

Allergies to sulfonamide antibiotics and sulfur-containing drugs

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Objective: To provide a literature review and clinical summary of the evaluation and management of sulfonamide drug reactions.

Data Sources: Published English-language medical literature.

Study Selection: Selected trials of drug desensitization protocols.

Results: Obtaining a detailed history is invaluable in assessing a history of reactions to sulfonamide medications, because allergy to these drugs remains a clinical diagnosis at present. Numerous efficacious drug desensitization protocols for management have been published and are reviewed in detail.

Conclusions: The term *sulfa allergy* is imprecise and misleading and therefore should be discouraged. There are important distinctions between sulfonylarylamines (antimicrobial sulfonamides), nonarylamine (nonantimicrobial) sulfonamides, and sulfones, with regard to allergic and other adverse drug reactions. Most reactions to sulfonylarylamines probably result from multifactorial immunologic and toxic metabolic mechanisms, whereas less is known about the precise mechanisms of reactions to other sulfur-containing drugs.

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INTRODUCTION

After the β -lactams (penicillins and cephalosporins), sulfonamide-containing antibiotics are among the most frequent causes of drug reactions. There are however significant differences between the evaluation and management of β -lactam allergy versus reactions to what are commonly referred to as *sulfa* drugs. This imprecise term does not distinguish among important immunologic differences of antimicrobial sulfonamides (sulfonylarylamines, which all contain an arylamine chemical moiety), nonantimicrobial sulfonamides (which do not contain an arylamine group), and sulfones. The inappropriate continued use of the term *sulfa drugs* has contributed to ongoing confusion about relevant cross-reactivity relationships among medications in these classes. Although this

article primarily focuses on antimicrobial sulfonamides, particularly trimethoprim-sulfamethoxazole, reactions to commonly encountered medications of the other classes are briefly addressed as well. The chemistry, mechanisms of action, pharmacodynamics, and pharmacokinetics of trimethoprim-sulfamethoxazole have been extensively reviewed elsewhere.¹

A number of medications also have sulfur atoms in their chemical structure but without specific sulfonamide or sulfone moieties. Interestingly, these are not generally thought of as *sulfa* medications and include amoxicillin, captopril, omeprazole, ranitidine, and others.² With regard to drug reaction categories, amoxicillin is instead categorized with the penicillins and β -lactams, captopril with angiotensin-converting enzyme (ACE) inhibitors and sulfhydryls, and so forth. Some medications also contain sulfate (SO_4^{2-}) ions, such as albuterol sulfate, which are part of the pH balance of the drug and entirely unrelated to allergic or immunologic issues. Finally, sulfites have often been used as preservatives for

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certain foods and medications and are relatively commonly associated with a distinct constellation of symptoms known as sulfite sensitivity, which are primarily mediated via non-immunologic mechanisms. Reactions to these medications and substances are outside the scope of this article.

It is also important to clarify terms regarding adverse drug reactions. Although there may be slight differences in terms and classification among various authorities (such as the Medical Dictionary for Regulatory Activities and the World Health Organization Adverse Reaction Terminology), an adverse drug reaction can be defined as any undesired and unintended response that occurs at appropriate doses of a drug, given for the therapeutic, diagnostic, or prophylactic benefit of the patient, and occurring within a reasonable time after administration of the drug (excluding therapeutic failure).³⁻⁶ These reactions can be further characterized as predictable versus unpredictable; unlike the former (which includes indirect secondary effects and side effects), the latter are usually dose independent, usually unrelated to the drug's pharmacologic actions, and often related to the patient's immunologic responsiveness.^{3,7} The detail and complexity of these systems of categorization continue to evolve.⁸⁻¹⁰ Only when the origin of these reactions is known (or strongly presumed) to be specifically immunologic in nature are they classified as allergic reactions. Note that nonimmunologic, yet unpredictable, reactions may occur and include drug intolerances and idiosyncratic metabolic reactions. Most adverse drug reactions are *not* immunologic, or allergic, in nature. Only approximately 6% of inpatient adverse drug reactions are due to allergic reactions.¹¹

This article discusses the evaluation of patients with reported sulfa allergy and management options if medications of these classes need to be considered for their future use but does not specifically address the treatment of drug reactions. The published English-language medical literature was examined, and selected trials of drug desensitization protocols were selected for inclusion in this review.

