Considerations when prescribing trimethoprim–sulfamethoxazole

Joanne M.-W. Ho MD, David N. Juurlink MD PhD

Introduced in 1968, trimethoprim–sulfamethoxazole remains a popular antibiotic because of its low cost, effectiveness and familiarity among clinicians. It is the most frequently prescribed antibiotic for urinary tract infections in Canada.[1] Other indications include treatment of infections caused by *Pneumocystis jiroveci, Toxoplasma gondii, Stenotrophomonas maltophilia* and community-associated methicillin-resistant *Staphylococcus aureus*. In addition, among patients with depressed CD4 counts from infection with HIV, the use of low-dose trimethoprim–sulfamethoxazole for prophylaxis against *P. jiroveci* and *T. gondii* is associated with decreased mortality caused by opportunistic infections.[2] With up to 4000 prescriptions for trimethoprim–sulfamethoxazole dispensed each week in Ontario,[3] this drug is used by hundreds of thousands of Canadians each year.

More than 40 years of widespread use has provided ample opportunity to identify the many adverse events associated with trimethoprim–sulfamethoxazole. Although this drug is well tolerated by many patients, it is associated with several potentially serious adverse reactions. Most of these associations are supported only by case reports and case series, but some have been the subject of volunteer studies and observational studies. Many of these adverse effects are rare, however others are predictable and several can be life-threatening. Here we provide an overview of the various toxicities associated with the use of trimethoprim–sulfamethoxazole and offer a simple mnemonic — "NOT RISKY?" — to help clinicians recall the various toxicities associated with this drug (Table 1).

Literature review

We performed a search using MEDLINE (1950 to August 2011) and Embase (1980 to 2011), along with a manual review of relevant bibliographies. We used the permuted index search tool in Ovid to search MEDLINE with the term "trimethoprim–sulfamethoxazole combination" and the subheadings "adverse effects" and "toxicity." Using the keyword search, we searched for the terms "cotrimazole" and "trimethoprim–sulfamethoxazole combination," and then combined each term with each of the following terms: "cytochrome P450," "hyperkalemia," "hypoglycemia," "hematologic," "anemia," "neutropenia," "thrombocytopenia," "hemolysis," "hypersensitivity," "drug interaction," "renal" and "methemoglobinemia." We used a similar search strategy for the Embase database.

We included all types of reports (case reports, volunteer studies, observational studies and randomized trials), and we excluded articles that were not available in English, were conducted in animals or did not include information about the safety of trimethoprim–sulfamethoxazole.

We identified 925 publications that described adverse events involving trimethoprim–sulfamethoxazole. After we assessed the citations for eligibility, 88 articles were reviewed and 70 were included in this review. J.H. reviewed all citations for eligibility and full-text articles for quality. D.J. reviewed selected articles for quality. Conflicts were resolved by consensus.

N: Neurologic effects

Trimethoprim–sulfamethoxazole readily crosses the blood–brain barrier[40] and is associated with various adverse neurologic events, all of which have been described only in case reports. Numerous instances of aseptic meningitis (involving high doses of trimethoprim alone or trimethoprim–sulfamethoxazole) have been reported, many of them involving patients with pre-existing autoim-

Key points

- Trimethoprim–sulfamethoxazole is an effective antimicrobial, but it has numerous adverse effects, some of which can be severe.
- Important drug–drug interactions include the development of hyperkalemia with renin-angiotensin system blocking agents or drugs that inhibit kaliuresis, and hypoglycemia with the concomitant use of some hypoglycemic agents.
- Hyperkalemia in conjunction with use of trimethoprim–sulfamethoxazole can also occur in patients with impaired renal function, diabetes, older age or AIDS.
- Other toxicities include neurologic, renal and reproductive abnormalities, decreased oxygen-carrying capacity and other hematologic effects, and drug hypersensitivity syndromes.

Competing interests: Joanne Ho is a fellow of the Canadian Institutes of Health Research Drug Safety and Effectiveness Cross-Disciplinary Training Program. None declared by David Juurlink.

This article has been peer reviewed.

