Lee et al. World Allergy Organization Journal (2024) 17:100856
http://doi.org/10.1016/j.waojou.2023.100856

WORLD ALLERGY ORGANIZATION JOURNAL

REVIEW

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Antibiotic prophylaxis in immunosuppressed patients – Missed opportunities from trimethoprim-sulfamethoxazole allergy label

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ABSTRACT

Trimethoprim-sulfamethoxazole (TMP-SMX) is a broad spectrum antibiotic in use for more than 50 years. It has an important indication as first line agent in the prophylaxis of opportunistic infections, particularly *Pneumocystis jirovecii* pneumonia (PJP), in immunosuppressed patients. For those who have a history of allergy or severe intolerance to TMP-SMX, pentamidine, dapsone or atovaquone may be substituted; however there is evidence that TMP-SMX offers superior coverage for PJP, toxoplasmosis, and nocardiosis. Compared to pentamidine, it has the added benefit of cost-effectiveness and self-administration as opposed to required hospital attendance for administration. Many patients who report a history of allergy or adverse reaction to TMP-SMX (or "sulfur allergy") will be found not to be allergic; and even those who are allergic may be able to be desensitized. The evaluation and, where appropriate, removal of TMP-SMX allergy label enables the use of TMP-SMX for prophylaxis against opportunistic infections. This is a cost-effective intervention to optimize antimicrobial prescribing and reduce the risk of opportunistic infections in immunosuppressed patients.

Keywords: Trimethoprim-sulfamethoxazole, Co-trimoxazole, Drug allergy, Immunosuppression, PJP prophylaxis

INTRODUCTION

Trimethoprim and sulfamethoxazole (TMP-SMX) also known as *co-trimoxazole*, is a combination antibiotic first introduced in the 1960s and widely used due to its low cost and broad antibacterial effectiveness. In recent years it has found an important role in prevention of *Pneumocystis jirovecii* pneumonia (PJP)[1] in immunocompromised patients. However, patients who have a history of allergy to TMP-SMX (or "sulfur") may be precluded from using this effective drug and instead be prescribed suboptimal second-line agents. In this paper we focus on the reasons why TMP-SMX is superior to alternative drugs for long-term prophylaxis, and the potential benefits of delabelling or desensitization of those with a history of TMP-SMX allergy.

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http://doi.org/10.1016/j.waojou.2023.100856

Received 18 May 2023; Received in revised from 30 November 2023; Accepted 11 December 2023
Online publication date xxx

MECHANISM AND ANTIMICROBIAL COVERAGE

TMP-SMX is a combination of 2 antimicrobial agents that act synergistically to inhibit enzymes involved in the bacterial synthesis of tetrahydrofolic acid, which is an essential component for the biosynthesis of proteins and nucleic acids.[2,3]

TMP-SMX provides broad coverage against a wide range of aerobic Gram-positive and Gram-negative bacteria. TMP-SMX can be used for treatment of skin infection (*Staphylococcus aureus, including MRSA*), urinary tract infection (*Escherichia coli, Klebsiella pneumonia, Proteus mirabilis*), and respiratory tract infection (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*).[2] However, the most important indication for TMP-SMX is as first line antimicrobial prophylaxis for immunosuppressed patients.[4]

ANTIBIOTIC PROPHYLAXIS IN IMMUNOCOMPROMISED PATIENTS

Impaired cell-mediated immunity predisposes to opportunistic infections such as PJP, toxoplasmosis, or nocardiosis, whilst humoral immunodeficiency predisposes predominantly to infection with encapsulated bacteria.[5] Immunosuppressive drugs used to prevent transplant rejection or treat autoimmune or inflammatory disease often cause lymphopenia and/or impair lymphocyte activation and proliferation.[6] Therefore, long-term antibiotic prophylaxis to prevent infection in immunosuppressed patients is often recommended. Optimal antimicrobial agents for prophylaxis should be bactericidal, nontoxic, inexpensive, have few drug-drug interactions, and be effective against a broad range of pathogens.

Consensus guidelines from specialties involved in care of immunosuppressed patients including haematology, infectious disease, and organ transplantation consistently recommend TMP-SMX as the first line for PJP prevention whereas pentamidine, atovaquone, and dapsone should only be considered if TMP-SMX is contraindicated or poorly tolerated.[7-9] There are various recommended regimes for PJP prophylaxis include TMP-SMX 80/400 mg daily, or 160/800 mg daily, or 160/800 mg 3 times weekly, or 160/800 mg twice daily on 2 days per week.[1,4,10]

Indications for antibiotic prophylaxis in patients with autoimmune or inflammatory diseases on immunosuppressive treatment are not clearly stated across various guidelines and the use of PJP prophylaxis is inconsistent.[11] The inconsistent and practitioner-dependent prescription of PJP prophylaxis for patients with autoimmune and inflammatory disorders on immunosuppressive drugs is likely derived from a lack of updated clinical practice guidelines.[11]

COMPARATIVE EFFICACY OF TMP-SMX FOR PJP PROPHYLAXIS

A meta-analysis of randomized controlled trials (RCTs) involving non-HIV immunosuppressed patients demonstrated that TMP-SMX prophylaxis was highly effective in preventing PJP infections, showing a 85% reduction in PJP incidence with the number needed to prevent one PJP infection being 19 patients.[1] It should be noted that in contemporary HIV management, many patients will have undetectable viral loads and no significant immunosuppression, and hence do not require such prophylaxis.