HISTORY AND EPIDEMIOLOGY

Sulfonamides have a prominent role in medical history as the first (synthetic) antibiotic medications to be used clinically.¹ In the early 1930s, Gerhard Domagk discovered that the red dye prontosil was effective in treating staphylococcal and streptococcal bacterial infections¹² and was later awarded the 1939 Nobel Prize for this work. Although Alexander Fleming had already noted the antimicrobial properties of a natural substance derived from the *Penicillium* mold several years earlier, it took until the 1940s to produce and isolate sufficient quantities of penicillin for medical use.

Despite their long history as the earliest group of antibiotics, sulfonamides remain important medications with a wide variety of indications and are in common use to this day. Currently, the most frequently encountered sulfonamide antibiotic is the combination of trimethoprim and sulfamethoxazole. In the 1960s, trimethoprim was found to add a synergistic bactericidal therapeutic benefit when used with

sulfamethoxazole, as a selective inhibitor of microbial dihydrofolate reductase.^{13,14} The antimicrobial sulfonamides (sulfonarylaminines) are second only to the β -lactams as the most common cause of drug allergy.¹⁵

The epidemiology of sulfonamide reactions has changed markedly with the occurrence and spread of human immunodeficiency virus (HIV) infection. Before the AIDS epidemic, adverse reactions to trimethoprim-sulfamethoxazole were reported in 8% of 1,121 hospitalized patients receiving oral or parenteral forms of this medication from 1966 to 1980, in a large multicenter review.¹⁶ Most of these reactions were gastrointestinal (3.7% of patients) or dermatologic (3.3%), with less than 1% having other reactions, including fever, vertigo, thrombocytopenia, renal tubular acidosis, and elevated creatinine levels. The gastrointestinal symptoms included both upper gastrointestinal tract symptoms such as nausea, vomiting, and anorexia (3.2% of patients) and lower symptoms such as diarrhea (0.5%). The skin symptoms included erythema, urticaria, and pruritus. Notably, no cases of Stevens-Johnson syndrome (SJS) were reported. Most of these reactions occurred within the first 3 days of therapy, although some occurred up to 2 weeks after onset of treatment with trimethoprim-sulfamethoxazole. Of interest, adverse reactions appeared to be twice as common in women as in men. All reactions resolved promptly after drug therapy discontinuation.

However, in patients with HIV, the situation is strikingly different. Early reports on HIV-infected patients requiring trimethoprim-sulfamethoxazole for *Pneumocystis carinii* (*jiroveci*) pneumonia (PCP) prophylaxis found up to 34% experiencing fever and rash, resulting in drug therapy discontinuation.¹⁷ In the setting of both active AIDS and PCP, reactions to trimethoprim-sulfamethoxazole were reported to be as high as 50%.¹⁸ In this patient population, cutaneous drug reactions to sulfonamides and sulfones are even more frequent than to penicillins.¹⁹ A wide variety of clinical and immunologic factors may influence the relative risks of sulfonamide reactions in this setting,^{1,20} but many of these have not been conclusively proven. Although little has been published on changes in the epidemiology of sulfonamide reactions since the advent of highly active antiretroviral therapy (HAART), it appears that the incidence of these reactions has decreased precipitously with the recent significant improvements in effective anti-HIV treatment.

Large national adverse drug reaction registers in the United Kingdom and Sweden have provided valuable epidemiologic data with regard to sulfonamide and sulfone reactions. Of more than 8,000 reactions to these medications that were reported during more than 20 years, most involved the skin (45%), and many were serious (42% of all reactions, 12% of the skin reactions).²¹ Approximately 7% of the serious reactions were fatal, and rates of reaction appeared to increase with both increased duration and dosage of therapy with these drugs. Among the sulfonamides (and sulfones), trimethoprim-sulfamethoxazole was the most commonly impli-

cated drug for total reactions, as well as fatalities, accounting for approximately two-thirds of each.²¹

