Overview

Trimethoprim-sulfamethoxazole related bone marrow suppression

Supervisor: VS 楊松昇
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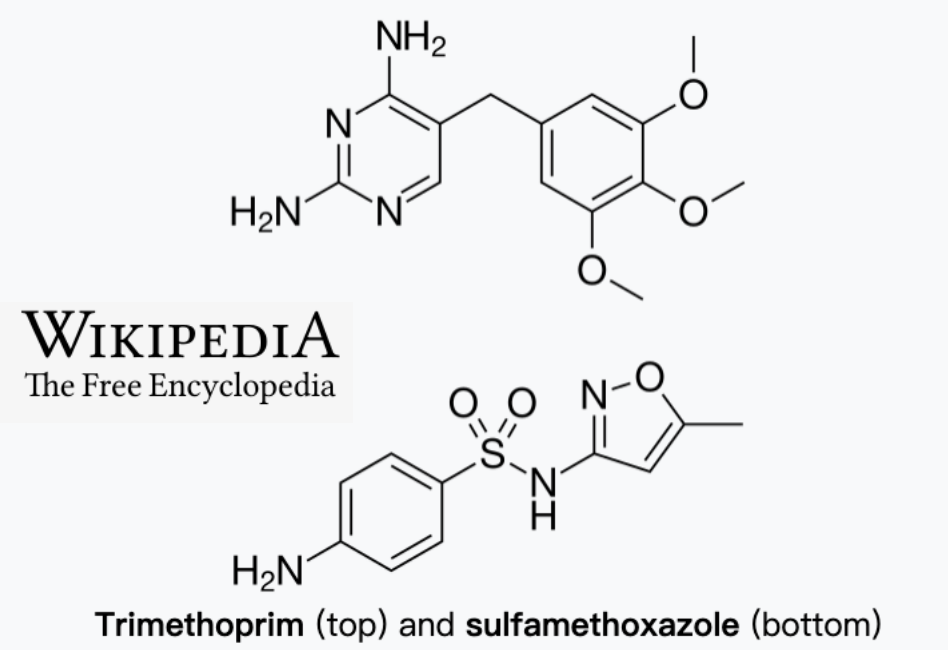
2021/09/16

Introduction

- TMP-SMX, also known as co-trimoxazole, is a combination of two antimicrobial agents that act synergistically against a wide variety of bacteria



Trimethoprim (top) and **sulfamethoxazole** (bottom)

Introduction

Organisms susceptible to trimethoprim-sulfamethoxazole

Urinary tract pathogens
Escherichia coli
Klebsiella pneumonia
Proteus mirabilis
Enterobacter sp.
Morganella morgani
Respiratory tract pathogens
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Pneumocystis jirovecii

Gastrointestinal pathogens
Enterotoxigenic E. coli
Shigella sp.
Salmonella typhi (and other species)
Vibrio cholerae
Cyclospora cayetanensis
Isospora belli
Yersinia
Other pathogens
Nocardia sp.
Listeria monocytogenes
Mycobacterium marinum