TMP-SMX prophylaxis offers superior protection against PJP compared to aerosolized pentamidine and dapsone (Table 1). A meta-analysis of RCTs involving HIV patients showed the risk ratio for PJP of TMP-SMX versus aerosolized pentamidine was 0.59 (95% CI, 0.45, 0.76), and that of TMP-SMX versus dapsone was 0.49 (95% CI, 0.26, 0.92).[12] In another single-centre RCT, the incidence of developing PJP whilst on prophylaxis was 2.0 per 100 person-years for TMP-SMX, 10.2 for pentamidine, and 32.1 for dapsone.[13]

Only 1 randomised controlled study of very small cohort (n = 39) compared TMP-SMX versus atovaquone as prophylaxis; therefore, the result needs to be interpreted with caution (Table 1).[14] For treatment (as opposed to prophylaxis) of PJP, TMP-SMX was superior to and offered mortality benefit compared to atovaquone in a large cohort randomized controlled trial of HIV patients.[15]

Year of pub	Country (centre)	Indication for prophylaxis	Study design	TMP-SMX group	Pentamidine group	Third group	Efficacy in reducing PJP	Reference
1992	Australia (single)	HIV (secondary prophylaxis)	Retrospective controlled study	160 mg/800 mg twice a day, twice a week (n = 60)	300 mg every 4 weeks (n = 73)	ND	TMP-SMX superior (stat significant)	100
1992	Holland and Denmark (multi)	HIV (primary prophylaxis)	RCT	80 mg/400 mg daily or 160 mg/800 mg daily (n = 142)	300 mg every 4 weeks (n = 71)	ND	TMP-SMX superior (stat significant)	18
1992	America (multi)	HIV (secondary prophylaxis)	RCT	80 mg/400 mg daily (n = 154)	300 mg every 4 weeks (n = 156)	ND	TMP-SMX superior (stat significant)	16
1996	America (single)	HIV	Retrospective chart review	(1110 patient-months)	(164 patient-months)	Dapsone (418 patient-months)	TMP-SMX superior (stat significant)	101
1992	America (single)	HIV	Retrospective chart review	160 mg/800 mg twice a day, thrice a week (981 patient-months)	300 mg monthly (1166 patient-months)	Dapsone (437 patient-months)	TMP-SMX superior	102
1995	Italy (single)	HIV (primary prophylaxis)	RCT	160 mg/800 mg every second day	300 mg monthly	Dapsone (100 mg weekly) plus pyrimethamine (25 mg bi-weekly)	TMP-SMX superior (stat significant)	13
1999	America	Auto PBSCT	RCT	160/800 mg daily (n = 19)	ND	atovaquone 1500 mg daily (n = 20)	Similar	14
1993	France	HIV (primary prophylaxis)	RCT	ND	300 mg monthly	dapsone (50 mg per day) plus pyrimethamine (50 mg per week)	Similar	103

Table 1. Comparison of PJP prophylaxis. *Pub: publication; TMP-SMX: trimethoprim-sulfamethoxazole; stat: statistically; RCT: randomized controlled study; Auto PBSCT: autologous peripheral blood stem cell transplant; ND: not done*

However it is unclear how generalizable this is to the non-HIV setting.

COMPARATIVE EFFICACY OF TMP-SMX FOR PROPHYLAXIS OF OTHER OPPORTUNISTIC INFECTIONS

For HIV patients, there are other advantages of TMP-SMX in preference to aerosolized pentamidine. The time to first bacterial infection in immunosuppressed patients on trimethoprim-sulfamethoxazole prophylaxis was longer compared to aerosolized pentamidine.[16] Extrapulmonary pneumocystosis remained a concern in those receiving aerosolized pentamidine due to poor systemic absorption.[16,17] TMP-SMX prophylaxis also offers increased protection against cerebral toxoplasmosis compared to pentamidine.[13,18] A meta-analysis of RCTs involving HIV patients showed the risk ratio for cerebral toxoplasmosis of TMP-SMX versus aerosolized pentamidine was 0.78 (95% CI, 0.55, 1.11).[12]