TYPES OF SULFONAMIDE ALLERGIC REACTIONS AND THEIR RESPECTIVE IMMUNOLOGIC MECHANISMS

Allergists and immunologists have long used the relatively simple Gell and Coombs scheme to classify allergic reactions, but unfortunately many sulfonamide reactions do not neatly fit into these categories. Type 1 reactions, known as immediate-type hypersensitivity, are mediated primarily by specific humoral IgE antibodies. When these are cross-linked by exposure to the relevant antigen, sensitized mast cells (and basophils) are triggered to degranulate, releasing histamine, and rapidly synthesizing related vasoactive mediators (such as leukotrienes). For many drugs, the relevant antigen is not found on the intact drug itself. Instead, reactive haptenated metabolites may become bound in large numbers to serum carrier proteins and thereby create a multivalent immunologic stimulus. This fact substantially limits the utility of simple skin testing with the original (unmetabolized) medication in most cases. For example, sulfonamide metabolism via cytochrome P450 N-oxidation is thought to lead to N⁴-sulfonamidoyl haptenization, as well as to sulfonamide hydroxylamines and nitrososulfonamides, also major haptenic antigens for allergic reactions to these drugs.^{20,22,23} Therefore, slow acetylation and/or glutathione deficiency states (such as in HIV infection) may thereby increase the likelihood of this allergic reaction.²⁰ Recent studies attempting to elucidate the details of these (likely multifactorial) cytotoxic and immunopharmacologic mechanisms have been extensively reviewed elsewhere.^{1,2,24}

Immune-complex mediated (type 3) drug allergy is also a humorally mediated immunologic reaction, but this typically involves large-molecular-weight complex biological agents (such as heterologous serum proteins), instead of relatively small and simple organic chemicals (such as sulfonamides). These large immunologically foreign compounds cause widespread activation of complement via IgM and IgG, thereby creating signs and symptoms of serum sickness. However, sulfonamides (particularly in the setting of HIV infection) more commonly cause a drug fever of delayed (1- to 2-week) onset, often accompanied by a morbilliform rash, and occasionally followed by multisystem involvement and inflammation. The more severe form of this with systemic involvement has sometimes been termed the DRESS syndrome (drug rash with eosinophilia and systemic symptoms).²⁵ The specific immunologic cause of these latter reactions has not yet been completely elucidated, but it appears to be somewhat distinct from simple IgE-mediated and immune complex-mediated (IgM/IgG) mechanisms. In particular, certain investigations suggest T cells and toxic metabolites as central mediators in this process.^{1,26}

The 2 remaining classic Gell and Coombs reactions, type 2 (antibody-mediated cytotoxic) and type 4 (delayed-type hypersensitivity), are not particularly commonly involved in

sulfonamide allergy. However, SJS is another distinct type of sulfonamide reaction of uncertain pathogenesis that occurs by immunologic mechanisms that remain somewhat enigmatic. In this article, the term *SJS* refers to the entire spectrum of this condition, which can range from relatively mild erythema multiforme minor to erythema multiforme major (a severe exfoliative dermatitis) to life-threatening toxic epidermal necrolysis (TEN; or Lyell syndrome). Although relatively rare, with an incidence of approximately 1 case per million person-years, antimicrobial sulfonamides are the most common medication etiologically associated with SJS and TEN.²⁷ Of interest, in that particular study, the nonantimicrobial sulfonamides (specifically including furosemide and thiazide diuretics and sulfonylurea hypoglycemics) were not associated with excess risk of SJS or TEN.²⁷

Sulfonamides are also contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, because this can result in hemolytic anemia. However, because these are genetic metabolic-type adverse drug reactions and not specifically allergic in nature, they are not dealt with further in this article.

EVALUATION AND MANAGEMENT OF PATIENTS WITH A REPORTED HISTORY OF SULFA ALLERGY

Obtaining a careful, thorough, and detailed history is the most important step in the evaluation of a patient who reports a sulfa allergy, which becomes even more important given the common improper use of this term. With the present lack of easy, safe, and definitive tests for either confirming or ruling out true sulfonamide allergy, combined with the potentially life-threatening severity of reactions to drugs of this class, consultation with a clinician experienced with evaluation and management of drug allergies may be prudent if acceptable alternative medications are not available.

When obtaining the history, focused and specific questions should be directed to address all relevant prior adverse drug events.²⁸ Details should include the following: (1) each exact agent reportedly associated with a reaction and the indication for its use; (2) the precise nature and severity of that reaction; (3) the dose and route of medication taken; (4) other concurrent medications and their prior duration of use; (5) the timing of onset of the reaction (from both the precipitating dose and the initiation of that course of therapy); (6) any treatment given and response to that treatment (including the duration of reaction); (7) length of time elapsed since last known exposure to medications of that same pharmacologic class; and (8) any prior or subsequent history of exposure to agents in that class and presence or absence of any associated reaction(s).