Correspondence to:
Dr. Joanne M.-W. Ho,
jmho2001@gmail.com

***CMAJ* 2011. DOI:10.1503/cmaj.111152**

Table 1: Summary of the adverse effects associated with the use of trimethoprim–sulfamethoxazole

	Adverse effect	Manifestation	Postulated risk factor	Frequency
N	Neurologic effects	Aseptic meningitis[4]	Autoimmune disease and HIV[4]	Uncommon
		Tremor[5]		Rare
		Delirium[5,6]	Older age, previous neurologic injury, infection, metabolic disturbances[5,6]	Relatively uncommon
		Gait disturbances[5,6]		Rare
O	Decreased oxygen-carrying capacity and other hematologic abnormalities	Methemoglobinemia[7,8]	• Neonates less than 6 weeks of age • Nicotinamide adenine dinucleotide–dependent methemoglobin reductase (also known as cytochrome-b_5 reductase) deficiency	Rare
		Blood dyscrasia[9,10]	• Malnutrition, specifically folic acid deficiency • Glucose-6-phosphate dehydrogenase deficiency	Uncommon
T	Toxic epidermal necrolysis and other hypersensitivity reactions	Drug hypersensitivity (fever, rash and internal organ involvement, such as blood dyscrasia, hepatitis and acute interstitial nephritis)[11–16]	Previous or family history of drug hypersensitivity syndrome	Uncommon
		Simply exanthema or fixed drug eruption[17]		Common
R	Reproductive toxicity	Structural malformations (neural tube, cardiovascular and possible oral cleft and urinary system)[18]	• Low levels of folic acid[19] • Exposure during the first trimester[20]	Uncommon
		Small-for-gestational-age[21]	Exposure during the second and third trimesters[21]	Uncommon
		Hyperbilirubinemia[20]	Exposure after 32 weeks' gestation[20]	Rare
I	Interactions with other drugs	• Inhibition of the cytochrome P450 system (2C8 and 2C9)[22] • Renal drug transporter inhibition (organic cation transporter and organic anion transporter)[23,24]	Polypharmacy	Common
S	Sugar	Hypoglycemia[25–30]	• Renal insufficiency[25] • High-dose trimethoprim–sulfamethoxazole[25] • Concomitant use of sulphonylureas or meglitinides[26–30]	Common as a drug–drug interaction; rare when trimethoprim–sulfamethoxazole is used in isolation
K	Hyperkalemia and other kidney effects	Hyperkalemia[31–37]	• Renal insufficiency[34,35] • High-dose trimethoprim–sulfamethoxazole[32,35] • Older age[34] • Diabetes[34] • AIDS[39] • Concomitant use of ACE inhibitors, angiotensin receptor blockers, spironolactone or NSAIDs[36,37]	Common
		Acute interstitial nephritis[15]		Uncommon
		Obstructive tubulopathy[38]		Uncommon
		Hyponatremia[31,35]		Uncommon
Y?	Why not consider an alternate antimicrobial?			

Note: ACE = angiotensin-converting enzyme, NSAID = nonsteroidal anti-inflammatory drug.

mune disease or HIV infection.[4] The mechanism of toxicity is not well defined, but an immunologic process is suggested.[4] Clinically, drug-induced meningitis is indistinguishable from other causes of aseptic meningitis, and the diagnosis is suggested by negative results of microbiologic testing, temporal association with drug initiation, prompt improvement following discontinuation of the offending drug and the absence of another identifiable cause.

Other rare adverse neurologic effects include delirium and milder effects such as tremor,[5] which typically occurs in the first week of therapy, and gait disturbances.[5,6] In general, neurologic symptoms occur within days of continuous treatment and resolve following discontinuation of trimethoprim–sulfamethoxazole.

O: Decreased oxygen-carrying capacity and other hematologic abnormalities

Several case reports describe methemoglobinemia in patients taking trimethoprim–sulfamethoxazole.[7,8] Although this adverse effect is rare, the sulfamethoxazole component can induce methemoglobinemia, which occurs when more than 1% of heme iron exists in the ferric (Fe^{3+}) redox state, rather than the usual ferrous (Fe^{2+}) state. Methemoglobin cannot bind oxygen, resulting in functional anemia and bluish-brown discoloration of the skin.

Several uncommon but potentially serious blood dyscrasias have been reported following the use of trimethoprim–sulfamethoxazole. The incidence of severe hematologic toxicity is unknown, but estimates range up to 1.7–5.5/100 000 prescriptions.[9,10] Several mechanisms have been implicated and described in case reports (Table 2). Generation of antibodies to the glycoprotein IIb/IIIa complex on platelets can cause immune thrombocytopenia, which is typically observed within the first week of treatment and is generally reversible on discontinuation of the drug.[47–49]

Although uncommon at therapeutic doses, the inhibition of folate metabolism by trimethoprim can cause dose-related leukopenia and megaloblastosis, both of which are responsive to folinic acid.[41,42] Periodic monitoring of the complete blood count may be advisable in patients receiving a high dose of trimethoprim–sulfamethoxazole for extended periods.