Similar to HIV patients, cancer patients and transplant recipients are also at increased risk of *Toxoplasma gondii* infection. However controlled trials to assess effectiveness of prophylaxis regimes in these patient populations are lacking and practice guidelines mostly derive from experiences with HIV patients. The incidence of toxoplasmosis after haematological HSCT is low (3.9% in a single centre retrospective study), however mortality attributed to toxoplasmosis was very high (43.5% in the same study).[19] Given the most important risk factor for toxoplasmosis was the absence of effective prophylaxis (odds ratio 11.95),[19] the anti-toxoplasma activity of antibiotic prophylaxis is relevant. Based on evidence from retrospective case series, TMP-SMX and atovaquone are both effective and superior to aerosolized pentamidine (which does not penetrate central nervous system).[20]

COMPARATIVE COST OF TMP-SMX FOR OPPORTUNISTIC INFECTION PROPHYLAXIS

In addition to being more efficacious for opportunistic infection prophylaxis than alternative medication regimens, TMP-SMX is far less costly. The current Australian dispensed price is $1.43 (Australian dollars [AUD]) per 160 mg/800 mg tablet.[21] With a 3 times per week dosing regimen, the annual per patient cost is $223.08AUD, or $521.95AUD for daily dosing. Atovaquone in Australia costs $981.16AUD per 210 ml (750 mg/5 ml solution).[22] For a dosing regimen of 750 mg twice per day, this price would equate to an annual per patient cost of $17,053.49AUD. Economic analyses of pentamidine conducted in UK identified the minimum cost of one pentamidine clinic visit in 2009 as £47.00.[23] With current AUD to British Pound exchange rate been 1.8:1, this would equate to approximately $1,015AUD per patient per year, undoubtedly greater at the current time due to inflation. Furthermore, the personal and societal costs in terms of patient and caregiver time should be considered. Particularly in the oncologic population, increasing attention is being given to time-toxicity (the time lost to medical interventions).[24]

TMP-SMX INTOLERANCE AND ALLERGY

TMP-SMX has been reported to cause adverse reactions in up to 8% of hospitalized patients in one study.[25] Adverse reactions occurred more frequently in patients on TMP-SMX as PJP prophylaxis compared to aerosolized pentamidine.[18] Both type A non-immune-mediated adverse reaction (eg, gastrointestinal upset, cytopenia), and type B immune-mediated adverse reactions (eg, rash, anaphylaxis) are common and can result in discontinuation of TMP-SMX prophylaxis.[16,18,26] Higher dose TMP-SMX prophylaxis (160 mg/800 mg daily compared to 80mg/400 mg daily) can lead to faster onset of adverse reaction.[18]

Cytopenia is a type A adverse reaction of concern particularly in haematology, in many cases leading to drug cessation, or choice of alternative drugs in the first instance. *In vitro* studies demonstrated that trimethoprim can inhibit granulopoiesis and erythropoiesis in a dose-dependent fashion; sulfamethoxazole is also capable of impairing haematopoiesis.[27] However, the mean total white cell count at 3 and 9 months in HIV patients taking TMP-SMX as secondary PJP prophylaxis was only slightly lower than those on pentamidine.[26] Late-onset neutropenia may occur

with a 10-day course of TMP-SMX, but this adverse reaction can be mitigated with co-administration of folinic acid.[28] Risk of cytopenia is an especially important consideration for haematological patients undergoing HSCT. The effect of TMP-SMX on neutrophil engraftment post HSCT has not been widely studied, however two studies have shown no significant delay in neutrophil engraftment with using TMP-SMX as PJP prophylaxis,[14,29] suggesting that avoidance of TMP-SMX in these patients may be unnecessary particularly when alternatives are costly and less effective.

Many patients, upon experiencing adverse reactions with TMP-SMX, were immediately labeled as having "sulfur allergy", a misleading term.[30] Ironically, in the case of immediate type B (IgE-mediated) adverse reactions (eg, urticaria or anaphylaxis), trimethoprim is more often the culprit.[31–35] Incorrect allergy labeling of patients who have had an allergic reaction to TMP-SMX as "sulfur allergic" may result in them receiving trimethoprim which could be dangerous.

A range of delayed-onset type B adverse reactions can occur. Fixed drug eruption (FDE) is commonly reported after TMP-SMX or TMP alone and may be limited and relatively benign, or extensive (generalised bullous FDE).[36,37] Severe cutaneous adverse reactions (SCAR) such as Steven-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) are potentially dangerous manifestations of TMP-SMX allergy.[38–45] Although rare outcomes of TMP-SMX treatment, TMP-SMX is one of the more frequently implicated drugs in SJS/TEN.[46,47] Aseptic meningitis, manifesting as fever, headache, neck pain, and altered mental status, associated with cerebrospinal fluid changes, can occur on TMP-SMX; fortunately symptoms typically remit within 48–72 h after drug cessation.[48] It should be noted that TMP-SMX is also commonly associated with benign maculopapular exanthemata which have a low rate of recurrence on subsequent exposure.

