



# Sulfonamide Drug Allergy

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Published online: 6 June 2018

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## Abstract

**Purpose of Review** We sought to review past and current literature on sulfonamide drug allergy and distill it in a practical manner to assist the clinician, specifically focusing on cross-reactivity and desensitization.

**Recent Findings** There do not appear to be consistent genetic markers to reliably predict features of or the presence hypersensitivity reactions. Recent evidence continues to alleviate early concerns cross-reactivity between sulfonamide antibiotics and non-antibiotics.

**Summary** Sulfonamide drug allergy is frequently encountered by the practicing clinician. For sulfonamide antibiotics, delayed rash is the most common clinical manifestation. There is no current evidence to support avoidance of all non-antibiotic sulfonamides in those with a reported allergy to sulfonamide antibiotics, although certain scenarios require caution. Available evidence supports the cautious reintroduction of sulfonamide antibiotics via desensitization, which is usually well tolerated and should be considered in those with strong indications for trimethoprim-sulfamethoxazole and a reported sulfonamide allergy.

**Keywords** Sulfonamide · Hypersensitivity · Drug allergy · Cross-reactivity · Cross-sensitivity

## Introduction

Sulfonamide antibiotics and other sulfonamide medications, defined by their inclusion of the sulfonamide structure (Fig. 1a), are commonly used medications. Sulfonamide antibiotics are a very common cause of drug-induced cutaneous reactions and are one of the two most common antibiotics (along with penicillins) to be listed as an allergy in the patient's medical record [1–3]. Sulfamethoxazole is also well-known to cause hematologic abnormalities including cytopenias and bone marrow suppressive effects [4]. Trimethoprim-

sulfamethoxazole remains an essential medication for the treatment and prevention of pneumocystis pneumonia (PCP) in those who have human immunodeficiency virus (HIV), have undergone hematopoietic stem cell transplantation, or are otherwise immunosuppressed [5]. Thus, it is important to understand the nature of these hypersensitivity reactions as well as their clinical implications and possible management including drug desensitization. Cross-reactivity of sulfonamide antibiotics with other non-antibiotic sulfonamides is still frequently discussed. The following is a review of sulfonamide drug hypersensitivity focusing on recent developments with an emphasis on cross-reactivity and desensitization.

This article is part of the Topical Collection on *Anaphylaxis and Drug Allergy*

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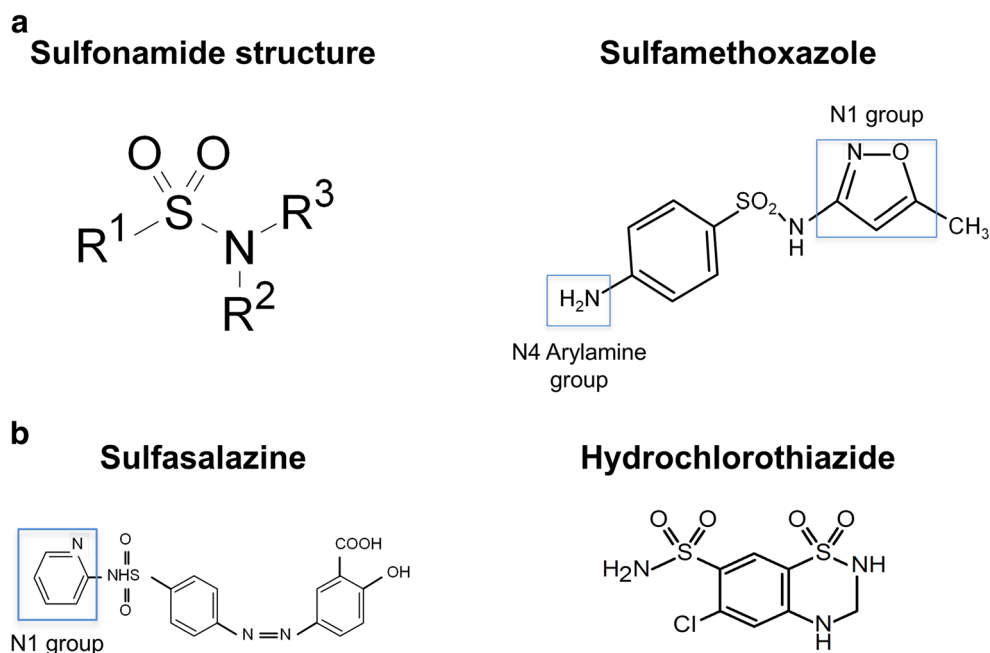
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## Sulfonamide Structure and Classification