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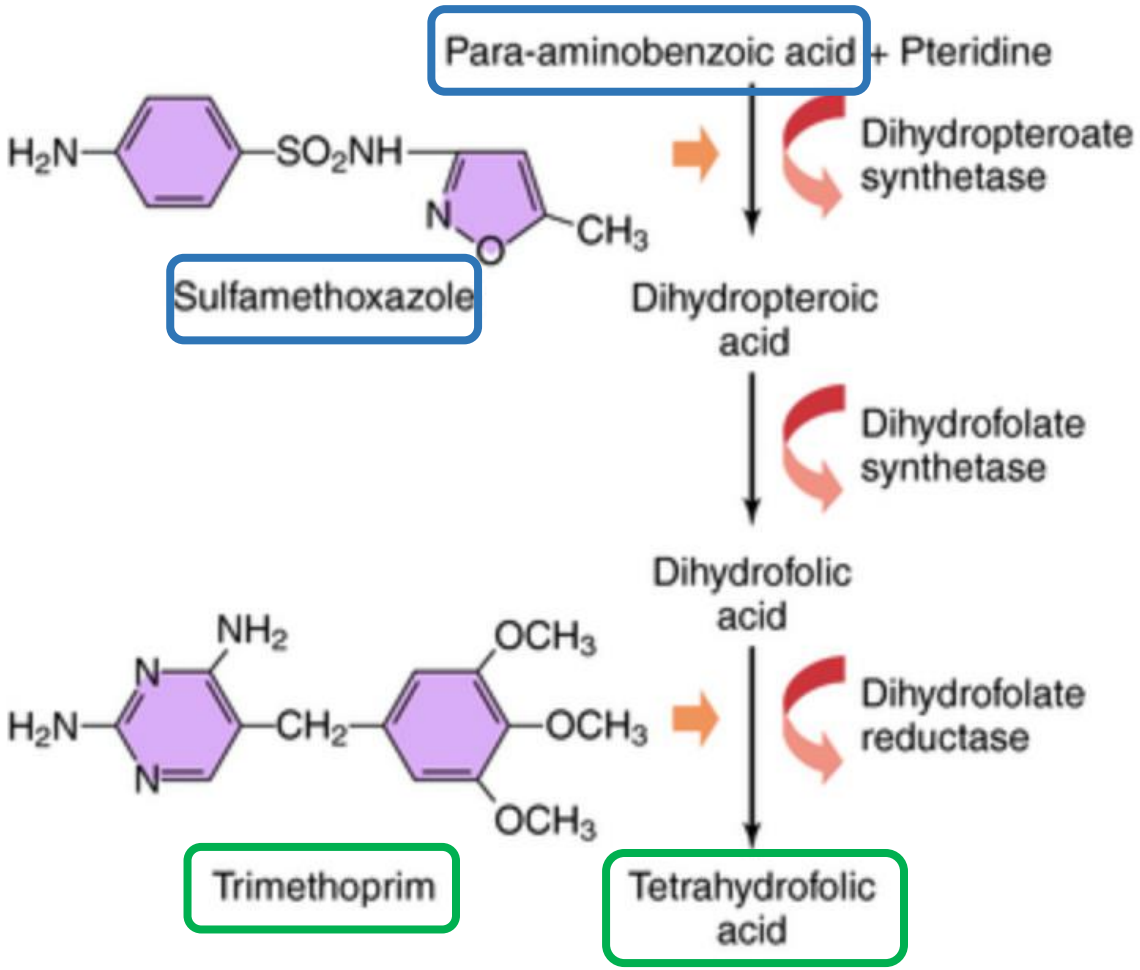
Mechanism of Action



Overall mechanism:
Inhibit enzyme of synthesis of tetrahydrofolic acid (THF)

SMX is a structural analog of para-aminobenzoic acid (PABA) to inhibit the synthesis of dihydrofolic acid

TMP binds to bacterial dihydrofolate reductase (in preference to human dihydrofolate reductase) also preventing the formation of THF

Metabolism and Excretion

- 50 percent of the drug

→Excreted in the urine in the first 24 hours

- Accumulation occurs when CCr < 30 mL/min

- Uremic and hypoalbuminemic patients may have reduced protein binding and an increased volume of distribution of SMX component

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Precautions

- Considered first-line therapy (PJP in patients with HIV) treat with TMP-SMX if no life threatening adverse reactions

- Adverse reaction rate:
  - without HIV: 6 to 8 %
  - with HIV: 25 to 50%

Adverse Effects

- Common
  - Gastrointestinal tract (nausea, vomiting)
  - Skin (rash and pruritus)
  - Hepatitis
  - Hypoglycemia
  - Hyponatremia
- Uncommon
  - Nephrotoxicity
  - Renal tubular acidosis
  - Hemolysis in patients (G6PD deficiency)

Adverse Effects

Major adverse effects of trimethoprim-sulfamethoxazole

Systemic allergic reactions
Anaphylaxis
Serum sickness
Cutaneous reactions
Rash
Stevens-Johnson syndrome
Erythema muliforme
Urticaria
Toxic epidermal necrolysis
Photodermatis
Gastrointestinal and hepatic reactions
Nausea and vomiting
Diarrhea
Hepatotoxicity