In patients who bear a label of "sulfur allergy", it is critical to take a thorough history to ascertain the basis of the allergy label as it may be entirely spurious (eg, sulfite preservative intolerance) in which case there is no contraindication to TMP-SMX. If there is a history of rash, it is crucial to determine whether associated features such as urticaria, angioedema and collapse (to indicate acute IgE-mediated allergy) or blistering, peeling, or mucosal lesions (to indicate SCAR) were present. This history is essential for risk stratification, as the absence of such features potentially indicating a more benign reaction type and lower risk on re-exposure.

Many patients who have a history (drug allergy label) of allergy to Bactrim or "sulfur" might be found not to be allergic after appropriate evaluation.[49] De-labelling efforts have classically focused on penicillins. Whilst testing for sulfonamide allergy (TMP-SMX) has been advocated as standard of care in immunocompromised patients,[50] there are few large studies exist in the literature and no standardized protocols of evaluation have been published.

INVESTIGATION OF PATIENTS WITH A HISTORY OF TMP-SMX ALLERGY

In those with a history of an immediate reaction to a drug, skin testing (skin prick test and intradermal test [IDT]) and IgE to relevant drugs (or their components) are commonly employed as part of the allergy work-up. If the history is of a delayed reaction, IDT with delayed reading and/or patch test may be used. Whilst validated protocols exist for some drugs, particularly penicillins, the sensitivity and specificity of skin testing for TMP-SMX against the gold standard, oral provocation testing, are not well established for TMP-SMX.

Positive skin prick test (SPT) and positive in vitro IgE to trimethoprim have been reported in patients suffering immediate-onset hypersensitivity reaction to TMP-SMX (Table 2).[33,35,51] The positive SPT to trimethoprim was confirmed by oral graded challenge in Alonso et al.'s case report.[35] In the same study, all three patients had negative skin testing to sulfamethoxazole and tolerated therapeutic doses of 800 mg of sulfamethoxazole in subsequent challenge. SPT to trimethoprim was negative at the concentration of 0.1 mg/ml and positive at 1 mg/ml.[35] Given small sample size, a larger cohort is required to further validate this concentration as the optimum for detection of IgE-mediated reactions to trimethoprim.

Mode	Index reaction	In vivo test	Concentration used		Ref
SPT	Type 1	TMP	10 mg/ml in glycerol	Case report (n = 1)	33
SPT	Type 1	TMP	1 mg/ml in N/S	Case report (n = 3)	35
IDT	Various	TMP, SMX	0.1 mg/ml	Case series (n = 24)	57
PT	FDE	SMX	10% in DMSO under occlusion for 24 h	Case series (n = 24)	58
PT	FDE	TMP, SMX	10%, 20%, 50% in DMSO (step-wise increase) open topical test, apply every 12 h (up to 4 times)	Case series (n = 27)	59

Table 2. In vivo testing methods against TMP or SMX. *SPT: skin prick test; IDT: intradermal test; PT: patch test; FDE: fixed drug eruption; Type 1: consistent with type 1 hypersensitivity reaction; TMP: trimethoprim; SMX: sulfamethoxazole; N/S: normal saline*

At least 2 IgE epitopes were demonstrated to exist on TMP using the serum of a TMP-allergic individual.[52] Serum IgE to SMX has also been detected in patients with immediate-onset hypersensitivity reaction to TMP-SMX,[53] but this is rare as most immediate-onset allergic reaction to TMP-SMX are mediated by TMP. In animal and in human studies, false positive SMX antibodies have been reported in individuals receiving TMP-SMX without any apparently clinical reaction, therefore this test would not be suitable for screening.[54,55]

TMP-SMX concentration of 0.8 mg/4 mg/ml was identified as the non-irritating intradermal test (IDT) concentration for normal healthy control subjects without a history of reaction to TMP-SMX.[56] However, there have not been studies that rigorously test the sensitivity and specificity using this concentration. Ideally, oral graded challenge should be done for all patients with both positive and negative IDT, for validation purposes.

Shapiro et al used 0.1 mg/ml as the concentration for both SPT and IDT for TMP and SMX (sulfamethoxazoylpoly-L-tyrosine) (tested separately).[57] All skin test negative patients (n = 20) with previous history of sulfonamide antibiotic allergy proceeded to have a TMP-SMX oral challenge without adverse reaction. Four patients had positive SPT or IDT to SMX (2 immediate, 2 delayed IDT) but were not challenged, therefore test specificity was not determined. Considering the paucity of evidence, 0.1 mg/ml may have reasonable negative predictive value.

