



Sulfonamide Hypersensitivity

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Accepted: 18 June 2021

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Abstract

Sulfonamides, particularly antimicrobial sulfonamides, have been implicated as a common cause of a spectrum of hypersensitivity reactions. Immediate IgE-mediated reactions have been reported but are much less common than delayed cutaneous reactions. Delayed cutaneous reactions range from benign exanthems to severe cutaneous reactions such as Stevens Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms. Sulfonamides can be subclassified as antimicrobial sulfonamides and non-antimicrobial sulfonamides, which are also distinguished by key structural differences, resulting in very low risk of cross-reactivity between these two subclasses. Immediate and delayed skin testing and in vitro testing remain limited as options in evaluating antimicrobial sulfonamide hypersensitivity. Drug challenges continue to play an important role in the evaluation of both immediate and delayed reactions, with a growing body of evidence for the safety of direct challenges regardless of human immunodeficiency virus infection status. While numerous “desensitization” protocols have been described for the management of antimicrobial sulfonamide hypersensitivity, there is limited evidence that such procedures are successful because of an induction of tolerance.

Keywords Sulfonamide · Trimethoprim-sulfamethoxazole · Hypersensitivity · Allergy · Desensitization · Severe cutaneous adverse reaction

Introduction

Sulfonamides represent a diverse class of compounds that share a common SO_2NH_2 moiety. Since their discovery in the early 1900s, sulfonamides have been used for an increasingly wide range of clinical applications. Even with the rise of antimicrobial resistance, antimicrobial sulfonamides remain clinically relevant, as with the use of trimethoprim-sulfamethoxazole (TMP-SMX) as first-line therapy for the treatment and prevention of *Pneumocystis jirovecii* pneumonia (PJP) in immunosuppressed hosts [1]. Adverse reactions to sulfonamides, particularly antimicrobial sulfonamides, are common and include hypersensitivity reactions. In fact, antimicrobial sulfonamides are one of the most commonly listed allergies in electronic health records, affecting approximately 7% of patients exposed to these agents [2]. These have also been implicated in a range of cutaneous

reactions ranging from benign exanthems to severe cutaneous adverse reactions (SCARs) such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). Given the severity of some of these reactions, there has been much discussion over the last two decades regarding cross-reactivity between different agents within the class of sulfonamides. This review provides an overview of hypersensitivity reactions to sulfonamide agents including the clinical features and underlying pathophysiologic mechanisms, clinical evaluation with a focus on recent literature supporting the use of direct challenges as an important tool for allergists, and cross-reactivity.

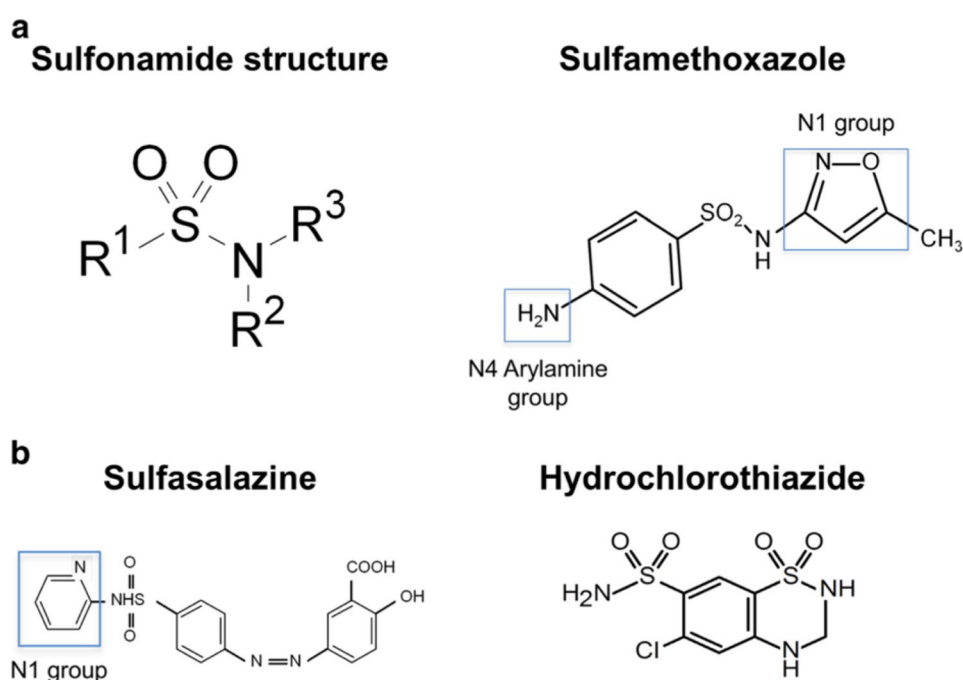
Chemical Structure and Properties

Sulfonamides were first synthesized in 1909 by German chemists seeking to develop novel dyes for textiles [3]. While in vitro antibacterial properties were noted for some of these dyes as early as 1919, it was not until the 1930s that potential clinical benefit was demonstrated. In 1935, Gerhard Domagk published his landmark discovery that

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Fig. 1 Sulfonamide structure: anti-microbial and non-antimicrobial sulfonamides



prontosil, a pro-drug whose active metabolite is sulfanilamide, was effective in preventing and treating otherwise fatal streptococcal infections in mice, for which he received the Nobel Prize in Physiology or Medicine in 1939 [3, 4]. This sparked further interest in sulfonamides leading to subsequent drug development for a wide range of clinical uses.