Hematologic reactions
Pancytopenia
Agranulocytosis
Anemia
Thrombocytopenia
Renal disorders
Transient rise in creatinine due to impaired secretion by trimethoprim
Acute interstitial nephritis
Crystalluria due to precipitation of sulfamethoxazole
Hyperkalemia due to trimethoprim-induced blockade of collecting tubule sodium channel
Other reactions
Central nervous system - headache, confusion, aseptic meningitis
Fever
Phlebitis

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Life threatening effects

- HIV and older adults
  - Neutropenia
  - Anaphylaxis
  - Stevens-Johnson syndrome
    - (involving the mucosal surfaces)
  - Exfoliative dermatitis
    - (a severe skin disorder with generalized erythema and scaling)
  - Toxic epidermal necrolysis
    - (an acute severe reaction with widespread erythema and detachment of the epidermis)

Life threatening effects

- Hyperkalemia :
  - Blockade of the collecting tubule sodium channel by trimethoprim
  - Common in patients with HIV
  - Sudden death if also receiving spironolactone, ACEI or ARB
- Increased risk of severe lactic acidosis:
  - Propylene glycol, solvent of intravenous TMP-SMX

Precautions

- With folate deficiency people and risk for complications of folate deficiency:
  - Trimethoprim weakly inhibits human dihydrofolate reductase
  - May cause megaloblastic changes
    - (eg, macrocytic anemia, mild thrombocytopenia, leukopenia)

CMAJ REVIEW

Considerations when prescribing trimethoprim–sulfamethoxazole

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

CMAJ November 08, 2011 183 (16) 1851-1858; DOI: https://doi.org/10.1503/cmaj.111152

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

CMAJ November 08, 2011 183 (16) 1851-1858; DOI: https://doi.org/10.1503/cmaj.111152

Precautions

- AIDS and *Pneumocystis* pneumonia:
  - Do not supplement with folic acid or leucovorin because with a higher risk of treatment failure
  - Pregnant women with *PJP*, folic acid should be used to reduce the risk of neural tube defects

- Leucovorin is favor for toxoplasmosis (cannot be metabolized by the parasite)

Precautions

- Sulfonamide allergy:
  - History of anaphylaxis
  - Stevens-Johnson syndrome
  - toxic epidermal necrolysis

- History of allergy to nonantimicrobial sulfonamides can often safely receive TMP-SMX
  - (past allergic reaction to nonantimicrobial sulfonamides)

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Pregnancy and Breastfeeding

- Avoided in the first trimester and last month of pregnancy
- Avoided in infants with G6PD deficiency

- Should be used on pregnancy with HIV who requires prophylaxis/treatment for *Pneumocystis* pneumonia

CMAJ REVIEW

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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.

NSAID

ARB, ACEI

(Lescol XL FC Tab 80 mg)

CMAJ November 08, 2011 183 (16) 1851-1858; DOI: https://doi.org/10.1503/cmaj.111152

Dose 要如何使用才適當？

Open Forum Infectious Diseases

MAJOR ARTICLE

Low-Dose TMP-SMX in the Treatment of *Pneumocystis jirovecii* Pneumonia: A Systematic Review and Meta-analysis

Guillaume Butler-Laporte,[1,] Elizabeth Smyth,[2] Alexandre Amar-Zifkin,[3] Matthew P. Cheng,[4,] Emily G. McDonald,[1,2,5,6,7] and Todd C. Lee[1,2,5,6,7,]

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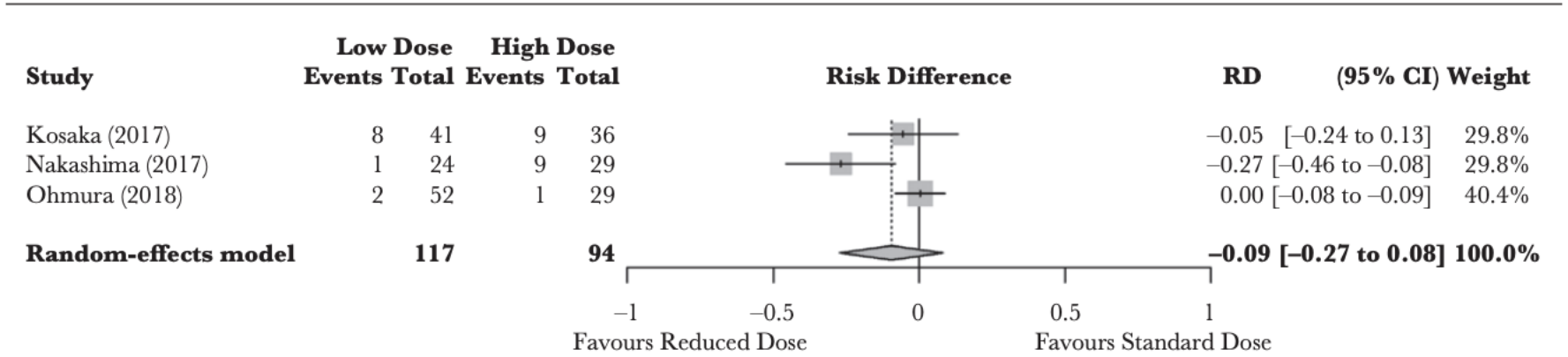