Some consideration must be given to the apparent reliability of the source of this information, because patients are often vague or uncertain regarding details of prior drug reactions. Sometimes, obtaining further details from relatives may be particularly helpful, especially if the prior reaction was remote and the patient was young at that time. Particular

caution should be accorded to patients who report emergency department visits or hospitalizations in association with prior drug reactions. Any associated objective medical records, if available, are invaluable in documenting vital signs, skin findings, and other important historical data. An excellent overview of these issues with particular attention to sulfonamides has been recently published.²²

It is prudent for patients to wear medical identification jewelry to notify health care personnel of significant medication allergies, in case of incapacity.³ This is especially important if reactions have been severe or involve medications that may be commonly used in an emergency setting.

If the suspected sulfonamide-containing drug was specifically a trimethoprim-sulfamethoxazole combination product, one should remain aware of the possibility that the trimethoprim component may be the culprit instead. In 2 studies of patients with HIV and history of reactions to trimethoprim-sulfamethoxazole, 5 of 31 (16%)²⁹ and 14 of 73 (19%)³⁰ did not tolerate trimethoprim alone on rechallenge.

Other health issues and medical conditions, as well as the reason for considering the use of a potentially contraindicated medication, should also be evaluated. In general, when faced with a possible, probable, or confirmed drug allergy, there are 3 major management approaches: use of an alternative acceptable medication of a different (and immunologically non-cross-reactive) pharmacologic class, consideration of carefully monitored test dosing, or a trial of a medication desensitization protocol.²³

Diagnostic Testing

Although a variety of immunologic testing techniques have been tried experimentally to evaluate sulfonamide medication reactions, none has yet been proved to be reliable, valid, and practical for clinical use. These techniques have included both in vivo tests, such as skin testing³¹ and patch testing,^{32,33} and in vitro tests, such as lymphocyte toxicity assays^{34–36} and enzyme-linked immunosorbent assay and radioallergosorbent testing for specific IgG and IgE.^{31,37,38} In contrast to sulfonamides and most other medications, penicillin and closely related β -lactams have specifically validated skin testing protocols, although reliably obtaining the relevant reagents remains problematic. However, for almost all other (nonbiological) drugs, including the sulfonamides, the relevant allergenic metabolites and mechanisms are not currently elucidated well enough to develop accurate testing methods. Non-specific irritant responses to trimethoprim-sulfamethoxazole may also result if intradermal skin testing is performed with concentrations greater than 100-fold dilution of a full-strength preparation.³⁹ Thus, for now, sulfonamide allergy remains primarily a clinical diagnosis.⁴⁰

Graded Drug Challenges

Also sometimes termed *test dosing* by allergists, graded drug challenges differ substantially from formal drug desensitization protocols. In an individual with a history of a drug reaction that was relatively mild and clinically unconvincing

for true immunologically mediated drug allergy, consideration can be given to cautiously administering small and increasing doses of a suspect medication under careful medical observation. This should be done if medically acceptable alternatives do not exist and just before anticipated use. It is done without premedication (which would obscure detection of early and mild allergic reactions) and after thorough discussion of risks vs benefits of the procedure (informed consent). Any other concurrent health issue must be under optimal control, particularly cardiopulmonary conditions. Patients must not be taking any medications that may increase the likelihood of anaphylaxis or interfere with the treatment of such reactions, such as β -blockers or ACE inhibitors. Although concern regarding the former is well known in this context, the latter medications have also been associated with possible increased risk of anaphylaxis during immunotherapy and thus listed as a contraindication in Food and Drug Administration package labeling for this entire class of medications.^{41,42} The test dosing should be performed in an appropriate medical setting, with proper monitoring in place and immediate availability of rescue medications and equipment. Consultation with specialists familiar with allergic reactions and medication allergy is prudent, if available. Various general approaches and guidelines for starting doses, dose escalation, frequency of dosing, and similar details have been published^{3,23} but are dependent on the specifics of each situation and often require individualized modification. In addition, if there is a history of desquamation or exfoliative dermatitis syndromes such as SJS, *any* rechallenge is strictly contraindicated—neither test dosing nor drug desensitization should be attempted.