The sulfonamide structure is defined by a sulfur atom double bonded to two oxygens along with nitrogen and a functional R1 group (Fig. 1a). Sulfonamide antibiotics contain two specific structures; an arylamine group at the N4 position and a five- or six-membered ring at the N1 position. Both of them are both important to their function and to the hypersensitivity reactions induced by them (Fig. 1b) [6, 7]. Non-antibiotic sulfonamides generally lack these structures or occasionally contain only one (Table 1) [8]. Others have further classified

**Fig. 1** Panel **a** shows the basic sulfonamide structure. Panel **b** shows the structure of sulfamethoxazole, sulfasalazine, and hydrochlorothiazide. The structures of importance are denoted by a blue box. Sulfamethoxazole has a five- or six-membered ring at the N1 group and an N4 arylamine, sulfasalazine has a five- or six-membered ring at the N1 group and no N4 arylamine, and hydrochlorothiazide has neither. These groups are important to the hypersensitivity reactions induced by sulfonamide antibiotics



the non-antibiotic sulfonamides into non-sulfonylarylamines (cyclical structure but no amine group at the N4 position) and sulfonamides (no benzene ring at N4 position) [6, 8–11]. The clinical relevance of this distinction is unclear.

## Mechanisms of Reactions and Risk Factors

Given the high rate of sulfonamide antibiotic hypersensitivity reactions, the mechanisms of these reactions have been heavily investigated. IgE-mediated reactions are rare but have been reported to occur and IgE to specific SMX determinants have been identified [6, 12, 13]. For delayed reactions, the sulfonamide drugs and intermediates are generally thought to be recognized by T lymphocytes either through pro-hapten formation, where drug or drug metabolite binds to a protein or peptide, or by the p-i concept which involves direct recognition of drug or metabolite by receptors on the T cell [6, 14, 15]. In HIV-positive patients, who have higher rates of reactions to sulfonamide antibiotics, there are likely additional factors contributing that may affect the metabolism of SMX such as abnormalities in glutathione or its synthesis [16]. Glutathione is required in SMX metabolism for the reduction of nitroso-SMX (a reactive intermediate) to *N*-hydroxylamine-SMX [16].

Genetic predisposition may also play a role in hypersensitivity reactions. Recently, adding to previous work [8], additional investigation into the contribution of specific genetic polymorphisms as a risk factor for sulfonamide hypersensitivity (HS) has been performed. A genome-wide association

study did not find any small nucleotide polymorphisms (SNPs) that were likely to be risk factors for exanthematous HS reactions [17•]. Additionally, Sacco et al. examined four CYB5A (encoding cytochrome b5), five CYB5R3 (encoding cytochrome b5 reductase), and all *N*-acetyltransferase 2 single nucleotide polymorphisms in 99 patients with SH and did not find evidence of substantial involvement in reactions for any of them [18]. Kongpan et al., however, did find evidence of association of three HLA alleles (HLA-B\*15:02, HLA-C\*06:02, and HLA-C\*08:01) with sulfonamide-induced SJS/TEN reactions [19]. Overall, it is not currently clear how specific genotypes or polymorphisms contribute to the likelihood of a reaction in a particular patient.

## Classification of Sulfonamide Hypersensitivity Reactions

Adverse drug reactions can be classified as either type A or type B reactions. Type A reactions are predictable and related directly to the pharmacology of the drug. For example, type A reactions for furosemide include ototoxicity, hypotension, and dizziness. These reactions are often dose-dependent. Type B reactions are unpredictable and are mediated by immunologic mechanisms [20, 21]. Traditionally, drug hypersensitivity reactions have been categorized using the Gell-Coombs system, which places reactions into one of four categories: immediate, cytotoxic, immune-complex derived, and delayed or cell mediated. As understanding of drug reactions has deepened, an alternate classification system by endotype and phenotype

was proposed by the recent PRACTALL consensus statement to allow for a more precise description of a given drug reaction based on improved understanding of pathogenesis [22]. Drug phenotypes are categorized by the timing of the reaction relative to the administration of the drug, while endotypes are a description of the mechanism of drug reaction, such as IgE-mediated or HLA-associated [22].

Sulfonamide-containing drugs can cause a diverse range of hypersensitivity (type B) reactions. The majority of the literature on hypersensitivity reactions for sulfa-class drugs is focused on the antimicrobials. Immediate IgE-mediated reactions to sulfonamide antimicrobials that range in severity from urticaria-only to anaphylaxis occur but are less common than delayed drug exanthems [23–25]. IgE-mediated hypersensitivity reactions to non-antimicrobials, which lack the arylamine moiety, have also been reported and include anaphylaxis [26]. Immunoglobulin G, IgM, and complement-mediated reactions can also be precipitated by sulfonamide-containing drugs. Serum sickness, a delayed reaction of immune complex deposition, has been reported with trimethoprim/sulfamethoxazole and often occurs 1 to 2 weeks after therapy is begun [27, 28]. It is also important to note that a small percentage of patients who have hypersensitivity reactions to TMP-SMX will actually be reacting to the trimethoprim component [29, 30]. Thrombocytopenia, hypothesized to occur secondary to the binding of drug to platelet GPIIb/IIIa and IgG, has also been reported with both sulfonaylarylamines and non-sulfonaylarylamines [31–33].