Sulfonamides are compounds defined by a shared SO_2NH_2 moiety and are derivatives of *p*-aminobenzene-sulfonamide (sulfanilamide) [5]. They can be classified as antimicrobial sulfonamides and non-antimicrobial sulfonamides, with key structural differences distinguishing the two groups; see Fig. 1. The first distinguishing feature is an aromatic amine group at the N4 position, which sulfonamide antimicrobials contain but most non-antimicrobial sulfonamides do not. The second distinguishing feature is a five- or six-member heterocyclic aromatic ring with one or more

nitrogen at the sulfonamide N1 position, which the antimicrobial sulfonamides contain and the non-antimicrobial sulfonamides do not [6]. Examples of antimicrobial and non-antimicrobial sulfonamides are summarized in Table 1. The structural definition of sulfonamides is important to keep in mind; colloquial terms such as “sulfa drug,” historically used to refer to sulfonamide antimicrobials, have contributed to confusion, with some patients unnecessarily avoiding all medications with a “sulf-” prefix which contain sulfur. There are many compounds that contain sulfur, sulfite, or sulfate salts, such as penicillins, cephalosporins, omeprazole, ranitidine, clopidogrel, captopril, albuterol sulfate, ferrous sulfate, as well as sulfite preservatives in foods, to name a few [7]. There is no risk of cross-sensitivity between sulfonamides and medications that contain sulfur but not the SO_2NH_2 moiety.

Table 1 Examples of antimicrobial and non-antimicrobial sulfonamides

Antimicrobial sulfonamides			
Sulfamethoxazole	Sulfamerazine	Sulfamethizole	Sulfamoxole
Sulfacetamide	Sulfanilamide	Sulfamerazine	Sulfadiazine
Sulfamethazine	Sulfisoxazole	Sulfapyridine	Sulfasalazine (metabolized to sulfapyridine)
Non-antimicrobial sulfonamides			
Tamulosin	Ibutilide	Sotalol	Topiramate
Acetazolamide	Methazolamide	Dorzoalamide	Celecoxib
Furosemide	Bumetanide	Metalozone	Torsemide
Hydrochlorothiazide	Chlorthalidone	Glimepiride	Glyburide
Glipizide	Naratriptan	Sumatriptan	Probenecid

Mechanisms of Hypersensitivity Reactions to Sulfonamides

There are multiple mechanisms underlying different sulfonamide hypersensitivity reactions, summarized in Table 2. For IgE-mediated reactions, two allergic epitopes have been identified. One of these is the single methyl group bound to the N1 heterocyclic ring at the carbon atom beta to the sulfonamide substitution, and the other is the N4-aromatic amine structure, the five- or six-member heterocyclic aromatic ring with one or more nitrogen at the sulfonamide N1 position [8, 9].

For non-IgE-mediated reactions, Gell and Coombs type II and III hypersensitivity reactions have been reported [10–13]. Type IV hypersensitivity reactions are more common. Sulfonamides or their metabolic intermediates may be recognized by T lymphocytes through pro-hapten formation or through the pharmacological interaction with immune receptor (p-i) concept, where they bind directly to HLA or T cell receptor molecules [14–16]. In particular, sulfonamide metabolic intermediates appear to be a significant driver of these delayed reactions [15]. Sulfonamides are metabolized in the liver by two pathways, *N*-acetylation and *N*-oxidation. Acetylation is mediated through *N*-acetyltransferase (NAT2), resulting in non-toxic metabolites that are renally excreted [17]. There is a bimodal distribution of NAT2 expression in the general population, with individuals with a homozygous poor metabolizer genotype demonstrating slow acetylation [18]. With slower rates of metabolism through acetylation, more substrate is available for alternative pathways of oxidation. *N*-oxidation of the primary arylamine moiety is mediated by cytochrome P450 isoenzyme 2C9 and results in the formation of hydroxylamines [19, 20]. These hydroxylamine metabolites can then be oxidized to form a reactive intermediate-nitroso species or be reduced with glutathione. Excess nitroso species can form non-catalytic adducts of cellular proteins forming haptens which are immunogenic [17]. Clinically, Shear et al. observed an inverse relationship between the rate of *N*-acetylation and development of drug hypersensitivity reactions. Compared to children who had a slow acetylator phenotype, children who demonstrated rapid acetylation of the amine group at the primary arylamine position on sulfamethoxazole were at lower risk for development of hypersensitivity reactions [21].

Table 2 Mechanisms of immunologic drug reactions to antimicrobial sulfonamides

Gell and Coombs Classification (References)
Type 1 (8,9)
Type 2 (11,13)
Type 3 (10,12)
Type 4 (14–16)

Further alterations in cellular metabolism, such as oxidative stress, can affect the production of reactive metabolites. In settings of oxidative stress, the decreased ratio of reduced/oxidized glutathione creates an unfavorable redox state that both promotes a shift to increased nitroso species and impairs the clearance of these species [22, 23]. This is one proposed mechanism underlying increased trimethoprim-sulfamethoxazole (TMP-SMX) hypersensitivity observed in human immunodeficiency virus (HIV)-infected individuals [24]. In HIV, intracellular viral replication results in oxidative stress through the production of large amounts of the Tat viral protein which subsequently inhibits superoxide dismutase and leads to a shift favoring oxidized glutathione [17]. However, two randomized controlled trials in HIV-infected subjects evaluating the use of *N*-acetylcysteine to increase intracellular glutathione demonstrated no effect in preventing TMP-SMX hypersensitivity [25, 26]. In addition, the slow-acetylator phenotype has not been demonstrated to be particularly predictive of hypersensitivity reactions in this population [27]. Taken together, this suggests that there are other factors beyond oxidative metabolic factors contributing to the development of TMP-SMX hypersensitivity in HIV-infected patients.