Patch test has been used to investigate delayed-onset hypersensitivity due to TMP-SMX. Different methodologies are used between studies (Table 2). Of 24 patients who had fixed drug eruption (FDE) with positive oral challenge to SMX alone, patch test to SMX [10% SMX in dimethylsulfoxide (DMSO) under occlusion], was positive in only 4 (17%), all on affected skin, whereas patch test on the back was negative.[58] In 27 patients with FDE and positive oral provocation test to TMP-SMX, 25 (92%) had a positive patch test to a DMSO preparation (5 to TMP, 20 to SMX), whereas a petrolatum preparation was negative.[59] A concentration of 50% was often required to elicit positive skin reaction on trunk and extremities, whereas 10% was sufficient

on the glans penis. Both TMP and SMX 50% in DMSO were negative in a series of control individuals. Therefore, patch test vehicle, drug concentration, and patch test application site are all important considerations that affect sensitivity.

Investigation for drug-related severe cutaneous adverse reactions (SCARs) is difficult and controversial. A frequent clinical scenario is when SCAR occurs in a patient receiving multiple drugs; exclusion (or confirmation) of causation can have important therapeutic implications for the patient. There is concern that in vivo skin testing (eg, patch test or intradermal test) might result in SCAR reactivation or cause severe localized reaction.[60,61] A small number of case series reported the utility of patch test in investigation of culprit drug for SCARs,[62–64] only a handful of patients were tested against TMP-SMX.[62,64] The sensitivity of the patch test in SCARs depend on the drug and the type of SCAR, eg, higher sensitivity for carbamazepine, and lower sensitivity for Steven Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) have been reported.[62–64] However, there were very few tests with TMP-SMX, so the sensitivity could not be determined. Of note, Córdoba et al described a case of patient with TMP-SMX-induced Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) who had a mild flare-up of the DRESS after patch testing.[61]

In vitro tests such as lymphocyte transformation test (LTT), enzyme-linked immunoSpot (ELISpot) assay, cytokine beads array assay can be technically challenging but offer the advantages of patient safety and allow multiple drugs (that might be implicated in causing the SCAR) to be tested at the same time. In general, high specificity and low sensitivity (with offending drug often deemed on the basis of history) have been reported in limited case series that use *in vitro* assays to test a variety of drugs (including TMP-SMX).[65,66] There are ways to increase sensitivity of the in vitro assays including T regulatory cell depletion for LTT or by combining different techniques.[65,67] However again due to the low number of cases involving TMP-SMX in these case series, a conclusion about *vitro* assays specifically for evaluation of TMP-SMX in SCAR could not be drawn. There is scope for multicenter collaborative evaluation of different in-vitro methods to maximize sample numbers.

PATHOPHYSIOLOGY OF TOXICITY/ HYPERSENSITIVITY REACTIONS TO TMP-SMX

SMX was thought to be small and chemically inert.[68] Bioactivation of SMX by cytochrome results in formation of SMX-hydroxylamine (SMX-HA) which can then oxidize to SMX-nitroso (SMX-NO). SMX-NO can act as a hapten and binds to proteins, which can elicit a specific T cell response.[68,69] There are detoxification pathways that prevent accumulation of SMX-NO such as N-acetylation of SMX and reduction of SMX-NO back to SMX-HA (by ascorbate or glutathione).[70,71] In SMX-allergic individuals, SMX- and SMX-metabolite-specific T cell clones can be isolated.[72]

Hypotheses to explain the elevated incidence of allergy to TMP-SMX in HIV patients include depletion of ascorbate and glutathione and impaired N-acetylation.[73,74] However despite an increased incidence of TMP-SMX reactions, patients with haematological malignancy do not appear to have deficiency in serum antioxidants and reduction in cytochrome activity to account for this.[75]

N-acetylcysteine (NAC) replenishes glutathione deficiency in paracetamol overdose.[76] However 2 randomized controlled studies did not show benefit of NAC in reducing incidence of TMP-SMX hypersensitivity reactions.[77,78] In addition, genetic polymorphisms in enzymes important in SMX transformation pathway do not appear to be over-represented in patients with TMP-SMX hypersensitivity compared to normal cohort.[79,80] These observations suggest that the current theory focusing on SMX-nitroso and protein adjunct as the allergen may be inaccurate.

CROSS-REACTIVITY OF SULFONAMIDE DRUGS

Sulfonamide drugs share a common (SO_2–NH_2) moiety, which is a structural feature seen in many drug classes including antibiotics, anti-virals, diuretics, COX-2 inhibitors, hypoglycaemics, and triptans.[81] Sulfonamide antibiotics contain an arylamine group at N_4 position (sulfonylarylamine) and a five- or six-membered nitrogen-containing ring at the N_1 position.[81] The majority of non-antibiotic sulfanomide drugs lack

these two additional chemical structures. Hence, allergic cross-reactivity is unlikely to exist between sulfonamide antibiotics and other sulfonamide drugs given these structural differences.