Delayed reactions are the most common hypersensitivity reaction caused by sulfonamide antibiotics; sulfonamides are the most common antibiotic to precipitate SJS/TEN [23, 25, 27, 34]. HIV infection significantly increases the risk of cutaneous drug reactions and overall reaction rate to sulfonamide antibiotics may be 40% or greater in this population [34, 35]. Exanthemas rashes are the most common manifestation of cutaneous drug hypersensitivity and usually appear after several days of therapy and peak around day 10 [36]. Fixed drug eruptions are also possible and HIV-positive patients seem to be at increased risk [25, 27]. If re-exposure to the culprit medication occurs, the rash can appear within a few hours [27, 36].

More severe delayed reactions, such as the cytotoxic-T cell-mediated Stevens-Johnson Syndrome (SJS) or the more severe toxic epidermal necrolysis (TEN), related to trimethoprim/sulfamethoxazole have been widely reported. A case control study of patients in Europe with SJS/TEN found that sulfonamide antibiotics accounted for 69% of cases [37]. Non-antibiotic sulfonamides have also been reported to cause SJS/TEN; however, this occurs much more rarely as compared with sulfa antibiotics [37, 38]. Another potentially life-threatening delayed

reaction, drug reaction with eosinophilia and systemic symptoms (DRESS), which by an exanthematous skin rash and is accompanied by eosinophilia and internal organ involvement. Twelve percent of cases in the RegiSCAR database were tied to sulfonamide use [39]. Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous reaction mediated by the activation of neutrophils to produce tiny pustules in the intertriginous areas and has been reported in association with trimethoprim-sulfamethoxazole [40, 41]. Fifty percent of these patients can also have skin peeling [40]. Of note, non-antibiotic sulfonamides do not seem to have an increased risk of severe cutaneous adverse reactions (SCAR), though have been noted to induce bullous pemphigoid [34, 42].

## Clinical Evaluation

In the evaluation of a patient with an adverse drug reaction, the history is the most essential component and the timing of the reaction in relation to the administration of medications is of paramount importance [23, 24, 27, 34]. The drug dose, duration of use prior to onset of symptoms and concurrent therapy are important factors in elucidating the culprit drug or drugs responsible for the reaction. A thorough review of the patient's medical records can be instrumental [23, 34]. Other factors, such as HIV infection or other current viral illnesses and patient factors such as ethnicity and gender, may increase the patient's risk of certain drug reactions [23, 43].

As cutaneous manifestations of allergic reactions are the most common, any evaluation should include a thorough examination of the skin including intertriginous areas [40, 44]. It is important to assess the conjunctiva and oropharynx, as life-threatening reactions, such as Steven's Johnson Syndrome/TEN, may manifest there. Laboratory evaluation such as liver function testing and complete blood count with eosinophil count can assist in monitoring for end-organ damage. Skin biopsies can also be useful in the setting of drug rashes; for example, pustule biopsy is helpful for the diagnosis of AGEP [45].

## Testing for Sulfonamide Antibiotic Allergy

Unfortunately, there is no reliable or validated laboratory diagnostic test for sulfonamide antibiotic allergy currently available. Previous evaluations of skin testing, patch testing, and in-vitro testing have not produced a clinically reliable test for sulfonamide hypersensitivity [34, 46–50]. In vivo tests, such as skin prick testing, are commonly used for the evaluation of beta-lactam antibiotic

hypersensitivity. One evaluation of skin prick testing for sulfonamide hypersensitivity with sulfamethoxazol-poly-L-tyrosine was only positive in 10 out of 34 (29%) patients with a clinical history of SMX hypersensitivity [46]. Patch testing with co-trimoxazole did not predict who would react to oral graded administrations of co-trimoxazole [47].