With regard to predisposing genotypes or polymorphisms to sulfonamide hypersensitivity, significant associations have not yet been identified in the general population. Evaluation of small nucleotide polymorphisms (SNP) in genes encoding cytochrome b5, cytochrome b5 reductase, and NAT2 in subjects with sulfonamide hypersensitivity compared to controls did not reveal any significant associations [28]. A subsequent genome-wide association study did not identify any significant SNPs that were likely risk factors for sulfonamide hypersensitivity reactions [29]. However, there may be significant predisposing genotype factors for sulfonamide hypersensitivity in specific patient populations such as HIV-infected subjects and subjects with sulfonamide-related SCARs. In HIV-infected patients, a SNP in glutamate cysteine ligase catalytic subunit (GCLC), involved in glutathione synthesis, was associated with reduced GCLC expression and TMP-SMX hypersensitivity reactions [30]. There has been reported association of three HLA alleles (HLA-B*15:02, HLA-C*06:02, and HLA-C*08:01) with SJS and TEN associated with TMP-SMX [31]. HLA-B allele screening was not helpful in preventing SCARs related to sulfonamides in a Thai population [32]. There may be a relationship between HLA variants and risk of developing TMP-SMX-attributed drug-induced liver injury (DILI). Evaluation for genetic factors predisposing to TMP-SMX-attributed DILI in a prospective US cohort revealed an association with HLA-B*14:01 in European Americans and potential association with HLA-B*35:01 in African Americans [33].

Clinical Presentation

Adverse reactions to sulfonamides are common. In review of electronic health records (EHR) of three large health systems in the United States (US), an allergy to sulfonamide antibiotics was labeled in 5.1–7.4% of patients [2, 34, 35]. In the Partners HealthCare System cohort, sulfonamide antibiotics were the 2nd leading cause of immediate and non-immediate hypersensitivity reactions behind penicillin and were the leading cause for fixed drug eruptions and SCARs [36].

In particular, HIV-positive patients demonstrate higher rates of hypersensitivity reactions to TMP-SMX compared to the general population. In initial studies of patients with AIDS from the 1980s, 33–50% developed cutaneous reactions [37, 38]. In a prospective study of 136 HIV-positive patients with a history of PJP or cerebral toxoplasmosis who were treated with TMP-SMX, 48 of 136 (35%) developed a delayed rash after a median of 9 days. Of these cutaneous reactions, 85% were maculopapular exanthema; three cases were severe including 1 case of SJS [39]. Evaluating for risk factors associated with development of adverse drug reactions within this group, there was no association with slow acetylation genotype or phenotype, previous reaction to TMP-SMX, viral load, or use of concomitant steroids [39]. More recent retrospective studies of HIV-positive patients with PJP who were treated with TMP-SMX have demonstrated relatively unchanged rates of cutaneous reactions, ranging from 19 to 44% [40, 41]. A pharmacogenomic study evaluating 136 HIV-positive patients, 53 with a history of TMP-SMX hypersensitivity, revealed no significant difference in polymorphisms of genes in the major histocompatibility complex compared to controls [42].

Immediate reactions to sulfonamide antibiotics are less common than delayed hypersensitivity reactions [2]. Reactions may be isolated to immediate cutaneous manifestations, including typical urticaria and contact urticaria, but can also include systemic reactions including anaphylaxis [43, 44]. Rarely, trimethoprim has been reported as a cause of hypersensitivity reactions including anaphylaxis [45]. While non-antimicrobial sulfonamides lack the N4-arylamine structure identified as one of the IgE-binding epitopes of sulfonamide antimicrobials, immediate systemic hypersensitivity reactions have been reported [46].

Delayed reactions to sulfonamides most commonly present with cutaneous manifestations, but a wide range of other organs can be affected. In a prospective study involving 1121 hospitalized patients receiving TMP-SMX, cutaneous reactions and upper gastrointestinal reactions were the most commonly reported, with 3.3% and 3.2% reported

respectively [47]. These cutaneous reactions were characterized as erythema, itch, or urticaria, with half of reactions occurring within 72 hours of TMP-SMX initiation and the rest occurring within 13 days of initiation. All reactions were self-limited with resolution after TMP-SMX discontinuation [47]. This predominance of cutaneous reactions continues to be observed in EHR-labeled sulfonamide allergy [36]. The occurrence of cutaneous reactions may be dose-dependent; a retrospective review of patients taking high-dose TMP-SMX (≥ 4 double strength tablets/day) found a statistically significant increase in occurrence of rash compared to patients receiving standard dosing, with 1.8% and 0.2% developing a rash respectively [48]. Further characterizing cutaneous reactions, a retrospective review of 191 Thai patients receiving TMP-SMX observed that maculopapular rashes were most common, affecting 37.7%, followed by fixed drug eruptions (22%). SCARs were reported in 11.5%, with SJS and DRESS accounting for 8.4% and 3.1% of these reactions, respectively; there was no statistically significant difference between HIV infection status [49]. This represents a significantly higher rate of SCARs compared to previous studies regardless of HIV infection status and has not been replicated.

Sulfonamide antimicrobials are commonly implicated as a cause of SCARs and have been identified as the leading cause in one cohort study [36]. The term SCARs encompasses a number of different reactions including SJS/TEN, DRESS, and acute generalized exanthematous pustulosis (AGEP). There is evidence demonstrating that sulfonamide antimicrobials may cause SJS/TEN most commonly out of the SCARs, followed by DRESS and then by AGEP. Non-antimicrobial sulfonamides have been reported as a cause of SJS much less commonly than antimicrobial sulfonamides [50].

In the EuroSCAR study surveilling for SJS and TEN, TMP-SMX accounted for 24 of 379 cases (6.3%) and was the most commonly implicated antimicrobial; sulfasalazine and sulfadiazine each accounted for 5 of 379 cases (1.3%) [51]. A US study of 82 patients with TEN also demonstrated that TMP-SMX was the most commonly implicated drug, accounting for 36.6% of cases [52]. In contrast, DRESS appears to be less commonly caused by TMP-SMX compared to other agents. In the prospective RegiSCAR study on DRESS, TMP-SMX was implicated in 2 of 115 (1.7%); sulfasalazine and dapsone were implicated in 7% and 2.6% of cases respectively [53]. Similarly, in Australia, “sulfur antimicrobials” accounted for 50% and 21% of SJS and TEN occurrences respectively, compared to only 14% of DRESS occurrences [54]. Interestingly, a seasonal variation of TMP-SMX-attributed SJS/TEN was suggested in a small case series of 50 patients, but this was not replicated in the much larger SCAR/

EuroSCAR studies [55]. Compared to SJS/TEN and DRESS, AGEP is much less common, with case reports implicating sulfamethoxazole [56].