Patients with sulfonamide antibiotic allergy are often told to avoid all "sulfur drugs" but this is inappropriate. Firstly, a subset of patients who have reacted to TMP-SMX are actually allergic to TMP and not to SMX. Secondly, there is little or no evidence of cross-reactivity of immunological responses to sulfamethoxazole with non-antibiotic (non-sulfonylarylamine) sulfonamide-containing drugs. The exception is sulfasalazine, which although not an antibiotic, contains a sulfapyridine (sulfonylarylamine) moiety and hence is potentially cross-reactive.[82] There are no reports of cross-reactivity with antiviral sulfonylarylamines such as fosamprenavir.

The rare type 1 hypersensitivity reactions to sulfamethoxazole have been shown to be mediated by IgE to the 5-methyl-3-isoxazolyl group on the sulfamethoxazole molecule, an extension of the arylamine group that is lacking in non-antibiotic sulfonamide drugs.[53]

Cross-reactivity between sulfonamide antibiotics (sulfamethoxazole, sulfadiazine, sulfamethizole) has been investigated by patch testing in patients with FDE.[58] Of those with positive patch tests to SMX, 42.8% were positive to sulfamethizole and 31.8% to sulfadiazine, whilst none were positive to hypoglycaemic and diuretic sulfonamides.

Those with a history of allergic reaction to TMP-SMX have a higher risk of allergy to other drugs of *any* other class including sulfonamides and non-sulfonamides, due to a general drug allergy propensity. For example in a meta-analysis of arthritis clinical trials, those with a history of "sulfur drug" allergy had a higher risk of reacting to the sulfonamide celecoxib, but the risk was the same for other non-steroid anti-inflammatory drugs and for placebo.[83] Similarly, in a very large general practice database series,[84] whilst a reaction to a sulfonamide-containing antibiotic was associated with an increased risk of allergy to a non-antibiotic sulfonamide (adjusted odds ratio, 2.8; 95% confidence interval, 2.1 to 3.7) there was an even higher risk of allergic reaction to penicillin (adjusted odds ratio, 3.9; 95% confidence interval, 3.5 to 4.3), clearly not mediated by cross-reactivity but representing an underlying predisposition to drug allergy.

DRUG ALLERGY DE-LABELLING TO TMP-SMX

The majority of drug allergy de-labelling effort had been focused on penicillins. Despite a high incidence of self-reported penicillin allergy (10% of general population), the incidence of true penicillin allergy remains low after drug allergy assessment (less than 1%).[85] The 4 features that are associated with positive penicillin allergy test outcome are allergy index reaction less than 5 years ago, history of angioedema (or anaphylaxis), severe cutaneous adverse reaction (SCARs), and medical treatment required for the allergy index reaction.[86]

In a mostly non-immunosuppressed patient population with self-reported "sulfa antibiotic allergy", oral drug challenge to TMP-SMX was safely conducted after excluding SCARs or organ failure associated with index reaction. In a series of 204 patients, 94% tolerated direct oral TMP-SMX challenge without reaction; of those challenge negative patients who reported subsequent TMP-SMX treatment, 83% tolerated a treatment course of TMP-SMX.[49] Those who passed oral challenge had a longer time since index reaction compared to those who failed challenge (mean 23.4 years vs. 6.5 years). A recent study demonstrated that 43 of 45 patients (96%) with reported non-severe allergy to sulfonamide or TMP-SMX had a negative direct oral challenge and their allergy labels were subsequently removed.[87]

There was a higher risk of unsuccessful oral drug challenge to TMP-SMX in HIV-positive patients with a history of non-life-threatening adverse reactions to TMP-SMX (about 64% in a small study, some to TMP, most to SMX).[88] Given the increased incidence of adverse reaction of HIV patients to TMP-SMX compared to general population, there has been a focus on desensitization rather than delabelling in HIV patients with prior history of TMP-SMX hypersensitivity. Desensitization involves the gradual reintroduction of the drug, starting with a dose thought too low to provoke a reaction, using fractionated doses, gradually increasing to reach full therapeutic dose.

A meta-analysis of three RCT comparing TMP-SMX desensitization vs re-challenge in HIV positive patients with prior history of TMP-SMX hypersensitivity reported a lower incidence of reactions and higher continuation rate a 6 months with desensitization compared to re-challenge.[89] However it should be noted that desensitization protocols require ongoing regular use of the medication to prevent re-sensitisation. Thus, in patients whose drug compliance cannot be guaranteed, drug challenge may prove more useful as it can enable delabelling of the allergy, and therefore allowing ongoing intermittent drug use.