Due to the serious nature of many possible sulfonamide reactions, there is significant interest in a reliable *in vitro* test. Particularly, lymphocyte transformation tests have been used to evaluate for non-immediate reactions, which are commonly seen in sulfonamide hypersensitivity [48]. One *in vitro* study using a lymphocyte transformation test assessed sulfonamide-reactive lymphocytes in patients with sulfonamide drug-induced eruptions revealed positive results in only 3 out of 24 patients (13%) [49]. These results revealed a high rate of false negatives, suggesting low clinical utility [48, 49]. Lymphocyte toxicity assays have also been evaluated as a potential diagnostic test. One lymphocyte toxicity assay study in the HIV-positive population revealed a sensitivity of 80% and specificity of 75% for SMX testing [50]. *In vitro* testing has shown some promise, but further research is needed to develop a reliable and practical test for the clinical diagnosis of sulfonamide antibiotic hypersensitivity. Currently, the diagnosis relies on the clinical history and drug challenge testing.

One method of drug challenge includes test dosing (or graded drug challenge). This is a term used to describe the cautious administration of small and increasing doses of a medication under medical observation. Test dosing is appropriate for patients who are unlikely to be allergic to the drug in question. It does not alter the patient's immune response to the drug, so patients who tolerate a graded challenge prove that they are not allergic to that drug.

Oral drug challenges are the gold standard for confirming or ruling out an allergy. However, the clinical utility of oral challenges is limited based on the lack of reliable diagnostic tests and the risks associated with sulfonamide hypersensitivity. One study in HIV-positive patients with a previous adverse reaction to TMP-SMZ revealed 57% of patients were able to tolerate a direct rechallenge of TMP-SMX and tolerate daily therapy for 6 months [51].

## Cross-Reactivity

### Cross-Reactivity Within Sulfonamide Antibiotics

Aside from the most commonly used sulfonamide antibiotic, trimethoprim-sulfamethoxazole, there are also several others. These include sulfamerazine, sulfamethizole, sulfamoxole, sulfacetamide, sulfanilamide, sulfamerazine,

sulfadiazine, sulfamethazine, sulfisoxazole, and sulfapyridine [7, 27, 52]. All of these contain an arylamine and a five- or six-membered ring at the N1 position (Fig. 1). While there are no large-scale clinical trials to determine true rates of cross-reactivity among sulfonamide antibiotics, there is some *in vitro* and *in vivo* data. One study looked at lymphocytes from three patients with a history of a clinical reaction (Exanthema, DRESS, and SJS respectively) to TMP-SMX [53]. The lymphocytes also proliferated to sulfapyridine and two of three proliferated to sulfadiazine [53]. Two of three patient's lymphocytes were also stimulated by the hydroxylamine and nitroso metabolites of the two other antibiotics [53]. The authors concluded that T cells may recognize cross-reactive antigens among the metabolites of these drugs [53]. Tornero et al. challenged patients with history of fixed drug eruption to SMX, with sulfadiazine and sulfamethiazole. Four of 12 patients reacted to 1 or both of the other antibiotics, and 8 to SMX alone [54]. The manufacturer's labeling for sulfonamide antibiotics does generally list 'hypersensitivity to sulfonamides' as a contraindication to usage [7]. Another consideration in those with previous sulfonamide antibiotic hypersensitivity is the use of topical sulfacetamide or sulfadiazine, which do share the necessary chemical structures of sulfonamide antibiotics and thus have a higher theoretical potential to cross-react [55]. This has not been well studied. Usually, reactions to topical sulfonamide antibiotics are mild; however, severe reactions have occurred [56]. If the index reaction to an oral sulfonamide antibiotic was severe (i.e., Stephens Johnsons Syndrome), then avoidance of topical sulfonamide antibiotics is likely appropriate as these can recur regardless of route of administration [56]. It is unclear, based on the limited data, whether or not some sulfonamide antibiotics may be more likely to cross-react compared to others. However, given the paucity of high-quality evidence and the structural similarity of these antibiotics, it is likely prudent to assume there may be clinical cross-reactivity.

### Cross-Reactivity Between Antibiotic and Non-antibiotic Sulfonamides

Questions regarding cross-reactivity between antibiotic and non-antibiotic sulfonamides have persisted given the shared sulfonamide structure, early reports of cross-reactivity, and the relative paucity of strong evidence-based literature on this topic. Questions also persist because of confusion stemming from lack of proper terminology. The presence of a sulfur atom often being confused with the sulfonamide structure itself and the use of the generic and non-specific term 'sulfa allergy.' [57] Several drugs contain the sulfonamide structure (Fig. 1), and several more contain a sulfur atom; however, sulfonamide antibiotics uniquely contain both an arylamine and a five- or six-membered ring at the N1 position (Fig. 1).

