There are a limited number of case reports which support this advice. However, a large cohort study found that allergy to a sulfonamide antibiotic was a risk factor for allergy to medicines in general, rather than cross-reactivity to other sulfonamides. The authors concluded that patients with a history of allergic reaction after taking sulfonamides (or penicillins) should be considered at increased risk for allergy to any medicine.¹¹

Practical advice would be to avoid prescribing other sulfonamide medicines (and sulphur-containing products) in patients with serious allergic reactions to sulfonamide antibiotics. Sulfonamide medicines could be prescribed in patients with only mild reactions if there was no other alternative, and the patient was monitored for signs of an adverse reaction.⁷

Older people are more at risk of adverse effects

Older people are generally more susceptible to adverse reactions when taking any medicine, and these effects are more likely to have serious consequences. This is compounded by multiple medicine use and the presence of impaired renal or hepatic function.

Although a rare adverse effect, there appears to be an increased risk of thrombocytopenia (with or without purpura) in older people who are prescribed co-trimoxazole and who are currently taking a diuretic such as a thiazide.⁶

Avoid co-trimoxazole in early and late pregnancy

Co-trimoxazole is a folate antagonist. Although its inhibitory effect is more selective for bacteria, co-trimoxazole should be avoided in women who are in the first trimester of pregnancy (as folate is essential during this period). Co-trimoxazole should also be avoided in women after 32 weeks gestation, as it is associated with an increased risk of neonatal haemolysis and methaemoglobinaemia.¹

Co-trimoxazole may be used in women who are breast feeding, but only if the infant is aged one month or older.¹

Medicine interactions with co-trimoxazole

Several clinically important medicine interactions can occur with co-trimoxazole (Table 2), which are more significant in elderly people and those taking multiple medicines.

References

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Table 2: Known drug interactions involving co-trimoxazole^{1, 12}

Drug	Mechanism of interaction	Complication	Management
Warfarin	CYP450 2C9 inhibition	Increased INR and haemorrhage	Monitor INR a few days after starting co-trimoxazole, and again after stopping
Sulfonylureas e.g. gliclazide, glipizide	CYP450 2C9 inhibition, CYP450 2C8 inhibition, and a direct effect on pancreatic cell release of insulin	Hypoglycaemia, which will take longer to resolve in renally impaired people	Consider reducing dose of gliclazide or glipizide when starting co-trimoxazole if creatinine clearance is less than 30 mL/min; increase blood glucose monitoring
Methotrexate	Organic anion transporter inhibition in the renal tubule, anti-folate effect	Methotrexate toxicity (cytopenia, hepatotoxicity, mucositis)	Monitor full blood count; may need to reduce dose of methotrexate (with specialist advice)
ACE inhibitors ARBs Spironolactone	Trimethoprim-induced antidiuretic effect due to chemical structure similarities	Hyperkalaemia	Monitor potassium levels a few days after starting co-trimoxazole if person is elderly, or has impaired renal function; review any potassium supplementation
Phenytoin	CYP450 2C9 and 2C8 inhibition (also metabolized by 2C19)	Phenytoin toxicity	Monitor for clinical signs of phenytoin toxicity; fever, rash, bradycardia, gingival hyperplasia, neurological effects, and monitor FBC, LFT, electrolytes
Clozapine	Additive effect of bone marrow suppression	Blood dyscrasias and potentially fatal agranulocytosis	Increased frequency of monitoring white cell count



For further information about drug interactions, see Stockley's alerts, accessed from the New Zealand Formulary: www.nzf.org.nz