Drug Desensitization Protocols

Drug desensitization protocols usually refer to procedures designed to allow patients with a history of type 1 (IgE-mediated, immediate-type hypersensitivity) drug allergy to safely tolerate readministration of these agents, such as for β -lactams. Protocols have also been developed for a certain few other medication reactions that occur via different immunologic pathways (such as to aspirin and allopurinol and to sulfonamides), and this same term is also confusingly applied to these as well, despite the significant differences in presumed mechanisms of action.²⁰ These procedures are *strictly* contraindicated if there is a history of desquamative or exfoliative reactions, SJS, or any similar clinical syndrome. These protocols are also completely different from allergen specific immunotherapy, which is used to induce immunologic tolerance to aeroallergens such as pollens, animal danders, and dust mites. Although currently not in common use, it may be preferable to use the term *drug hyposensitization* or *induction of tolerance* for these procedures given their significant risks and limited duration of effect, instead of *desensitization*.

Several prospective trials of trimethoprim-sulfamethoxazole desensitization have been published, 2 of which are presented in detail herein.^{38,43} Both trials involved HIV-positive patients, with a history of trimethoprim-sulfamethox-

azole-associated fever or nonexfoliative rash, needing PCP prophylaxis. Their protocols are listed in Table 1 and Table 2, respectively.

The largest published study involved 48 patients followed up for a mean of 16 months after the 2-day protocol outlined in Table 1.⁴³ By day 3, the dose escalation had reached a full (single-strength) trimethoprim-sulfamethoxazole tablet, and 77% of those undergoing this regimen were able to tolerate the course of therapy without adverse effects. Eleven of the 48 were not able to complete the full course, 8 of these stopped within the first 2 days. One patient experienced hypotension and acute nonfatal myocardial infarction. Higher relative and absolute CD4 cell counts were associated with trends toward higher risk of failure.

Another study of 22 patients used a different and longer protocol (Table 2) and was associated with a higher (86%) rate of completion.³⁸ Only 3 individuals were not ultimately successful with this protocol, although significant reactions occurred in 8 of the 22 patients. All of these reactions were mild to moderate rash or fever, which resolved after a brief course of systemic corticosteroid treatment. No episodes of hypotension or anaphylaxis occurred. Of note, despite their clinical history of sulfonamide sensitivity, all of these patients had negative skin test results to sulfamethoxazole. These 2 protocols, along with 9 other similar studies involving sulfonamide desensitization in HIV-positive patients, have been compared in detail in a recent review on drug desensitization.²⁰

There have since been conflicting studies comparing sulfonamide desensitization directly with cautious test dosing that have called into question the effectiveness of these procedures. In one trial, statistically similar numbers of patients were able to tolerate reexposure, in a group undergoing a desensitization protocol compared with a group rechallenged directly with sulfonamides.³⁰ This finding may suggest that some of the patients who were able to complete the prior desensitization studies without reaction may have not been truly at risk of reacting because of immunologic changes over time, an inaccurate or incorrect clinical history, or other

unknown reasons. There was a trend noted toward lower rate of reaction in the desensitization group; thus, this study may have been underpowered to detect a limited improvement in rates of tolerance.³⁰ In addition, 14 of the 73 patients in this study (19%) were excluded because of reactions to trimethoprim alone before rechallenge or desensitization procedures.³⁰ A larger, more recently published similar trial was halted early by its Data and Safety Monitoring Board after enrolling 191 patients when the dose-escalation group was found to have significantly higher rates of tolerating reexposure to trimethoprim-sulfamethoxazole.⁴⁴ It is always important to remain particularly cognizant of selection bias that may potentially confound all trials of drug desensitization protocols, since patients with a clear history of extremely severe drug allergy are generally excluded for obvious ethical and safety reasons.

Most of the published trimethoprim-sulfamethoxazole desensitization trials have used the oral route, because this is presumed generally safer than intravenous protocols. More rapid protocols have also been published for trimethoprim-sulfamethoxazole but may warrant additional caution for potentially increased risks of these procedures.⁴⁵ Desensitization protocols for sulfonamides other than sulfamethoxazole, such as sulfadiazine (for cerebral toxoplasmosis in patients with AIDS), have been published as well.⁴⁵