One of the main sources of continued confusion is the manufacturer's package inserts of the non-antibiotic sulfonamides [7, 9, 52]. Ghimire et al. reviewed drug monographs from six different countries and three drug compendia [9]. They found there were significant discrepancies in the cautionary recommendations of these resources. Many sources listed warnings or contraindications to the use of specific non-antibiotic sulfonamides in patients with a history of hypersensitivity to sulfonamide antibiotics. There was also poor agreement between sources and many statements on cross-reactivity were primarily theoretical without primary evidence [9].

There have been two larger studies examining the question of cross-reactivity of antibiotic and non-antibiotic sulfonamides in a more general sense. A retrospective cohort study by Strom et al. examined patients who had a presumed allergic reaction after sulfonamide antibiotic and subsequently received a non-antibiotic sulfonamide [58]. Compared to patients who did not have history of sulfonamide antibiotic reaction, there was higher odds of a reaction to a sulfonamide non-antibiotic (adjusted odds ratio, 2.8 [95% CI 2.1 to 3.7]). However, in those with previous reaction to sulfonamide antibiotic, there was an even higher rate of reactions after receiving penicillin (adjusted odds ratio 3.9; [95% CI 3.5–4.3]). The authors concluded that the increased rate of reactions may be due to an increased predisposition to drug allergy in general rather than cross-reactivity from structural components of the drugs. Hemstreet et al. examined 94 patients during hospital admission that had a history of sulfonamide allergy [59]. Just under half (42) were due to TMP-SMX and the rest were due to another sulfonamide (most non-antibiotics and some unknown). Fifty-two percent had received another sulfonamide containing medication as an outpatient or while they were inpatient. None had discernable adverse effects related to the use of these agents [59]. These two studies demonstrate that hypersensitivity reactions to sulfonamide non-antibiotics because of cross-reactive structures in a patient who reports sulfonamide allergy appears relatively unlikely.

A number of reviews with a focus on clinical or mechanistic cross-reactivity of antibiotic and non-antibiotic sulfonamides and less so among non-antibiotic sulfonamides have been published [6, 8, 10, 11, 57]. They outline the available literature which proposes potential for cross-reactivity. This primarily includes case reports and small case series. A recent review by Wulf et al. detailed the cross-reactivity literature from 1966 through 2011 and found a total of nine case reports indicating possible cross-reactivity [7]. The methodologic quality of the reports was questionable in some instances, as adequate investigation or testing may not have been performed. Overall, it was concluded that based on the available evidence, withholding these medications because of concern for cross-reactivity would not be strongly justified [7]. A summary of existing evidence for each specific commonly

recognized non-antibiotic sulfonamide drug class and potential cross-reactivity with sulfonamide antibiotics is located in Table 1. This summary also includes a newly recognized sulfonamide containing drug class, B-Raf kinase inhibitors, which are used in melanoma and non-small cell lung cancer [60]. B-Raf inhibitors do not contain an arylamine group.

## Desensitization

Drug desensitization is a procedure designed to induce tolerance to a particular drug after an adverse drug reaction. Desensitizations have classically been described in patients with a history of a type 1, IgE-mediated, hypersensitivity. However, the term desensitization has also been applied to many different protocols to induce tolerance to sulfonamide antibiotics, particularly SMX-TMP, despite different mechanisms of hypersensitivity. The terms graded administration and induction of drug tolerance have also been used to describe these procedures. Desensitization is contraindicated in patients with a history of reaction involving skin desquamation, such as SJS or TEN, DRESS/drug-induced hypersensitivity syndrome, acute generalized exanthematous pustulosis (AGEP), serum sickness reaction, nephritis, or hepatitis.

Trimethoprim-sulfamethoxazole is the first line therapy for pneumocystis pneumonia (PCP) prophylaxis in immunocompromised patients. While alternatives exist, TMP-SMX has been shown to be more effective than the alternatives [61–63]. There is extensive literature on TMP-SMX desensitization in HIV-positive patients; however, there is more limited published data in the HIV-negative population.

Many different protocols for TMP-SMX desensitization have been published for HIV-positive patients [51, 64, 65]. A Cochrane review found that co-trimoxazole (sulfamethoxazole-trimethoprim) desensitization, compared to rechallenge, for prophylaxis of opportunistic infections resulted in fewer treatment discontinuations and overall adverse reactions in HIV-infected patients with a previous history of mild or moderate hypersensitivity to co-trimoxazole [66•]. However, the Cochrane review found no significant difference in the rate of rashes between the desensitization and rechallenge groups in the included studies [66•]. One study revealed improved tolerance at 6 months with desensitization versus re-challenge [51]. Of note, this difference was due to fever and headache, which may not be due to a hypersensitivity reaction. Further research is needed to definitively recommend desensitization versus re-challenge.