Other delayed cutaneous reactions have been associated with sulfamethoxazole including psoriaform dermatitis, acute febrile neutrophilic dermatosis (Sweet syndrome), symmetrical drug-related intertriginous and flexural exanthema (Baboon syndrome), and linear IgA bullous dermatitis [57–61].

Numerous extracutaneous delayed reactions have been reported in association with sulfonamides, as noted in Table 3. Sulfonamide antimicrobials, particularly TMP-SMX, have been associated with drug-induced liver injury (DILI). A prospective study of DILI in the US demonstrated TMP-SMX as one of the most common single causative agents of DILI [62]. Rare occurrences of non-antimicrobial sulfonamides as well as trimethoprim alone as a cause of DILI have also been described [62, 63].

Clinical Evaluation and Testing

The clinical evaluation of potential hypersensitivity reactions to sulfonamides begins with a thorough history and physical, as outlined in numerous drug allergy consensus guidelines [64, 65]. In general, subsequent skin and in vitro testing should be guided by the pre-test probability of a given reaction and its suspected underlying pathophysiologic mechanism. Skin testing has been evaluated for patients with immediate reactions. In a study of 34 patients with a history of immediate reactions to TMP-SMX, ranging from cutaneous-only reactions with urticaria to anaphylaxis, Gruchalla and Sullivan evaluated the performance of a sulfamethoxazole poly-L-tyrosine conjugate developed for skin testing [66]. They demonstrated that 29% had positive skin tests. Serial skin testing and sulfamethoxazole-IgE by radioallergen sorbent tests (RAST) were performed on 3 patients, one with a history of anaphylaxis and two with cutaneous-only reactions. The patient with a history of anaphylaxis lost skin reactivity within 3 months of first positive skin test, and of

the two with cutaneous-only reactions, one lost skin reactivity within 1 year of first positive skin test. Sulfamethoxazole-IgE decreased in two of the 3 patients and was negative in the other [66]. This sulfamethoxazole conjugate has never been commercially available. Skin testing can be performed with native TMP-SMX with a non-irritating intradermal concentration using a 1:100 dilution of the 16 mg/80 mg per mL concentration of the intravenous formulation of TMP-SMX [67]. Given the unclear positive and negative predictive values of such testing, some experts only perform skin testing in those with a convincing history of anaphylaxis [6].

Delayed skin prick and intradermal testing have also been evaluated. In a study of 34 HIV-positive patients with a history of cutaneous reactions to TMP-SMX, delayed prick and intradermal testing were performed prior to performing an 11-day desensitization procedure. While none of the patients had positive skin testing, 14 of the 34 subjects went on to develop cutaneous reactions. Shapiro et al. evaluated 24 immunocompetent patients with a history of an adverse reaction to TMP-SMX, 16 of which had cutaneous reactions, with immediate and delayed prick and intradermal testing. Two patients were positive on immediate testing, one with a history of diarrhea with TMP-SMX and the other with unknown reaction. Two patients were positive on delayed intradermal testing, one with a history of cutaneous reaction and the other with unknown reaction [68].

Patch testing has also been performed with overall unimpressive results. In a small study investigating a TMP-SMX desensitization protocol in 19 HIV-positive patients, four patients reacted to TMP-SMX after completing the desensitization protocol, and patch testing in all four patients was negative [69]. Kardaun et al. reported an HIV-positive patient who had negative TMP-SMX patch testing prior to undergoing a desensitization procedure and subsequently developed a non-pruritic flare at the previous patch testing sites during the procedure [70]. There are mixed results regarding patch testing in evaluating fixed drug eruptions (FDE) to TMP-SMX. Positive patch testing in the setting of TMP-SMX-associated FDE has been reported [71]; however, in a study of 27 patients with FDE from TMP-SMX, tape-stripping followed by patch testing was negative in all patients. Interestingly, open application of TMP-SMX in dimethyl sulfoxide was much more sensitive in comparison, yielding a positive result in 25 of the 27 patients [72]. In another study of 24 patients with FDE from SMX confirmed by oral challenge, patch testing was positive in 20% [73]. Rarely, a FDE reaction may be caused by the trimethoprim component [74]. There is a single report of a patient with TEN who had a positive sulfamethoxazole patch test when applied to previously affected skin [75]. While these are small studies, taken together, delayed prick and intradermal testing and patch testing appears to be of limited value in both HIV and immunocompetent subjects.

Table 3 Extracutaneous delayed reactions to sulfonamide antimicrobials

Extracutaneous delayed reactions (references)

Drug-induced liver injury (57,58)
Drug-induced pancreatitis (59)
Hemorrhagic pancreatitis (60)
Eosinophilic Gastritis (61)
Cytopenias (62–65)
Acute Kidney Injury (66,67)
Aseptic meningitis (68)

A number of *in vitro* assays have been used to evaluate both immediate and delayed sulfonamide reactions. However, these are still limited to a research setting as none are validated clinically. As such, the use of *in vitro* assays is not recommended as part of the evaluation of sulfonamide hypersensitivity at this time [76, 77]. As discussed above, for immediate reactions, IgE-binding epitopes of sulfamethoxazole have been identified and specific IgE assays developed [9]. For delayed reactions, assays such as lymphocyte transformation test (LTT) and the lymphocyte toxicity assay (LTA) have been investigated with disappointing results. The LTT evaluates the proliferation of drug-specific T cells upon exposure to a drug in question. In a study of 18 patients with delayed eruptions to TMP-SMX, LTT was positive in only 3 of 24 patients [78]. There are case reports of positive LTT to sulfonamides in the setting of drug-induced acute pancreatitis and diffuse exanthema [79, 80]. The LTA assesses lymphocyte cell death with exposure to culprit drug. Shapiro et al. reported ten patients with delayed reactions to TMP-SMX who underwent LTA testing, with 2 of the 10 yielding a positive LTA result [68]. In a more recent study comparing ten patients with delayed reactions to TMP-SMX and ten control subjects, there was no difference in LTA results between the two groups [81]. Other markers such as granzyme B secretion and CD107a expression by flow cytometry after culture with TMP-SMX have been reported as elevated compared to control in subjects with TMP-SMX reactions [79].