Figure 2. Standard-dose vs reduced-dose trimethoprim-sulfamethoxazole mortality meta-analysis. Results are reported as relative risk difference. Abbreviations: CI, confidence interval; RD, risk difference.

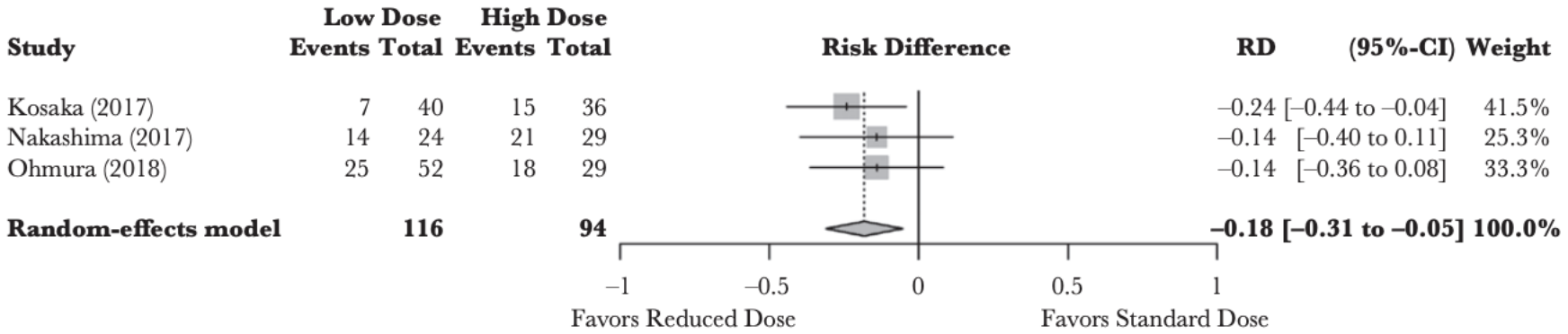


Figure 3. Standard-dose vs reduced-dose trimethoprim-sulfamethoxazole adverse events meta-analysis. Results are reported as relative risk difference. Abbreviations: CI, confidence interval; RD, risk difference.

- No modern data suggest that standard-dose TMP/SMX improves clinical outcomes in PJP.
- Standard doses lead to an absolute increase of 18% (95% CI, 5% to 31%) in the risk of adverse events

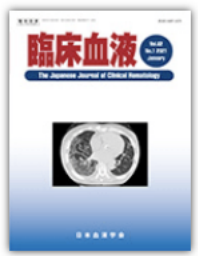
- In this systematic review, treatment of PJP with doses of ≤10 mg/kg/d of trimethoprim was associated with similar rates of mortality when compared with standard doses and with significantly fewer treatment-emergent severe adverse events.
- Although limited by the observational nature of the studies included, this review provides the most current available evidence for the optimal dosing of TMP-SMX in the treatment of PJP

Open Forum Infectious Diseases
MAJOR ARTICLE

Low-Dose TMP-SMX in the Treatment of *Pneumocystis jirovecii* Pneumonia: A Systematic Review and Meta-analysis

> Rinsho Ketsueki. 2019;60(5):365-371. doi: 10.11406/rinketsu.60.365.