Finally, oxidative hemolysis has rarely been reported in patients with glucose-6-phosphate dehydrogenase deficiency.[44–46] Although a few small observational studies have shown that patients with this deficiency often tolerate the drug without difficulty, clinicians should be aware of this potential risk.[51–53]

T: Toxic epidermal necrolysis and other hypersensitivity reactions

Immune-mediated idiosyncratic reactions are often associated with a reactive metabolite, lead-

Table 2: Hematologic abnormalities associated with the use of trimethoprim–sulfamethoxazole

Hematologic abnormality	Mechanism	Clinical manifestation	Risk factor
Bone marrow suppression	Folate deficiency[41,42]	Megaloblastic anemia, thrombocytopenia	Poor nutritional status, concomitant anti-folate drugs (e.g., methotrexate)[43]
	Drug hypersensitivity syndrome	Any hematologic abnormality in conjunction with fever and rash, most commonly lymphopenia or lymphocytosis	Family history of drug hypersensitivity
Oxidative hemolysis	Oxidative stress[44–46]	Hemolytic anemia	Glucose-6-phosphate dehydrogenase deficiency[44–46]
Drug-induced thrombocytopenia	Antibody-mediated destruction of platelets with specificity for the glycoprotein IIb/IIIa complex[47–49]	Thrombocytopenia	
Methemoglobinemia	Increase in methemoglobin (iron moiety in the hemoglobin tetramer is in the ferric state [Fe^{3+}] instead of the usual ferrous state [Fe^{2+}])[7,8]	Cyanosis, "chocolate-coloured" blood, and falsely low oxygen saturation on pulse oximetry but a normal oxygen saturation on arterial blood gas measurement ("saturation gap")	Neonates less than 6 weeks of age,[50] nicotinamide adenine dinucleotide–dependent methemoglobin reductase (cytochrome-b_5 reductase) deficiency

ing to drug-specific antibodies or T-lymphocyte activation. Simple exanthems and fixed drug eruptions are some of the most common adverse effects of trimethoprim–sulfamethoxazole, occurring in about 3% of hospital inpatients taking the drug.[54] Less common is a classic drug hypersensitivity syndrome manifesting with a triad of fever, exanthem and varying degrees of internal organ involvement. Typical manifestations vary in presentation and severity. They include hematologic abnormalities (most commonly lymphopenia or lymphocytosis, but occasionally eosinophilia), cholestatic or hepatocellular hepatitis (which may progress to fulminant hepatic failure), renal dysfunction (including acute interstitial nephritis),[11–15] Stevens–Johnson syndrome and potentially life-threatening toxic epidermal necrolysis.[16] If there has been no previous exposure to trimethoprim–sulfamethoxazole, these reactions typically begin after at least four or five days of therapy but may occur after several weeks of prolonged therapy. Importantly, the presence of fever can mislead clinicians by suggesting an unresolved infection, thereby delaying discontinuation of trimethoprim–sulfamethoxazole.

R: Reproductive toxicity

Folic acid is important for normal development of the fetus and placenta.[19] Although the inhibitory effect of trimethoprim on dihydrofolate reductase is more selective for the bacterial isozyme than for the human isozyme, the rapid rate of cell division during pregnancy potentiates the drug's anti-folate effect in humans. A host of adverse effects have been well described with use of trimethoprim–sulfamethoxazole during pregnancy and the neonatal period.

Case–control studies have reported an association between exposure to trimethoprim–sulfamethoxazole during the first trimester and an increased risk of structural malformations. These include defects of the neural tube, cardiovascular system and possibly oral cleft and urinary system.[18,19,55] The risk of major malformations, however, is reduced with supplementation with folic acid.[56,57] In patients with first-trimester exposure to trimethoprim–sulfamethoxazole, detailed ultrasonography should be performed at 18–20 weeks' gestation.[20]

A recent case–control study reported a 60% increased risk of small-for-gestational-age among the offspring of women exposed to trimethoprim–sulfamethoxazole during the second and third trimesters, compared with those exposed to other urinary antimicrobials.[21] The use of sulfamethoxazole has classically been discouraged for pregnant women at 32 weeks' gestation or later because of the risk of hyperbilirubinemia resulting from the drug's displacement of bilirubin from albumin. Although there are no case reports describing this toxicity in the literature, the use of an alternative antibiotic should be considered in most situations.