Diagnostic drug provocation testing has also been evaluated. Initially, most of the clinical data came from HIV-positive populations. Leoung et al. reported a randomized, double-blind, controlled study comparing direct challenge with single dose of TMP-SMX with a 6-day oral outpatient dose-escalation in HIV-positive patients with a history of a mild-moderate rash or fever related to TMP-SMX. They demonstrated that over 90% tolerated TMP-SMX at the end of the 6-day blinded period in both groups [82]. In another study of 25 HIV-positive patients, 72% passed direct single-dose challenge [83].

More recently, there have been additional studies in non-HIV-infected populations. Krantz et al. reported 204 patients with history of immediate or delayed TMP-SMX reactions, excluding severe delayed reactions such as SCARs, who underwent single or two-dose drug challenge based on predetermined features of index reaction. In this cohort, only 9 of the 204 were HIV-positive. Oral challenge was tolerated in 191 of 204 (94%) patients. In the HIV-positive group, oral challenge was tolerated in 7 of 9 (79%). For the 13 patients who failed oral challenge, the vast majority of reactions were cutaneous-only, and none were severe [84]. Increased risk of challenge failure was associated with HIV-positive status and reduced time since index reaction; the median time elapsed from index reaction between those who passed the

TMP-SMX challenge and those who failed was 20 years and 3 years, respectively [84]. In another study of 27 renal transplant patients who underwent single-dose oral challenge with TMP-SMX, 20 of the 27 patients tolerated challenge. Of the remaining seven who failed the challenge, all reactions were mild and self-limiting [85]. Grinlington et al. reported a retrospective study of 46 children with adverse reaction to TMP-SMX. Sixteen patients had symptoms of immediate reaction, 27 had delayed reactions, and three had reactions of unknown timing. Thirty-one of 46 (67%) patients passed oral challenge with TMP-SMX. For the 15 patients who failed the challenge, seven reactions were immediate, of which two were considered severe with one patient developing facial angioedema and abdominal cramping and another developing chest tightness, shortness of breath, abdominal cramping, and vomiting within 1 h of TMP-SMX administration. Eight reactions were delayed, four of which were classified as severe [86]. Taken together, direct provocation testing to evaluate for TMP-SMX hypersensitivity is generally tolerated in the majority of patients; additional prospective studies are needed to further characterize the risks of challenge failure across different populations.

Cross-Reactivity

Before discussing the nature of cross-reactivity between sulfonamide medications, it is important to emphasize a few principles foundational to the concept of cross-reactivity between different structurally similar medications. Cross-reactivity between structurally similar medications is mediated through the recognition of a shared epitope of either the drug molecule itself, a metabolite, or hapten-carrier molecule which elicits a subsequent immunologic response. This is important to keep in mind as different moieties are implicated in different immunologic reactions, and a hypothesis of cross-reactivity falls apart when the clinical reactions and suspected underlying pathophysiology do not align with a shared suspected moiety. As discussed above, immediate IgE-mediated reactions are mediated by specific IgE against one of two epitopes, the N1 substituent or the N4 aromatic amine structure. These moieties are present in antimicrobial sulfonamides but not in non-antimicrobial sulfonamides. As such, there would be no expectation for cross-reactivity between these two groups for IgE-mediated reactions. Similarly, this aromatic amine moiety has also been implicated in DRESS and SJS/TEN, and thus, non-antimicrobial sulfonamides would not be expected to cross-react if an antimicrobial sulfonamide was attributed as the culprit of one of these reactions.

Even if a patient develops reactions to two structurally similar medications marked by clinical reactions consistent with a shared moiety, it cannot be assumed that the reactions

were due to cross-reactivity between the two. This is illustrated by the following two studies which looked at patients with a history of an adverse drug reaction and their risk of developing subsequent adverse reactions to both structurally similar and distinct medications. In a large retrospective cohort study from the UK, patients with a history of immediate or delayed reactions to penicillin were at increased risk for having adverse reactions with subsequent administration of both cephalosporins and antimicrobial sulfonamides [87]. In another study of the same cohort, Strom et al. compared patients with or without a presumed allergic reaction within 30 days of antimicrobial sulfonamides who received a non-antimicrobial sulfonamide greater than 60 days later [88]. The primary outcome was development of presumed allergic reaction within 30 days of the first prescription of a non-antimicrobial sulfonamide; they also evaluated the development of presumed allergic reaction to penicillin in both groups. Patients with a reaction to an antimicrobial sulfonamide had increased odds of reaction to a non-antimicrobial sulfonamide, with an adjusted odds ratio (OR), 2.8 (95% CI, 2.1–3.7]. Notably, patients with an allergic reaction to an antimicrobial sulfonamide had an even greater increased odds of reaction to penicillin, with an adjusted OR, 3.8 (95% CI, 3.4–4.2]. Since histories of reaction to antimicrobial sulfonamides and structurally dissimilar penicillin are both risk factors for development of reactions to non-antimicrobial sulfonamides, this indicates that cross-reactivity is very unlikely to be driving this increased risk. As such, a history of reaction to an antimicrobial sulfonamide should not be considered a contraindication to the use of a non-antimicrobial sulfonamide, just as it is not considered a contraindication to the use of penicillin [88].