[Pneumocystis pneumonia prophylaxis with low-dose trimethoprim/sulfamethoxazole during rituximab-containing chemotherapy]



[Article in Japanese]

Rie Shimizu [1], Reona Sakemura [1 2], Satoshi Iwata [1], Hiroshi Hayakawa [1], Kotaro Miyao [1], Tomohiro Kajiguchi [1]

Affiliations + expand

PMID: 31167996 DOI: 10.11406/rinketsu.60.365

- Patients were categorized into two groups based on the TMP/SMX regimen:
  - group A (33 patients; 80 mg/400 mg×3/week)
  - group B (65 patients; 160 mg/800 mg×2/week)

- Both lymphocytes count and IgG level declined during R-CTX.
- No patient developed PCP

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MAJOR ARTICLE

Low-Dose TMP-SMX in the Treatment of *Pneumocystis jirovecii* Pneumonia: A Systematic Review and Meta-analysis

- Patients in group B exhibited a significantly higher incidence of adverse effects (18.2% vs. 63.1%; $p<0.05$) and increased AST (6.1% vs. 26.6%; $p<0.05$), compared with those in group A.
- TMP/SMX (80 mg/400 mg×3/week) effectively prevents PCP and is preferable because of the lower rates of AEs

Open Forum Infectious Diseases
MAJOR ARTICLE

Low-Dose TMP-SMX in the Treatment of *Pneumocystis jirovecii* Pneumonia: A Systematic Review and Meta-analysis

Yamashita *et al. BMC Infectious Diseases* (2021) 21:664
https://doi.org/10.1186/s12879-021-06374-3

BMC Infectious Diseases

RESEARCH Open Access

Safety and efficacy evaluation of low-dose trimethoprim-sulfamethoxazole for prophylaxis of *Pneumocystis pneumonia* in HIV uninfected patients undergoing hemodialysis: a retrospective observational study

Kanae Yamashita[1*], Yoshimitsu Shimomura[2], Hiroaki Ikesue[1], Nobuyuki Muroi[1], Akihiro Yoshimoto[3] and Tohru Hashida[1]