Although the overall risk of methemoglobinemia is low with trimethoprim–sulfamethoxazole, it may be increased in neonates younger than six weeks because of lower levels of nicotinamide adenine dinucleotide–dependent methemoglobin reductase activity.[50] If there is a strong clinical

Table 3: Potential and proven drug interactions involving trimethoprim–sulfamethoxazole

Drug	Mechanism of interaction	Complication
S-warfarin	CYP450 2C9 inhibition[22]	Increased international normalized ratio and hemorrhage[60–62]
Oral hypoglycemic drugs: Sulfonylureas (e.g., glyburide, gliclazide, glimepiride, glipizide) Meglitinides (e.g., repaglinide)	CYP450 2C9 inhibition, CYP450 2C8 inhibition[22]	Hypoglycemia[25–30]
Methotrexate	Organic anion transporter inhibition in the renal tubule,[23,24] anti-folate effect	Methotrexate toxicity (cytopenia, hepatotoxicity, mucositis)[43]
Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, celecoxib, piroxicam)*	CYP450 2C9 inhibition Trimethoprim-induced antikaliuretic effect[31]	Hypertension, hyperkalemia
Angiotensin receptor blocking agents and angiotensin-converting enzyme inhibitors Spironolactone	Trimethoprim-induced antikaliuretic effect	Hyperkalemia[36,37]
Fluvastatin*	CYP450 2C9 inhibition	Myalgia, myositis, rhabdomyolysis
Phenytoin (also metabolized by 2C19)	CYP450 2C9 and 2C8 inhibition	Phenytoin toxicity[17,63]

*Potential interaction.

indication for trimethoprim–sulfamethoxazole therapy in a newborn, it is recommended to start the drug after four to six weeks of age.[58] Although trimethoprim–sulfamethoxazole is detected in breast milk, exposure through breast milk appears to be safe in healthy breastfed infants.[59]

I: Interactions with other drugs

Drug interactions occur when one drug alters the clinical response to another. Several important drug interactions can occur with trimethoprim–sulfamethoxazole (Table 3).

Interactions involving the cytochrome P450 enzyme system

The cytochrome P450 enzyme system is responsible for the oxidative metabolism of hundreds of drugs. Among the various cytochrome P450 enzymes, the 2C8 and 2C9 isoforms are of particular relevance in patients receiving trimethoprim–sulfamethoxazole because the 2C8 isoform is inhibited by trimethoprim and the 2C9 isoform is inhibited by sulfamethoxazole. Consequently, drugs metabolized by cytochrome P450 2C8 or 2C9 can accumulate during treatment with trimethoprim–sulfamethoxazole.[22] Whereas several interactions are theoretically possible under this mechanism, two merit particular emphasis: oral hypoglycemic agents and warfarin.

Sulfonylurea agents (e.g., glyburide, gliclazide, glimepiride and glipizide) are metabolized by cytochrome P450 2C9, whereas repaglinide, a meglitinide, is metabolized by cytochrome P450 2C8.[64] Pharmacokinetic studies have shown that trimethoprim–sulfamethoxazole increases plasma levels of sulfonylureas[65] and repaglinide,[26] leading to an increased release of pancreatic insulin and symptomatic hypoglycemia.[27,28] The clinical consequences of the interaction between trimethoprim–sulfamethoxazole and sulfonylureas have been described in case reports and observational studies, which have reported four- to sixfold increases in the risk of hospital admission for hypoglycemia following the addition of trimethoprim–sulfamethoxazole to regimens containing a sulfonylurea.[28–30]

Warfarin also has the potential to interact with trimethoprim–sulfamethoxazole. Commercially available warfarin exists as two enantiomers, R- and S-warfarin. Of these, the latter is roughly five times more biologically active and is metabolized by cytochrome P450 2C9.[66,67] Co-prescription of trimethoprim–sulfamethoxazole increases S-warfarin levels in most patients.[60] Two recent population-based studies have shown that among patients receiving warfarin, the use of trimethoprim–sulfamethoxazole is associated with a two- to threefold increased risk of gastrointestinal hemorrhage relative to other antibiotics.[61,62]

Interactions involving drug transporters

Trimethoprim also inhibits the renal organic cation transporter and sulfamethoxazole inhibits the organic anion transporter,[68,69] transport systems that normally facilitate the renal elimination of several drugs. In children receiving methotrexate, treatment with trimethoprim–sulfamethoxazole decreases organic anion transporter–mediated renal clearance of methotrexate by 40%,[23,24] increasing the risk of methotrexate toxicity (including cytopenia, mucositis, hepatotoxicity and gastrointestinal symptoms). The anti-folate effect of trimethoprim may also contribute to this interaction, as documented in several case reports and one observational study.[43] Consequently, the Canadian 3E Initiative in Rheumatology[70] has formally recommended against the use of trimethoprim–sulfamethoxazole by patients receiving methotrexate.

S: Sugar (hypoglycemia)

In patients taking trimethoprim–sulfamethoxazole, the most common reason for hypoglycemia is the potentiation of concomitant sulfonylurea or repaglinide therapy.[26–30,65] However, sulfamethoxazole itself can directly cause pancreatic insulin release, particularly at higher doses and in patients with renal impairment.[25] This likely reflects the drug's structural similarity to the sulfonylureas. Hypoglycemia typically develops shortly after the patient begins to receive trimethoprim–sulfamethoxazole, and resolution may be delayed in patients with renal failure. To minimize the risk of hypoglycemia, reduction of dosage should be considered in patients with a creatinine clearance of less than 30 mL/min.