Within the class of antimicrobial sulfonamides, cross-reactivity would be expected across the class. As such, for patients with a history of serious hypersensitivity reactions to one of the antimicrobial sulfonamides, avoiding all other antimicrobial sulfonamides regardless of route of administration is reasonable. Sulfasalazine should also be avoided as it is metabolized to sulfapyridine. There are rare case reports of hypersensitivity reactions to trimethoprim, and as such, unless targeted evaluation is performed investigating trimethoprim as culprit agent, trimethoprim should be avoided in patients who have had severe hypersensitivity reactions to TMP-SMX.

In HIV-positive patients with a history of adverse reaction to TMP-SMX, there have been reports of hypersensitivity reactions to darunavir, which contains an arylamine group; fosamprenavir, a derivative of sulfanilamide; and dapsone, a sulfone. In general, there are high rates of hypersensitivity reactions to each of these agents as well as TMP-SMX in this population, and it is not clear that there is a conclusive increased risk given a history of hypersensitivity to TMP-SMX. For darunavir,

in a retrospective cohort study with nested case-control study of 405 HIV-positive patients, 79 had a history of TMP-SMX hypersensitivity. Hypersensitivity reactions to darunavir, which were exclusively cutaneous reactions, were observed in 4 of the 79 patients (5.1%) with TMP-SMX hypersensitivity, compared to 4 of 326 (1.2%) without TMP-SMX hypersensitivity. They found that patients with TMP-SMX hypersensitivity were at increased risk for reaction to darunavir with odds ratio 4.29 and 95% confidence interval, 1.05–17.56 [89]. However, the rates of rash secondary to darunavir in this study were well below the listed incidence of 10% reported in the darunavir package insert [90], and it is worth noting that the vast majority of the TMP-SMX hypersensitivity patients tolerated darunavir with no issue. As such, it is not entirely clear how much of a true risk factor prior history of TMP-SMX hypersensitivity is. Similar findings have been observed with dapsone, with multiple studies showing variable rates, ranging from 0 to 20%, of hypersensitivity reactions to dapsone in patients with a history of TMP-SMX hypersensitivity [91–93]. The vast majority of reactions to dapsone were cutaneous, and the majority of patients in these studies with TMP-SMX hypersensitivity tolerated dapsone without issues. Theoretical concern has been raised for fosamprenavir, which has an arylamine group at the N4 position, but there are no clinical reports linking reactions to fosamprenavir with TMP-SMX hypersensitivity. Taken together, there is limited evidence for likely cross-reactivity between these agents and TMP-SMX.

Manufacturer drug monographs for non-antimicrobial sulfonamides have contributed to the confusion with inconsistent avoidance recommendations ranging from no warning to a contraindication for patients with a history of adverse reaction to antimicrobial sulfonamides [94]. While there are rare case reports suggesting cross-reactivity, Wulf et al. in a review found that most reports had inadequate testing to firmly establish cross-reactivity between antimicrobial and non-antimicrobial sulfonamides [95]. As such, there is very little conclusive evidence to suggest broad cross-reactivity between these two groups. Within the class of non-antimicrobial sulfonamides, there is no substantial evidence of cross-reactivity between agents in this class [6, 96].

Management

Desensitization/Multiple-Step Challenge

Numerous desensitization or multistep graded challenge protocols have been published [97]. While the term “desensitization” has been widely used for these procedures, it is

unclear whether these procedures truly desensitize patients as will be discussed later. The overwhelming majority of these protocols have been investigated in HIV-positive patients with a history of delayed exanthema who would benefit from treatment with TMP-SMX for PJP prophylaxis, recently summarized in this review [98]. Most of the protocols used in this setting perform up-dosing over several days, and even with wide variability across protocols, most are effective in achieving tolerance of reintroduction of TMP-SMX [99]. Shorter protocols have also been reported; Demoly et al. demonstrated a 95% success rate in achieving tolerance of TMP-SMX using a 6-h protocol in 44 HIV-positive patients [100]. Pyle et al. demonstrated similar efficacy in non-HIV-infected populations [101]. In a cohort of 72 patients, 60% underwent a single-day protocol with either a 6-step or 14-step up-dosing regimen and the remaining underwent a 10-day up-dosing protocol. There were similar rates of successful completion of the up-dosing protocol across groups, ranging from 93 to 98%. Furthermore, 90% of subjects continued to tolerate TMP-SMX with longitudinal follow up, with a mean follow up of 11 months [101].

Desensitization or multistep-graded challenge protocols have been used for other reactions to TMP-SMX. There are rare reports of desensitization for anaphylactic reactions to TMP-SMX. Gluckstein and Ruskin reported eight HIV-positive patients with a history of “anaphylactoid reactions,” five of which with hypotension requiring intensive care unit-level care, who underwent a 5-h desensitization protocol, outlined in Table 4. Six of the eight subjects completed the protocol and subsequently tolerated long-term TMP-SMX use [102]. Patriarca et al. describe a single case report of the use of a 10-day protocol in a patient with FDE [103]. While desensitization is considered generally contraindicated in the

setting of SCARs, Douglas et al. report successful induction of tolerance in two patients with a history of SJS to TMP-SMX using an 8-day desensitization protocol [104].