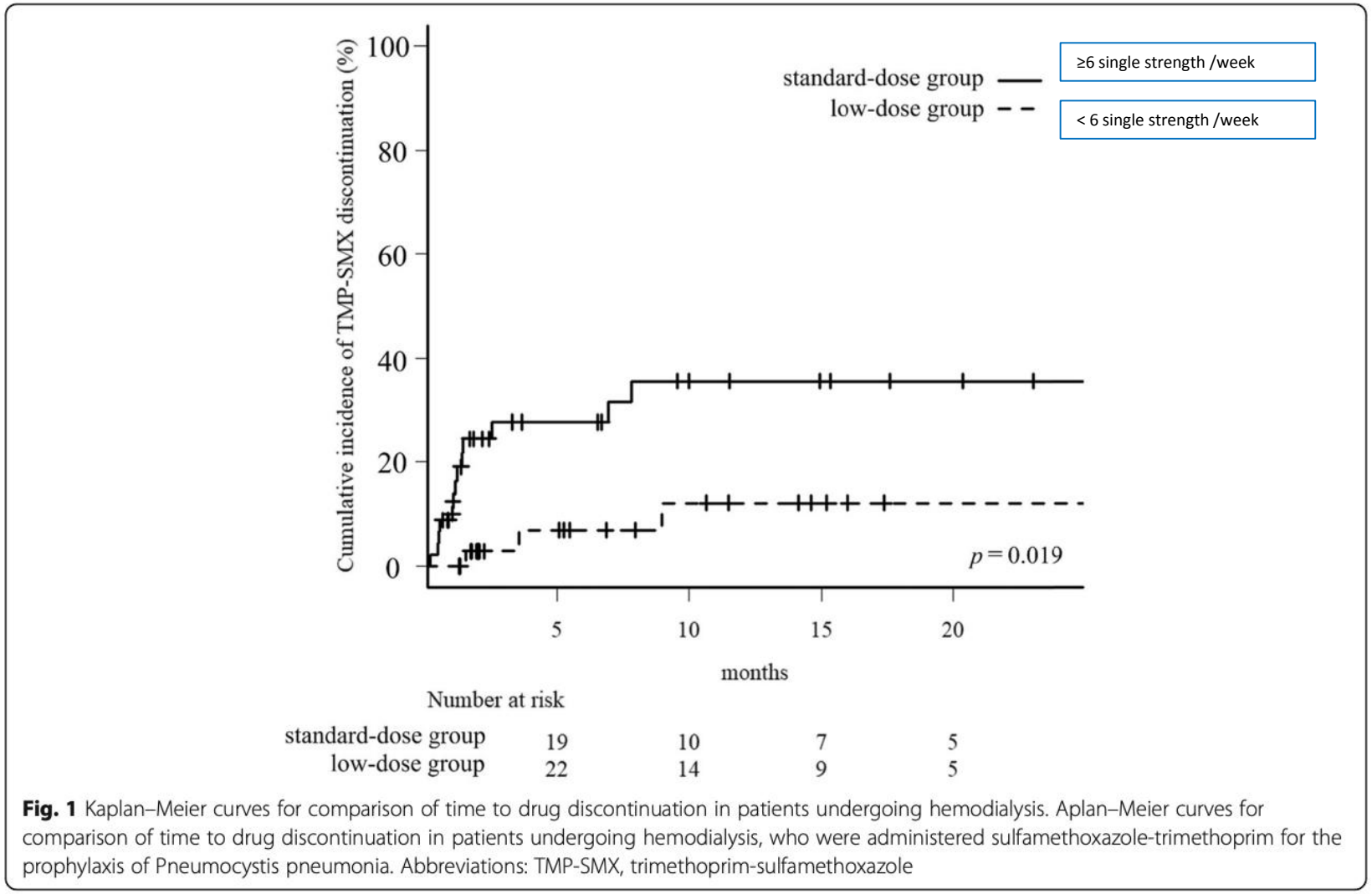

Fig. 1 Kaplan–Meier curves for comparison of time to drug discontinuation in patients undergoing hemodialysis. Aplan–Meier curves for comparison of time to drug discontinuation in patients undergoing hemodialysis, who were administered sulfamethoxazole-trimethoprim for the prophylaxis of Pneumocystis pneumonia. Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole

- No patients in either group developed PCP during the observation period
- The cumulative incidence of discontinuation was 12.1% (95% CI: 0.027–0.29) in the low-dose group and 35.6% (95% CI: 0.20–0.52) in the standard group (P = 0.019)

Table 3 Adverse event requiring TMP-SMX discontinuation

Adverse event	Low-dose group ($n = 36$)	Standard-dose group ($n = 45$)
Number of discontinued patients, n (%)	3 (8.3)	13 (28.9)
Details of adverse events		
Fever, n (%)	0 (0.0)	5 (11.1)
Rash, n (%)	0 (0.0)	6 (13.3)
Anorexia, n (%)	0 (0.0)	2 (4.4)
Thrombocytopenia, n (%)	3 (8.3)	6 (13.3)
Leukocytopenia, n (%)	3 (8.3)	2 (4.4)
Anemia, n (%)	2 (5.6)	6 (13.3)
Hyperkalemia, n (%)	1 (2.8)	2 (4.5)
Hyponatremia, n (%)	2 (5.6)	6 (13.3)
Increased alanine aminotransferase, n (%)	0 (0.0)	5 (11.1)
Increased aspartate aminotransferase, n (%)	0 (0.0)	5 (11.1)

The number of patients who discontinued due to adverse events and details of adverse events reported in each group are shown. Thirteen patients in the standard-dose group and three patients in the low-dose group discontinued TMP-SMX due to adverse events. Some patients experienced multiple adverse events
Abbreviation: *TMP-SMX* trimethoprim-sulfamethoxazole

The most frequent AE that caused TMP-SMX discontinuation

- Low-dose group was thrombocytopenia and leukocytopenia
- Standard-dose group, it was rash, thrombocytopenia, anemia, and hyponatremia

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PROPHYLAXIS GUIDELINES FOR THE ADULT HEMATOLOGY PATIENT

Antimicrobial Subcommittee Approval: 04/2016; 12/2020	Originated: 04/2016
P&T Approval: 02/2021	Last Revised: 02/2021
Revision History:	