K: Hyperkalemia and other kidney effects

Trimethoprim–sulfamethoxazole can influence kidney function in several ways, which can result in hyperkalemia and hyponatremia, among other kidney effects.

Hyperkalemia

Hyperkalemia was first recognized during high-dose trimethoprim–sulfamethoxazole therapy for *P. jiroveci,* but it is increasingly appreciated as a potential complication at doses usually prescribed. This is a predictable and potentially fatal adverse effect of treatment with trimethoprim–sulfamethoxazole. Structurally similar to the

potassium-sparing diuretic amiloride, trimethoprim inhibits potassium elimination in the distal nephron.[31] In a randomized controlled trial involving 97 outpatients taking trimethoprim–sulfamethoxazole, 6% of patients experienced hyperkalemia (serum potassium level > 5.5 mmol/L) and most patients (81.5%) experienced an increase in serum potassium level.[39] Among observational studies of patients in hospital, the incidence of hyperkalemia (serum potassium level > 5.0 mmol/L) has been reported to exceed 20%.[32–34]

Hyperkalemia tends to develop after several days of therapy,[32,34] and the risk factors predictably include diabetes,[34] renal insufficiency,[34,35] older age,[34] AIDS,[39] higher doses of trimethoprim[32,35] and treatment with other drugs that inhibit kaliuresis such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers[36] and spironolactone.[37] A recent population-based case–control study involving 439 677 patients taking ACE inhibitors or angiotensin receptor blockers found a sevenfold increased risk of hospital admission for hyperkalemia among those taking trimethoprim–sulfamethoxazole compared with those taking other antibiotics used for urinary tract infections.[36] We suggest that physicians monitor patients for hyperkalemia following a few days of trimethoprim–sulfamethoxazole treatment at a standard dose, especially patients with impaired renal function, which may include older patients, those with diabetes or AIDS, and those also taking ACE inhibitors, angiotensin receptor blockers or spironolactone.

Box 1: Applying the results of this review to a fictional case in clinical practice

A 67-year-old woman presents to her family physician with a nonspecific complaint of weakness and an unwell feeling. She recently completed a seven-day course of trimethoprim–sulfamethoxazole for a urinary tract infection. Her longstanding medications include ramipril for hypertension and metformin for type 2 diabetes. Her physical examination is unremarkable. Results of routine blood tests show hyperkalemia (serum potassium level 6.9 [normal 3.5–5.0] mmol/L) and are otherwise normal.

Hyperkalemia developed because of the potassium-sparing effect of trimethoprim on the distal tubule of the kidney, which was exacerbated by diabetes and the concomitant use of ramipril. Symptomatic treatment of hyperkalemia is started and ramipril is temporarily withheld. The patient's condition improves without consequence.

Box 2: Suggestions for reducing the risks of prescribing trimethoprim–sulfamethoxazole, based on the results of our literature review

When prescribing trimethoprim–sulfamethoxazole, consider the following:

- Prescribing an alternative antibiotic if clinically indicated, particularly for pregnant patients in the first trimester, patients with glucose-6-phosphate dehydrogenase deficiency or patients taking methotrexate.
- Monitoring electrolytes within a few days of starting therapy to identify hyperkalemia or hyponatremia in specific patient groups, including those with reduced renal function, diabetes, older age and AIDS. Electrolytes should also be monitored in those taking higher doses of trimethoprim–sulfamethoxazole and those also taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or spironolactone.
- Monitoring the international normalized ratio within three to four days of starting therapy in patients taking warfarin.
- Monitoring for hypoglycemia within a few days of starting therapy for patients taking oral hypoglycemic agents (e.g., sulfonylureas and meglitinides).

Other kidney effects

Although not as common as hyperkalemia, trimethoprim-mediated blockade of epithelial sodium channels in the distal nephron may also increase the risk of hyponatremia.[31,35]

Patients with chronic renal insufficiency are at increased risk of adverse effects associated with use of trimethoprim–sulfamethoxazole.[25,34,35] Although uncommon, this drug can also cause renal injury in otherwise healthy patients. This adverse effect generally manifests as a form of drug hypersensitivity syndrome, most commonly acute interstitial nephritis.[29] The classic findings include fever, rash and an elevated creatinine level. If present, eosinophilia and eosinophiluria support the diagnosis, but their absence does not exclude it.

A much less common mechanism by which trimethoprim–sulfamethoxazole may cause acute kidney injury is obstructive tubulopathy resulting from the intraluminal precipitation of sulfamethoxazole. This phenomenon has been described in one case report but is more typically associated with older sulfonamide antibiotics.[38]

Y: Why not consider an alternate antimicrobial?