The most recent drug allergy practice parameters recommend HIV-positive patients with a history of a typical delayed exanthematous reactions to TMP-SMX who require treatment or prophylaxis for PCP may undergo one of several published trimethoprim-sulfamethoxazole induction of drug tolerance protocols [23]. It is recommended to wait at least 1 month after

**Table 1** Cross-reactivity Between Sulfonamide Medications

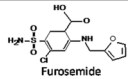
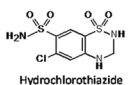
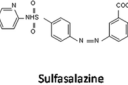
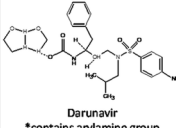
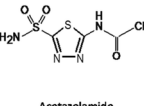
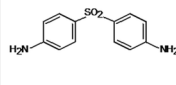
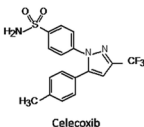
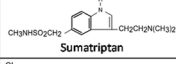
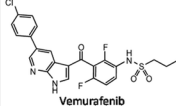
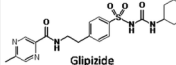
| Drug or class (drug pictured)                 | Sample structure                                                                                                                                        | Selected summary of evidence for or against cross-reactivity with sulfonamide antibiotics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Conclusions                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Loop diuretics                                | <br>Furosemide                                                         | <ul style="list-style-type: none"> <li>Case reports proposing clinical CR [61-63] and others not.[64]</li> <li>21 patients with 'sulfa allergy' tolerated furosemide.[65]</li> <li>28/28 pts with SMX or unknown sulfonamide allergy passed furosemide challenge.[54]</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Two series of patients without evidence of cross-reactivity</li> <li>Unlikely cross-reactivity</li> </ul>                                                                                                                                                                               |
| Thiazide Diuretics                            | <br>Hydrochlorothiazide                                                | <ul style="list-style-type: none"> <li>Case reports of thiazide diuretic reaction, in those with history of SA.[66-70]</li> <li>Case series of 13 patients with HSR to indapamide. Eleven who later took other thiazides did not have any reactions. Authors concluded likely not related to sulfonamide group, but to a reactive intermediate.[71]</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <ul style="list-style-type: none"> <li>Only case reports of potential CR between thiazides and SA</li> <li>Limited evidence</li> <li>Unlikely cross-reactivity</li> </ul>                                                                                                                                                      |
| Sulfasalazine                                 | <br>Sulfasalazine                                                      | <ul style="list-style-type: none"> <li>In vitro study which performed lymphocyte transformation in those allergic to sulfapyridine (active form of sulfasalazine which is a prodrug) and sulfamethoxazole. There was in-vitro cross reactivity in those that was not seen in controls.[72]</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <ul style="list-style-type: none"> <li>Theoretical potential for cross-reactivity because it does metabolize to sulfapyridine, which has an arylamine</li> <li>Limited evidence</li> <li>Possible cross-reactivity</li> </ul>                                                                                                  |
| Protease inhibitors (contain arylamine group) | <br>Darunavir<br>*contains arylamine group                             | <ul style="list-style-type: none"> <li>Series of 405 patients with HIV; 79 had previous reaction to TMP-SMX. 4/79 had reaction to Darunavir(DRV) compared to 4/326 without history of TMP-SMX reaction. Increased risk of DRV allergy (odds ratio 4.29; 95% CI, 1.05-17.56).[73]</li> <li>Observational reports exist showing higher rates of rash with amprenavir and history of SAnH. Concomitant use of abacavir which can cause rash, may have contributed as well.[10]</li> <li>Package insert states that in studies of Darunavir, incidence and severity of rash was similar with or without history of SA.[74]</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <ul style="list-style-type: none"> <li>Baseline rates of rash from DRV around 10.3% [74] thus it is unclear if there are truly higher rates of rash in SA allergic.</li> <li>Unlikely cross-reactivity</li> </ul>                                                                                                              |
| Carbonic Anhydrase inhibitors (CAI)           | <br>Acetazolamide                                                      | <ul style="list-style-type: none"> <li>Case reports of anaphylaxis to acetazolamide in patients who had SA; one of the reactions resulted in death.[75-77]</li> <li>Case series of three patients with history of severe rash to a SAn who tolerated acetazolamide.[78]</li> <li>Patients with history of SA had higher rates of reactions to topical CAI for glaucoma (9/28) than those without allergy (4/40) but statistically similar to those who had history of non-sulfonamide medication hypersensitivity (5/10).[79]</li> <li>27 patients who self-reported SA were treated with acetazolamide. 10/27 had no reaction, 2/27 had urticaria, and 15/27 had non-allergic adverse effects from the drug. No severe reactions occurred.[65]</li> </ul>                                                                                                                                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>Case reports claiming cross-reactivity while case series demonstrate that it is unlikely.</li> <li>Unlikely cross-reactivity</li> </ul>                                                                                                                                                 |