Indication	Antibacterial	Antifungal	PJP prophylaxis	Antiviral	Duration of Prophylaxis
Maintenance Anti-CD20 (e.g., rituximab, obinutuzumab)	No routine prophylaxis	No routine prophylaxis	No routine prophylaxis	**Acyclovir** 400 mg BID Hepatitis B screen prior to initiation	Throughout all chemotherapy cycles

Anti-CD20後的TMP-SMX要用多久？

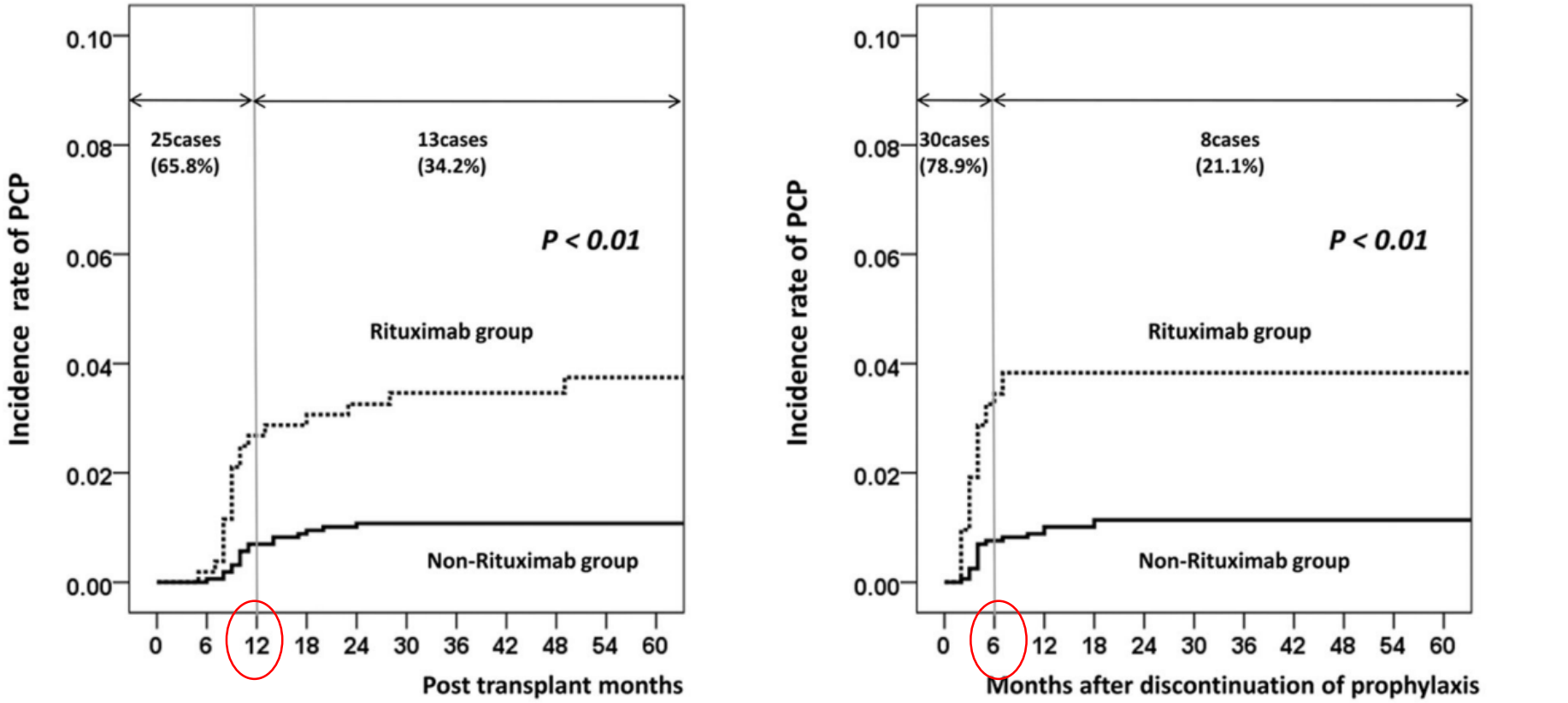
Kim *et al. BMC Nephrology* (2020) 21:93
https://doi.org/10.1186/s12882-020-01750-8

BMC Nephrology

RESEARCH ARTICLE Open Access

Pneumocystis pneumonia occurrence and prophylaxis duration in kidney transplant recipients according to perioperative treatment with rituximab