Although trimethoprim–sulfamethoxazole has numerous benefits, particularly in the care of patients with HIV and methicillin-resistant *S. aureus*, it is associated with multiple toxicities. However, all drugs carry adverse effects. When considering other antimicrobials, clinicians should remember that areas of uncertainty remain, particularly with newer agents.

Gaps in knowledge

Although trimethoprim–sulfamethoxazole is a popular, effective and inexpensive drug with a long history of use, it is associated with a range of adverse effects, some with fatal outcomes. Box 1 provides a fictional example of a drug–drug interaction with trimethoprim–sulfamethoxazole. The exact mechanisms of toxicity and occurrence for some of the adverse effects of trimethoprim–sulfamethoxazole have yet to be defined. In addition, more studies are needed to understand the

influence of pharmacogenomics on the safety profile of trimethoprim–sulfamethoxazole.

Clinicians should be cognizant of the potential consequences of prescribing trimethoprim–sulfamethoxazole, monitor patients for adverse events during therapy or use an alternate antibiotic when appropriate. Box 2 provides suggestions for reducing the risks associated with trimethoprim–sulfamethoxazole.

References

1. McIsaac WJ, Prakash P, Ross S. The management of acute uncomplicated cystitis in adult women by family physicians in Canada. *Can J Infect Dis Med Microbiol* 2008;19:287-93.
2. Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. *MMWR Recomm Rep* 2009;58:1-207.
3. Marshall D, Gough J, Grootendorst P, et al. Impact of administrative restrictions on antibiotic use and expenditure in Ontario: time series analysis. *J Health Serv Res Policy* 2006;11:13-20.
4. Jolles S, Sewell WAC, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. *Drug Saf* 2000;22:215-26.
5. Slavik RS, Rybak MJ, Lerner SA. Trimethoprim/sulfamethoxazole-induced tremor in a patient with AIDS. *Ann Pharmacother* 1998;32:189.
6. Dakin LE. Probable trimethoprim/sulfamethoxazole-induced higher-level gait disorder and nocturnal delirium in an elderly man. *Ann Pharmacother* 2009;43:129-33.
7. Damergis JA, Stoker JM, Abadie JL. Methemoglobinemia after sulfamethoxazole and trimethoprim. *JAMA* 1983;249:590-1.
8. Koirala J. Trimethoprim-sulfamethoxazole–induced methemoglobinemia in an HIV-infected patient. *Mayo Clin Proc* 2004;79:829-30.
9. Keisu M, Wiholm BE, Palmblad J. Trimethoprim-sulphamethoxazole-associated blood dyscrasias. Ten years' experience of the Swedish spontaneous reporting system. *J Intern Med* 1990;228:353-60.
10. Myers MW, Jick H. Hospitalization for serious blood and skin disorders following co-trimoxazole. *Br J Clin Pharmacol* 1997;43:649-51.
11. Zaman F, Ye G, Abreo KD, et al. Successful orthotopic liver transplantation after trimethoprim-sulfamethoxazole associated fulminant liver failure. *Clin Transplant* 2003;17:461-4.
12. Kouklakis G, Mpoumponaris A, Zezos P, et al. Cholestatic hepatitis with severe systemic reactions induced by trimethoprim-sulfamethoxazole. *Ann Hepatol* 2007;6:63-5.
13. Berg PA, Daniel PT. Co-trimoxazole-induced hepatic injury–an analysis of cases with hypersensitivity-like reactions. *Infection* 1987;15(Suppl 5):S259-64.
14. Thies PW, Dull WL. Trimethoprim-sulfamethoxazole-induced cholestatic hepatitis. Inadvertent rechallenge. *Arch Intern Med* 1984;144:1691-2.
15. Pusey CD, Saltissi D, Bloodworth L, et al. Drug associated acute interstitial nephritis: clinical and pathological features and the response to high dose steroid therapy. *Q J Med* 1983;52:194-211.
16. Wanat KA, Anadkat MJ, Klekotka PA. Seasonal variation of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with trimethoprim-sulfamethoxazole. *J Am Acad Dermatol* 2009;60:589-94.
17. Gillman MA, Sandyk R. Phenytoin toxicity and co-trimoxazole. *Ann Intern Med* 1985;102:559.
18. Sivojelezova A, Einarson A, Shuhaiber S, et al. Trimethoprim-sulfonamide combination therapy in early pregnancy. *Can Fam Physician* 2003;49:1085.
19. Scholl TO, Johnson WG. Folic acid: influence on the outcome of pregnancy. *Am J Clin Nutr* 2000;71:1295S.
20. Lee M, Bozzo P, Einarson A, et al. Urinary tract infections in pregnancy. *Can Fam Physician* 2008;54:853.
21. Santos F, Sheehy O, Perreault S, et al. Exposure to anti-infective drugs during pregnancy and the risk of small-for-gestational-age newborns: a case–control study. *BJOG* 2011 Jul 12. doi: 10.1111/j.1471-0528.2011.03041.x.