| Dapsone                                       | <br>Dapsone<br>*Sulfone, not sulfonamide                              | <ul style="list-style-type: none"> <li>Retrospective study showing 13/60 patients with HIV and previous TMP-SMX reaction had mild to moderate reactions to dapsone.[80]</li> <li>Retrospective study of 75 TMP-SMX allergic HIV-positive patients who received dapsone; 5/75 had adverse reactions thought to be due to dapsone.[81]</li> <li>Retrospective study showing 9/23 patients with HIV intolerant to TMP-SMX were also intolerant of dapsone.[82]</li> <li>Retrospective study of 60 total patients with HIV and sulfonamide intolerance, 13 of 13 subsequently exposed to dapsone tolerated it. An additional 6 patients reported dapsone intolerance prior to entrance into the health system.[83]</li> <li>Prospective study showing 7/9 patients with challenge positive TMP-SMX hypersensitivity tolerated a switch to TMP-dapsone.[84]</li> <li>Randomized control trial of dapsone vs TMP-SMX for PCP 21 had to discontinue one and cross over to the other. 6/11 tolerated switch from TMP/SMX to dapsone, and 4/10 tolerated Dapsone to TMP/SMX.[85]</li> </ul> | <ul style="list-style-type: none"> <li>Large amount of studies comparatively to other classes</li> <li>There are high rates of hypersensitivity reactions to both sulfonamides and dapsone especially in HIV-positive patients where they are commonly used and studied</li> <li>Low likelihood of cross-reactivity</li> </ul> |
| COX-2 Inhibitors                              | <br>Celecoxib<br>*Not all COX-2 inhibitors contain sulfonamide group | <ul style="list-style-type: none"> <li>Case report of proposed CR with previous reaction to topical sulfonamide antibiotic and then subsequent toxic epidermal necrolysis to celecoxib.[86]</li> <li>Case series of five patients with SMX allergy (urticaria, angioedema or anaphylaxis) confirmed by oral challenge who tolerated oral challenge test to celecoxib.[87]</li> <li>Prospective study of 28 patients with history of SAnH, some of which had positive <i>in vitro</i> testing to SMX were given celecoxib. It was tolerated by all 28.[88]</li> <li>Meta-analysis of celecoxib trials (with inclusions of placebo or active comparator drugs (i.e. COX-1 inhibitors)): 135 patients were previously SA. 73/135 received celecoxib with reaction rate of 11%, 32/135 received placebo with reaction rate of 18.8% and 30/135 received active comparator with reaction rate of 3.3%. These differences were not statistically significant.[89]</li> </ul>                                                                                                             | <ul style="list-style-type: none"> <li>Large amount of data on celecoxib demonstrating unlikely cross-reactivity in those with previous history of sulfonamide antibiotic reaction.</li> <li>Unlikely cross-reactivity</li> </ul>                                                                                              |
| 5-HT agonists                                 | <br>Sumatriptan                                                      | <ul style="list-style-type: none"> <li>Retrospective chart review (abstract) of 15 patients with SAnH who later received sumatriptan had no reported adverse effects.[90]</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>Limited data</li> <li>Unlikely cross-reactivity</li> </ul>                                                                                                                                                                                                                              |
| B-Raf enzyme inhibitors                       | <br>Vemurafenib                                                      | <ul style="list-style-type: none"> <li>Case report with vitro studies or one patient with Vemurafenib induced toxic epidermal necrolysis. This patient's lymphocytes also reacted to dabrafenib and SMX. Two patients with SMX HS had lymphocyte reactivity to Vemurafenib and Dabrafenib.[91]</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>High rate of cutaneous side effects in this B-Raf inhibitors [92,93]. Limited in vitro data, no in vivo data.</li> <li>Unable to draw conclusions</li> </ul>                                                                                                                            |
| Sulfonylureas                                 | <br>Glipizide                                                        | <ul style="list-style-type: none"> <li>Case reports of proposed CR between SAn and sulfonylurea. [94,95]</li> <li>Questionnaire of 82 patients who were taking sulfonylurea. 7 had previous SA, 1/7 had a mild rash to sulfonylurea.[96]</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <ul style="list-style-type: none"> <li>Few case reports, some of which have unclear or problematic methodology.[10]</li> <li>Unlikely cross-reactivity</li> </ul>                                                                                                                                                              |
| Other                                         | Zonisamide, Tamsulosin, Sotalol, Ibutilide, Topiramate, Probenecid                                                                                      | <ul style="list-style-type: none"> <li>Zonisamide: <ul style="list-style-type: none"> <li>In-vitro cross reactivity (via lymphocyte toxicity assay) to zonisamide in 2/20 patients who previously had SMX reaction.[61]</li> <li>Retrospective study showing 15/15 patients with self-reported sulfonamide reactions (8 where history was confirmed) tolerated zonisamide.[97]</li> </ul> </li> <li>Tamsulosin: <ul style="list-style-type: none"> <li>Few, if any, reports of cross-reactivity to tamsulosin.[7]</li> </ul> </li> <li>Other drugs: Sotalol, Ibutilide, Topiramate, Probenecid lack significant evidence of cross-reactivity.[7,9,10]</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Unlikely cross-reactivity</li> </ul>                                                                                                                                                                                                                                                    |