Young Hoon Kim[1], Jee Yeon Kim[1], Dong Hyun Kim[1], Youngmin Ko[1], Ji Yoon Choi[1], Sung Shin[1], Joo Hee Jung[1], Su-Kil Park[2], Sung-Han Kim[3], Hyunwook Kwon[1*] and Duck Jong Han[1]



PCP, incidence	Within 1 year	1 year after transplnat
Rituximab (N=20)	14 (70.0%)	6 (30.0%)
Non-Rituximab (N=18)	11 (61.1%)	7 (38.9%)

PCP, incidence	Within 6 months	6 months after discontinuation
Rituximab (N=20)	18 (90.0%)	2 (10.0%)
Non-Rituximab (N=18)	12 (66.7%)	6 (33.3%)

Fig. 2 Incidence of *Pneumocystis jiroveci* pneumonia after (**a**) transplant and (**b**) discontinuation of prophylaxis

Kim *et al. BMC Nephrology* (2020) 21:93
https://doi.org/10.1186/s12882-020-01750-8

- Recent studies showed that rituximab results in longterm elimination of B-cells up to more than 6 months, thereby suggesting prolongation of prophylaxis
- Due to the limited number of patients, this study could not analyze the effectiveness and necessity of 12-months prophylaxis after rituximab treatment for rejection treatment within 6 months after transplantation.
- However, they still suggest using 12-months prophylaxis for KT recipients who received rejection treatment, especially when they have other risk factors for PCP.

Kim *et al. BMC Nephrology* (2020) 21:93
https://doi.org/10.1186/s12882-020-01750-8

- This study report that KT recipients who received rituximab for desensitization or treatment of acute rejection had higher incidence of PCP than those who did not receive rituximab, and that most cases of PCP (90.0%) occurred within 6 months following discontinuation of prophylaxis.
- This results suggest that prolongation of PCP prophylaxis to 12 months may be beneficial in KT recipients who receive perioperative treatment with rituximab

Kim *et al. BMC Nephrology* (2020) 21:93
https://doi.org/10.1186/s12882-020-01750-8

是否要進行葉酸補充？

CFP·MFC
CANADIAN FAMILY PHYSICIAN • LE MÉDECIN DE FAMILLE CANADIEN
Official Publication of
The College of
Family Physicians of Canada

Can Fam Physician. 2014 Jan; 60(1): 53–56.

PMCID: PMC3994806
PMID: 24452563

Case Report

Methotrexate and trimethoprim-sulfamethoxazole

Toxicity from this combination continues to occur

Jessica Cudmore MD **Matthew Seftel** MD MPH FRCP FRCPC **Jeffrey Sisler** MD MCISc CCFP FCFP **Ryan Zarychanski** MD MSc FRCPC

- If pancytopenia is identified, consultation with a hematologist should be considered.
- Folic acid supplementation would not be expected to prevent dangerous drug interactions or to effectively treat them once they occur.
- Folinic acid, a reduced derivative of folic acid that supplies the necessary cofactor antagonized by MTX, does reverse the block in folate metabolism induced by both MTX and TMP- SMX, but would be expected to reduce the effectiveness of these agents to treat the conditions for which they were initiated.

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Family Physicians of Canada

Can Fam Physician. 2014 Jan; 60(1): 53–56.
PMCID: PMC3994806
PMID: 24452563

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- Does Trimethoprim-Sulfamethoxazole prophylaxis induce myelosuppression in primary immune deficiency disease patients; A retrospective, 3 groups comparative study
- Methotrexate and trimethoprim-sulfamethoxazole
- Trimethoprim-sulfamethoxazole Induced Pancytopenia: A Common Occurrence but A Rare Diagnosis
- HEME-ONC-ppx_ADULT.pdf (umich.edu)
- [Pneumocystis pneumonia prophylaxis with low-dose trimethoprim/sulfamethoxazole during rituximab-containing chemotherapy] - PubMed (nih.gov)
- Safety and efficacy evaluation of low-dose trimethoprim-sulfamethoxazole for prophylaxis of Pneumocystis pneumonia in HIV uninfected patients undergoing hemodialysis: a retrospective observational study