22. Wen X, Wang JS, Backman JT, et al. Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively. *Drug Metab Dispos* 2002;30:631-5.
23. Liegler DG, Henderson ES, Hahn MA, et al. The effect of organic acids on renal clearance of methotrexate in man. *Clin Pharmacol Ther* 1969;10:849-57.
24. Ferrazzini G, Klein J, Sulh H, et al. Interaction between trimethoprim-sulfamethoxazole and methotrexate in children with leukemia. *J Pediatr* 1990;117:823-6.
25. Strevel EL, Kuper A, Gold WL. Severe and protracted hypoglycaemia associated with co-trimoxazole use. *Lancet Infect Dis* 2006;6:178-82.
26. Niemi M, Kajosaari LI, Neuvonen M, et al. The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. *Br J Clin Pharmacol* 2004;57:441-7.
27. Roustit M, Blondel E, Villier C, et al. Symptomatic hypoglycemia associated with trimethoprim/sulfamethoxazole and repaglinide in a diabetic patient. *Ann Pharmacother* 2010;44:764-7.
28. Johnson JF, Dobmeier ME. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. *DICP* 1990;24:250-1.
29. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003;289:1652-8.
30. Schelleman H, Bilker WB, Brensinger CM, et al. Anti-infectives and the risk of severe hypoglycemia in users of glipizide or glyburide. *Clin Pharmacol Ther* 2010;88:214-22.
31. Velázquez H, Perazella MA, Wright FS, et al. Renal mechanism of trimethoprim-induced hyperkalemia. *Ann Intern Med* 1993;119:296.
32. Greenberg S, Reiser IW, Chou SY, et al. Trimethoprim-sulfamethoxazole induces reversible hyperkalemia. *Ann Intern Med* 1993;119:291-5.
33. Medina I, Mills J, Leoung G, et al. Oral therapy for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med* 1990;323:776-82.
34. Alappan R, Perazella MA, Buller GK. Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med* 1996;124:316.
35. Mori H, Kuroda Y, Imamura S, et al. Hyponatremia and/or hyperkalemia in patients treated with the standard dose of trimethoprim-sulfamethoxazole. *Intern Med* 2003;42:665-9.
36. Antoniou T, Gomes T, Juurlink DN, et al. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. *Arch Intern Med* 2010;170:1045-9.
37. Marinella MA. Severe hyperkalemia associated with trimethoprim-sulfamethoxazole and spironolactone. *Infect Dis Clin Pract* 1997;6:257.
38. Schwarz A, Perez-Canto A. Nephrotoxicity of antiinfective drugs. *Int J Clin Pharmacol Ther* 1998;36:164-7.
39. Alappan R, Buller GK, Perazella MA. Trimethoprim-sulfamethoxazole therapy in outpatients: is hyperkalemia a significant problem? *Am J Nephrol* 1999;19:389-94.
40. Dudley MN, Levitz RE, Quintiliani R, et al. Pharmacokinetics of trimethoprim and sulfamethoxazole in serum and cerebrospinal fluid of adult patients with normal meninges. *Antimicrob Agents Chemother* 1984;26:811-4.
41. Jenkins GC, Hughes DT, Hall PC. A haematological study of patients receiving long-term treatment with trimethoprim and sulphonamide. *J Clin Pathol* 1970;23:392-6.
42. Heimpel H, Raghavachar A. Hematological side effects of co-trimoxazole. *Infection* 1987;15(Suppl 5):S248-53.
43. Bourré-Tessier J, Haraoui B. Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. *J Rheumatol* 2010;37:1416-21.
44. Ermis B, Caner I, Karacan M, et al. Haemolytic anaemia secondary to trimethoprim/sulfamethoxazole use. *Thromb Haemost* 2003;90:158-9.
45. Ponte CD, Lewis MJ, Rogers JS II. Heinz-body hemolytic anemia associated with phenazopyridine and sulfonamide. *DICP* 1989;23:140-2.
46. Reinke CM, Thomas JK, Graves AH. Apparent hemolysis in an AIDS patient receiving trimethoprim/sulfamethoxazole: case report and literature review. *J Pharm Technol* 1996;11:256-62, quiz 293-5.
47. Kiefel V, Santoso S, Schmidt S, et al. Metabolite-specific (IgG) and drug-specific antibodies (IgG, IgM) in two cases of trimethoprim-sulfamethoxazole-induced immune thrombocytopenia. *Transfusion* 1987;27:262-5.
48. Curtis BR, McFarland JG, Wu GG, et al. Antibodies in sulfonamide-induced immune thrombocytopenia recognize calcium-dependent epitopes on the glycoprotein IIb/IIIa complex. *Blood* 1994;84:176-83.
49. Claas FH, van der Meer JW, Langerak J. Immunological effect of co-trimoxazole on platelets. *BMJ* 1979;2:898-9.
50. Vetrella M, Åstedt B, Barthelmai W, et al. Activity of NADH- and NADPH-dependent methemoglobin reductases in erythrocytes from fetal to adult age. *J Klin Wochenschr* 1971;49:972-7.
51. Chan TY. Co-trimoxazole-induced severe haemolysis: the experience of a large general hospital in Hong Kong. *Pharmacoepidemiol Drug Saf* 1997;6:89-92.