DESENSITIZATION PROTOCOLS

Numerous TMP-SMX desensitization protocols exist in the literature, most derived from research in HIV patients (Table 3). These protocols vary in patient selection, starting dose, dosing interval, duration to therapeutic dose, and maintenance dose. Often these studies recruit low-risk patients with self-reported previous rash, pruritus, fever, or gastrointestinal complaints to TMP-SMX. Because many studies did not include a confirmatory allergy test, patients who underwent "successful desensitization" may include some patients who were not actually allergic. One study did apply TMP-SMX patch test prior to desensitization.[90] However those who reacted were those whose patch test was negative; presumably due to low sensitivity of the method (4.5% and 9% TMP-SMX in paraffin).[90]

Fever and rash remains a concern even after patients initially tolerate desensitization and can lead to drug cessation in long term follow-up.[91-94] Most delayed reactions occur within 2–3 weeks of desensitization protocol completion.[90,91,93,94] However, it is possible for delayed reactions to occur up to 2–3 months after commencement.[92-94]

Acute systemic reaction is listed in the exclusion criteria for many studies that assess TMP-SMX desensitization.[93-95] However, successful desensitization in those with previous suspected anaphylaxis to TMP-SMX has been reported.[91] In the case of a history of FDE, a 2013 EAACI position paper endored consideration of drug desensitization.[96] Guidelines usually recommend against desensitization in patients who have a history of severe or life-threatening reaction.[97] However, successful desensitization to TMP-SMX in 2 patients with a history of SJS (starting with extremely low dose) has been reported.[98] The desensitization was attempted as a last resort after the patients failed several other methods of PJP prophylaxis. For those who fail initial TMP-SMX desensitization, protocol adjustment by prolongation is a consideration, which may allow more patients to convert to TMP-SMX.[95]

Starting dose T/S	Dosing interval	Duration*	N =	HIV	Number of acute Success*	Number of delayed reaction*	Reference
0.004 mg/0.002 mg	1-hr-ly	5 h	22	+	19 (86%)	3 (17%*)	91
1 µg/0.2 µg	0.5-hr-ly	6 h	44	+	44 (100%)	4 (9%)	95
2 ng/10 ng	variable	2 days	45	+	37 (82%)	10 (27%)	92
0.8 mg/4 mg	variable	3 days	48	+	40 (83%)	3 (8%)	93
0.4 mg/2 mg	12-hr-ly	5 days	17	+	15 (88%)	ND	104
10 mg/50 mg	variable	6–13 days	97	+	91 (94%)	8 (9%)	94
0.4 mg/2 mg	24-hr-ly	10 days	19	+	19 (100%)	4 (21%)	90
0.4 mg/2 mg	24-hr-ly	10 days	28	+	23 (82%)	4 (17%)	105

Table 3. Comparison of different desensitization protocols in literature. *Duration*: duration taken to achieve therapeutic dose; acute success rate*: rate of tolerating desensitization protocol by the end of the protocol (include patient who developed adverse reaction during the protocol but persisted to receive maximum dose and first maintenance dose); rate of delayed reaction*: rate of patients initially tolerated desensitization, but later developed adverse reaction during the follow-up phase and led to drug cessation; ND: not documented; hr: hour; 17%*: one of 19 was excluded from analysis due to death from infection.*

Our understanding of the optimal TMP-SMX desensitization protocol is limited. *In vitro* testing for lymphocyte activation and tolerance markers at different stages of and after desensitization may shed light on the mechanism of TMP-SMX desensitization. Further research is required to determine optimal protocols and whether protocol variation according to reaction type and other patient factors will be beneficial. Many units are currently using TMP-SMX desensitization protocols on immunosuppressed patients, which were developed and validated on HIV cohorts.

FUTURE RESEARCH

Observational studies evaluating the health economic implications of TMP-SMX allergies and their evaluation may be beneficial. Further studies are required to validate risk stratification and testing and challenge protocols. Penicillin allergy "delabelling" has become widely accepted and whilst TMP-SMX has more limited application, it can be extremely valuable and similar procedures should be developed. Again similar to penicillin allergies,[99] artificial intelligence could be applied to the identification and evaluation of described TMP-SMX allergies.

SUMMARY

TMP-SMX remains the optimal agent for antibacterial prophylaxis in immunosuppressed patients for reasons of efficacy, cost and patient convenience. It may be (probably needlessly) avoided in patients with haematological malignancies or transplantation due to previous adverse drug reactions or perceived myelosuppressive risk. Avoidance due to a history of an adverse reaction or a label of "sulfur allergy" should be investigated because often the label is incorrect, and the majority of patients are found not to be allergic with appropriate evaluation including oral challenge.