**Fig. 2** Sample desensitization protocols for TMP-SMX. Dosing can be 15 to 60 min apart. Adapted with permission from Pyle RC, Butterfield JH, Volcheck GW, Podjasek JC, Rank MA, Li JTC, et al. Successful outpatient graded administration of trimethoprim-sulfamethoxazole in patients without HIV and with a history of sulfonamide adverse drug reaction. *J Allergy Clin Immunol Pract.* 2014; 2:52–8

### Sample desensitization protocols for TMP-SMX

| TMP-SMX Desensitization Protocols:<br>TMP-SMX 6 step (1 day)* |                                                         | TMP-SMX Desensitization Protocols:<br>TMP-SMX 14 step (1 day) |                        |
|---------------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------------|------------------------|
| Step                                                          | Dose of TMP/SMX, mg/mg                                  | Step                                                          | Dose of TMP/SMX, mg/mg |
| 1                                                             | 0.004/0.02                                              | 1                                                             | 0.016/0.08             |
| 2                                                             | 0.04/0.2                                                | 2                                                             | 0.032/0.16             |
| 3                                                             | 0.4/2                                                   | 3                                                             | 0.064/0.32             |
| 4                                                             | 4/20                                                    | 4                                                             | 0.128/0.64             |
| 5                                                             | 40/200                                                  | 5                                                             | 0.256/1.28             |
| 6                                                             | Final dose: single, 80/400 PO,<br>or double, 160/800 PO | 6                                                             | 0.512/2.5              |
|                                                               |                                                         | 7                                                             | 1/5                    |
|                                                               |                                                         | 8                                                             | 2/10                   |
|                                                               |                                                         | 9                                                             | 4/20                   |
|                                                               |                                                         | 10                                                            | 8/40                   |
|                                                               |                                                         | 11                                                            | 16/80                  |
|                                                               |                                                         | 12                                                            | 32/160                 |
|                                                               |                                                         | 13                                                            | 64/320                 |
|                                                               |                                                         | 14                                                            | 88/440                 |

the reaction to increase the likelihood of success [23]. Many single day and multiple day protocols for HIV-positive patients have been published [51, 64, 65].

Recent evidence supports the safety and efficacy of sulfonamide antibiotic desensitization in the HIV-negative population. A retrospective analysis by Pyle et al. of 69 HIV-negative patients undergoing TMP-SMX graded administrations reported a 81–98% long-term success rate [67••]. The success rate of the 1-day desensitization protocols (98%) was markedly higher than > 1 day protocols (81%), although there may have been bias in who was selected for each protocol [67••]. Two of the desensitization protocols used in the article by Pyle et al. can be found in Fig. 2.

Organ and hematopoietic stem cell transplant patients are another immunocompromised population frequently requiring PCP prophylaxis. There have been several reported cases of successful TMP-SMX desensitization after hematopoietic stem cell transplantation in adults [67••, 68], and one reported successful TMP-SMX desensitization in a 7-year-old boy following HSCT [69]. A series of successful sulfonamide desensitization following lung transplant has also been reported [70]. However, the overall evidence is limited regarding the safety and efficacy of desensitization in the transplant population.

## Conclusion

Sulfonamide medications are commonly used in daily medical practice and frequently encountered by the practicing physician. Clinically, hypersensitivity reactions have a wide range of severity and, for sulfonamide antibiotic hypersensitivity, delayed exanthematous rashes are a common presentation. Currently, there is no clinically reliable testing for IgE or

non-IgE-mediated reactions to sulfonamides. Because of the shared sulfonamide structure and few case reports, general concerns of cross-reactivity between sulfonamide antibiotics and non-antibiotic sulfonamides have persisted; however, this concern has been largely alleviated by the available literature. When a sulfonamide antibiotic is needed in a patient with a previous hypersensitivity reaction, a desensitization procedure may be warranted.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare no conflicts of interest relevant to this manuscript.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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