52. Lexomboon U, Unkurapiana N. Co-trimoxazole in the treatment of typhoid fever in children with glucose-6-phosphate dehydrogenase deficiency. *Southeast Asian J Trop Med Public Health* 1978;9:576-80.
53. Markowitz N, Saravolatz LD. Use of trimethoprim-sulfamethoxazole in a glucose-6-phosphate dehydrogenase-deficient population. *Rev Infect Dis* 1987;9(Suppl 2):S218-29.
54. Jick H. Adverse reactions to trimethoprim-sulfamethoxazole in hospitalized patients. *Rev Infect Dis* 1982;4:426.
55. Briggs G, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Philadelphia (PA): Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.
56. Czeizel AE, Rockenbauer M, Sørensen HT, et al. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol* 2001;15:637-46.
57. Hernández-Díaz S, Werler MM, Walker AM, et al. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med* 2000;343:1608-14.
58. Mofenson LM, Brady MT, Danner SP, 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. *MMWR Recomm Rep* 2009;58(RR-11):1-166.
59. Tomasulo P. LactMed-new NLM database on drugs and lactation. *Med Ref Serv Q* 2007;26:51-8.
60. O'Reilly RA. Stereoselective interaction of trimethoprim-sulfamethoxazole with the separated enantiomorphs of racemic warfarin in man. *N Engl J Med* 1980;302:33-5.
61. Schelleman H, Bilker WB, Brensinger CM, et al. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. *Clin Pharmacol Ther* 2008;84:581-8.
62. Fischer HD, Juurlink DN, Mamdani MM, et al. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. *Arch Intern Med* 2010;170:617-21.
63. Antoniou T, Gomes T, Mamdani MM, et al. Trimethoprim/sulfamethoxazole-induced phenytoin toxicity in the elderly: a population-based study. *Br J Clin Pharmacol* 2011;71:544-9.
64. Flockhart DA. Drug interactions: cytochrome P450 drug interaction table. Indianapolis www.drug-interactions.com (accessed 2011 May 2).
65. Wing LM, Miners JO. Cotrimoxazole as an inhibitor of oxidative drug metabolism: effects of trimethoprim and sulphamethoxazole separately and combined on tolbutamide disposition. *Br J Clin Pharmacol* 1985;20:482-5.
66. O'Reilly RA. Studies on the optical enantiomorphs of warfarin in man. *Clin Pharmacol Ther* 1974;16:348-54.
67. Breckenridge A, Orme M, Wesseling H, et al. Pharmacokinetics and pharmacodynamics of the enantiomers of warfarin in man. *Clin Pharmacol Ther* 1974;15:424-30.
68. Kosoglou T, Rocci ML Jr, Vlasses PH. Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* 1988;44:467-77.
69. Fujita T, Urban TJ, Leabman MK, et al. Transport of drugs in the kidney by the human organic cation transporter, OCT2 and its genetic variants. *J Pharm Sci* 2006;95:25-36.
70. Katchamart W, Bourre-Tessier J, Donka T, et al. Canadian recommendations for use of methotrexate in patients with rheumatoid arthritis. *J Rheumatol* 2010;37:1422-30.

Affiliations: From the Division of Clinical Pharmacology (Ho, Juurlink); and the Department of Medicine, University of Toronto, the Institute for Clinical Evaluative Sciences, and Sunnybrook Health Sciences Centre (Juurlink), Toronto, Ont.

Contributors: Both authors conceived and drafted the article, revised it for intellectual content and approved the final version submitted for publication.

Acknowledgements: The authors thank Tony Antoniou for reviewing the manuscript, Anna Pupco from Motherisk for reviewing the section on reproduction, and Henry Lam from the Sunnybrook Health Sciences Centre Library for assisting with the literature search.