In vitro diagnostic testing for TMP-SMX allergy is not currently available. *In-vivo* tests (skin prick, intradermal and patch testing) are not validated but may provide supportive information when

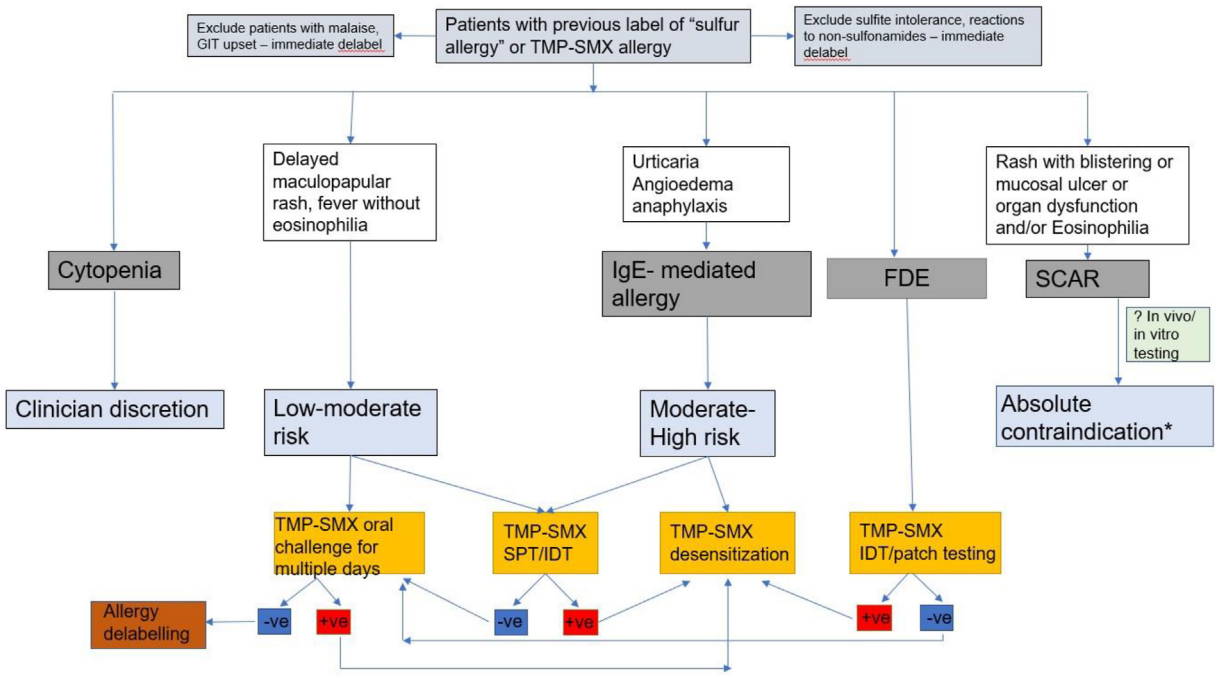

Fig. 1 Proposed flow chart of TMP-SMX allergy work-up. Figure Legend: Evaluation of TMP-SMX (or sulfur) allergy starts with careful history to classify and stratify reactions. For delayed rash and suspected IgE-mediated allergy, risk stratification on the basis of time from index reaction event and description of reaction severity can be helpful to decide whether to go directly with TMP-SMX oral challenge, TMP-SMX SPT/IDT, or TMP-SMX desensitization. Negative SPT, IDT, or patch testing should be followed by TMP-SMX oral challenge for confirmation of allergy de-labelling. For patients with positive SPT, IDT, patch testing, or oral challenge, TMP-SMX desensitization can be considered. *desensitization for SCAR is considered to be contraindicated but has rarely been reported and could be considered in specialist centres. TMP-SMX: trimethoprim-sulfamethoxazole; FDE: fixed drug eruption; SCAR: severe cutaneous adverse reaction; SPT: skin prick test; IDT: intra-dermal test; -ve: negative; +ve: positive

conducted in specialist units (Fig. 1). An oral challenge in selected low-risk cases may allow removal of the allergy label. Desensitization may be possible in those with intermediate allergy risk (and even some high risk patients), including those with a positive challenge test reaction. Investigation of TMP-SMX allergy and TMP-SMX desensitization tend to remain hospital- or specialist-based procedures due to the current lack of standard risk stratification guidelines and testing/desensitization protocols. However, substantial clinical, patient-centered and economic gains may be made through the establishment of such programs using validated procedures, in order to reinstate the use of this effective and convenient therapy in such patients.

Abbreviations

TMP-SMX, trimethoprim-sulfamethoxazole; PJP, Pneumocystis jirovecii pneumonia; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplant; RA, rheumatoid arthritis; SPT, skin prick test; IDT, intradermal test; FDE, fixed drug eruption; DMSO, dimethylsulfoxide; SCAR, severe cutaneous adverse reaction; SJS/TEN, Steven Johnson syndrome/ Toxic Epidermal Necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; LTT, lymphocyte transformation test; ELISpot, enzyme-linked immunoSpot; SMX-HA, Sulfamethoxazole-hydroxylamine; SMX-NO, sulfamethoxazole-nitroso.

Funding

Nil.

Availability of data and material

Not applicable.

Author contribution

Dr Wei-I Lee contribute to 90% of the write-up and content manuscript, the other authors contribute to remainder of the manuscript and edition.
All authors consent for publication for this manuscript to WAO journal.

Ethics approval

Not applicable.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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