It is not clear if these protocols represent true desensitization procedures, effecting an immunomodulatory change leading to induction of tolerance, or are instead just prolonged challenges. Three studies have compared full-dose rechallenge to graded challenge/desensitization in HIV-positive subjects. Bonfanti et al. performed a randomized, open-label, multi-center study in Italy evaluating a 3-day 40-step dose-escalation protocol in comparison to a 160-800 TMP-SMX direct challenge in 59 subjects [83]. The primary outcome was the ability to tolerate double-strength TMP-SMX for 6 months; this was achieved in 72% of the direct challenge group and 79% in the dose-escalation group, which was not statistically different [83]. Leoung et al. performed a randomized, double-blind controlled, multi-center study in the US evaluating a 6-day dose-escalation protocol with single-strength full-dose direct challenge [82]. The primary outcome was the ability to tolerate single-strength TMP-SMX for 6 months. Blinding lasted 6 days, during which all subjects received daily antihistamine, and then subsequently followed with open-label treatment. One hundred ninety-one subjects were randomized; at the end of the 6-day blinded period, 91.5% and 93.8% successfully tolerated the TMP-SMX in the full-dose challenge and dose-escalation groups respectively. After 6 months follow up, 75% in the dose-escalation group and 57% in the full-dose challenge group were continuing therapy, a difference that was statistically significant. However, the reasons for discontinuation during the open treatment phase were not based on typical drug hypersensitivity reactions, as rash and pruritus were no different between the 2 groups. Discontinuation rates were different for headache and fever, outcomes that are not typically considered manifestations of drug hypersensitivity. [82]. The third study was a randomized, open-label study from Brazil which compared a dose-escalation protocol with up dosing every 48 h to a double-strength TMP-SMX direct challenge in a group of 18 patients [105]. The primary outcome was ability to tolerate double-strength TMP-SMX three times a week at 6 months. All reactions were mild and were identical between the two groups, occurring in 40% and leading to discontinuation of TMP-SMX [105]. A Cochrane review evaluating these three studies concluded that rates of discontinuation of TMP-SMX prior to completion of 6-month follow up were less in the dose-escalation group compared to full-dose direct challenge group, with a risk ratio of 0.64 [0.45,0.91] [99]. When comparing the reactions leading to discontinuation between the two groups, fevers were more frequent in the full-dose challenge group, whereas there was no statistical significant difference in cutaneous reactions.

Table 4 Rapid oral TMP-SMX desensitization protocol

Rapid Oral TMP-SMX desensitization protocol	
Steps	TMP-SMX Dose (mg)
1	0.004/0.02
2	0.04/0.2
3	0.4/2
4	4/20
5	40/200
6	160/800

Modified from protocol by Gluckstein and Ruskin [102] using TMP-SMX oral suspension. Dosing intervals between steps may range between 15 and 60 min apart based on provider discretion; the original protocol was performed with 60-min intervals

There were no severe hypersensitivity reactions reported in either group [99]. When interpreting these studies, it is important to note that all three used continued tolerance of TMP-SMX after 6 months as the primary outcome. It is not clear what the clinical significance of this outcome is for allergists interested in drug hypersensitivity reactions. Typically, outcomes in drug allergy provocation testing evaluate tolerance at 24 h to 1 week, and when this measure was assessed, there was no difference between full-dose challenge and dose-escalation groups, highlighting that multiple dose-escalation protocols are unnecessary in the majority of cases. Taken together, it appears that the difference in reactions between dose-escalation and full-dose direct challenge in the meta-analysis is driven by symptoms such as a fever and headache (occurring weeks to months later) from a single study for which the mechanisms of desensitization would not be plausible to account for. The authors of the aforementioned Cochrane review also indicated that “more data are needed for these results to be conclusive.” As such, the evidence for true induction of tolerance through desensitization with dose-escalation protocols has not been convincingly demonstrated. With

all of this under consideration, Fig. 2 illustrates an algorithm for the evaluation and management of antimicrobial sulfonamide hypersensitivity reactions. While data is limited in children, we recommend a similar approach as outlined above. For those rare patients with recent and convincing histories of TMP-SMX anaphylaxis where a desensitization is successfully performed, another desensitization procedure would need to be performed if there is a gap in therapy of more than a few days due to risk of resensitization.

With regard to the acute management of benign exanthems attributed to TMP-SMX, clinicians are faced with the dilemma of discontinuing TMP-SMX or treating through symptoms. As mentioned above, numerous challenge and dose-escalation protocols used antihistamines to manage benign rashes as a “treat through” strategy [82]. Even apart from challenge or dose-escalation procedures, there are reports of management of rashes and fever attributed to TMP-SMX with antihistamines while continuing TMP-SMX treatment [106]. As such, a number of patients would likely tolerate the management of benign cutaneous-only symptoms while continuing TMP-SMX therapy. However,

Clinical History of Reaction to Antimicrobial Sulfonamide concerning for:

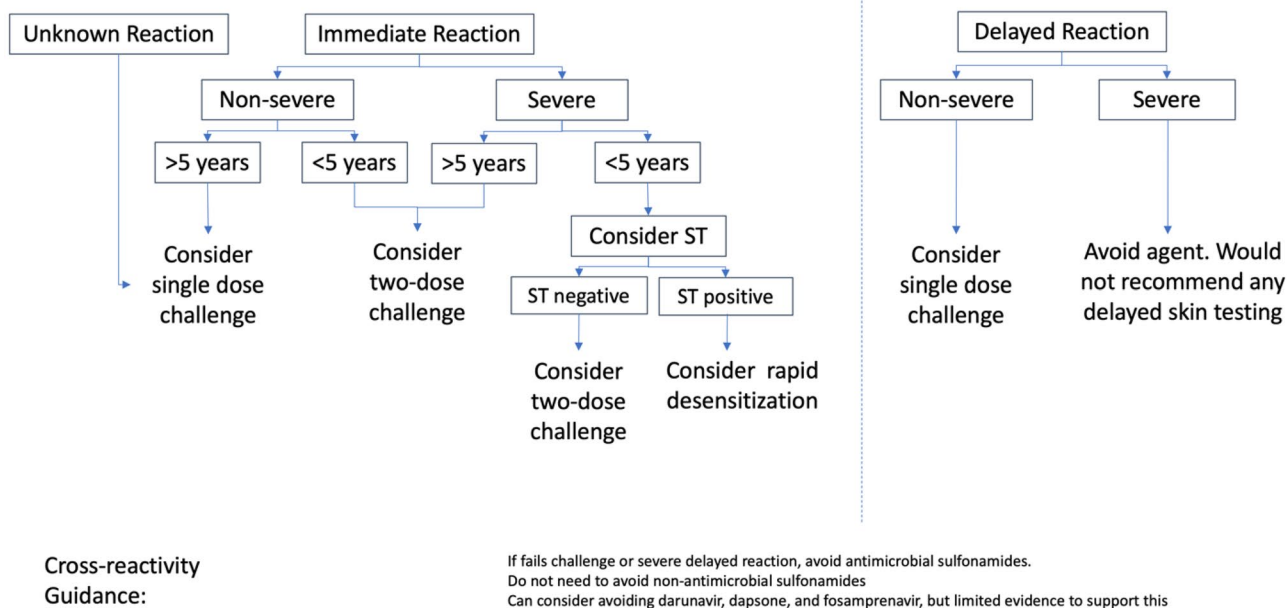
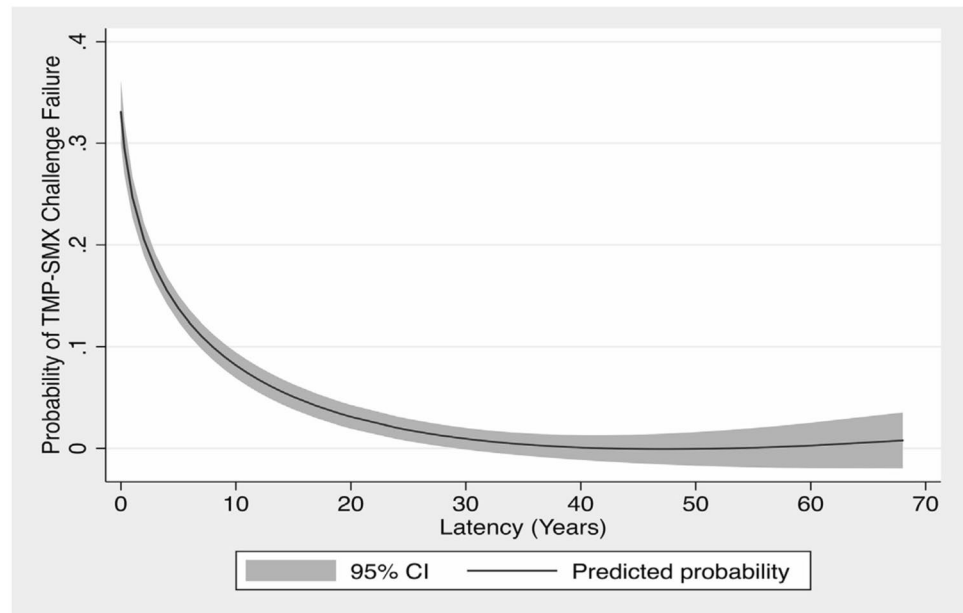


Fig. 2 Algorithm for diagnostic and treatment approach for antimicrobial sulfonamide hypersensitivity. Definitions: severe immediate reactions- multiple organ involvement concerning for anaphylaxis or severe single organ involvement (hypotension, respiratory failure) within 2 hours of administration; non-severe immediate reactions- reactions not otherwise included under severe immediate reactions (e.g. isolated urticaria, gastrointestinal symptoms) within 2 hours of administration; severe delayed reactions-severe cutaneous adverse reactions (SCARs), drug-induced nephritis/hepatitis/pancreatitis/cytopenias; non-severe delayed- otherwise not included under

severe delayed reactions (e.g. maculopapular exanthem). Single dose challenge: oral TMP-SMX 80–400 mg followed by 1 hour observation. Two dose challenge: oral TMP-SMX 8–40mg and 80–400 mg separated by 30 minutes and 1 hour observation after second dose. For skin testing (ST), perform skin prick testing, followed by intradermal testing if negative, with IV TMP-SMX 16mg/80mg 1:100 dilution with appropriate positive and negative controls. For an example of a rapid desensitization protocol, see Table 2. Algorithm can be used regardless of HIV status

Fig. 3 Probability of oral challenge failure and time from index reaction



given the risk of development of SCARs with TMP-SMX, clinicians must monitor for progression to more severe cutaneous or systemic reactions if the treat through approach is taken. Further research is needed to fully characterize which subjects would tolerate a treat through approach.

With regard to natural history of TMP-SMX hypersensitivity, similar to penicillin allergy, there appears to be an increased likelihood of subsequent tolerance of TMP-SMX as time from index reaction progresses; see Fig. 3. In their retrospective study of 204 patients who underwent oral TMP-SMX challenge, Krantz et al. reported that a 1-year increase in time since the index reaction was associated with decreased risk of oral challenge failure, with an unadjusted odds ratio of 0.87 (95% CI, 0.80–0.96; $p=0.005$) [84].

Summary and Conclusions

Hypersensitivity reactions to antimicrobial sulfonamides are common and can present within a wide clinical spectrum. Sulfonamides as a class are defined as sharing a common SO_2NH_2 moiety; however, this moiety is not a significant epitope for either immediate or delayed reactions. The implicated structural epitopes are distinguishing features of antimicrobial sulfonamides and are not shared by the vast majority of non-antimicrobial sulfonamides; consequently, clinical cross-reactivity between these two groups is unlikely. The evaluation of antimicrobial sulfonamide hypersensitivity is limited by the lack of clinically reliable testing available for either IgE or non-IgE-mediated reactions, and improved diagnostic tools are needed. There is

growing evidence supporting the safety and tolerability of direct challenge procedures in the evaluation of persistent antimicrobial sulfonamide hypersensitivity in both HIV-positive patients and, more recently, in non-HIV-infected populations. Further studies are needed to further characterize the risks of challenge failure across different populations. Finally, the high rates of tolerance of direct challenge suggest that many “desensitization” procedures may not be necessary.

Declarations

Conflict of Interest The authors declare no competing interests.

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