Indications and Technique

For patients with a convincing history of significant sulfonamide reactions, where there are no medically acceptable alternatives, a drug desensitization procedure may be attempted after obtaining informed consent by a physician experienced in the procedure. Patients should be specifically advised of the potentially life-threatening nature of possible allergic or anaphylactic reactions during the procedure and the alternative risks of using "second-best" therapy (and thereby simply avoiding medications of this class). It is essential that this occurs in an appropriate and carefully monitored medical setting, with rescue equipment, personnel, and medications available if needed. All comorbid medical conditions should be optimally managed, with special attention to cardiopulmonary status. Just as discussed earlier for graded drug challenges, patients must not be taking medications known to increase allergic reactions or interfere with their management, particularly ACE inhibitors and β -blockers (including eye drops). Premedication with antihistamines and steroids is not protective from anaphylaxis and may mask early sentinel signs of allergic reactivity and thus is generally avoided. During dose escalation, reactions of varying severity may occur, necessitating treatment and/or dose adjustment. Although guidelines for management of these reactions have been published elsewhere, clinical judgment is essential, ideally in consultation with an allergist or other expert in managing severe allergic reactions (such as intensivist or anesthesiologist). The risks of continuing the procedure must be continually evaluated and balanced against the risks of using alternate "second-best" therapy.

Table 1. Oral Trimethoprim-Sulfamethoxazole Desensitization Protocol^a

	Trimethoprim, mg	Sulfamethoxazole, mg
Day 1		
9 AM	0.8	4
11 AM	1.6	8
1 PM	4	20
5 PM	8	40
Day 2		
9 AM	16	80
3 PM	32	160
9 PM	40	200
Day 3		
9 AM	80	400 (1 single-strength tablet)

^a Adapted from Caumes et al.⁴³

Table 2. Oral Ambulatory Incremental Regimen for Patients Sensitive to Trimethoprim-Sulfamethoxazole (3 Doses Given Each Day)^a

Day	Sulfamethoxazole concentration, mg/mL	Volume per dose, mL	Total daily sulfamethoxazole dose, mg
1	0.00002	1, then 3, then 7	0.00022
2	0.0002	1, then 3, then 7	0.0022
3	0.002	1, then 3, then 7	0.022
4	0.02	1, then 3, then 7	0.22
5	0.2	1, then 3, then 7	2.2
6	2	1, then 3, then 7	22
7	20	1, then 3, then 7	220
8	40	5, then 10, then 20	1,400
9 and thereafter		1 double-strength tablet (160 mg/800 mg)	

^a Adapted from Rich et al³⁸ (revised August 20, 2007).

Risks

Risks of drug desensitization procedures include, but are not limited to, the entire spectrum of allergic reactions. This includes dermatologic reactions such as urticaria and angioedema or other types of rash (including SJS), pulmonary reactions such as asthma, and cardiovascular reactions such as hypotension to frank multisystem anaphylaxis. Other types of serious and life-threatening reactions have also been reported in association with these procedures, including myocardial infarction.⁴³

Duration of Efficacy

Once patients successfully complete a desensitization protocol and are finally able to tolerate standard daily doses of this drug, it must be continued throughout the treatment duration without missing a single daily dose. Within 24 to 48 hours of the last dose, medication resensitization can recur, and thus patients should be informed that they still remain allergic to these particular drugs.⁴⁶ The mechanisms of this resensitization for non-IgE-mediated drug allergy remain unknown at present. If a repeat course of similar therapy becomes necessary in the future, another desensitization procedure would again need to be performed before safely restarting use of this medication.

DISCUSSION

Among patients with a history of reactions associated with various sulfur-containing medications, a number of particular clinical situations may commonly arise.

Sulfonamide Cross-reactivity Issues

Allergists have long known that most, though not all, patients with a convincing history of antimicrobial (arylamine-containing) sulfonamide allergy appear to tolerate other non-arylamine sulfonamide medications. A history of drug allergy to one pharmacologic class may be associated with some generalized increased risk of reactions to medications of other distinct and non-cross-reactive classes.⁴⁷ A prominent retrospective cohort study has recently been published that has helped to clarify these important issues. Using a large UK medical practice database (data on more than 8 million pa-

tients during a 12-year period), individuals who had a documented allergic reaction to a sulfonamide antibiotic reacted more commonly to a sulfonamide nonantibiotic (9.9%) than others who had specifically tolerated sulfonamide antibiotics in the past (1.6%).⁴⁸ However, those same individuals with documented sulfonamide antibiotic reactions reacted to the pharmacologically distinct class of penicillins even more often (14.0%), strongly suggesting that this reflects a propensity for immunologic drug reactions in general, as opposed to specific cross-reactivity within the chemically diverse category of sulfonamides themselves.⁴⁸ Interestingly, the converse was also noted, with a higher risk of reaction to sulfonamide nonantibiotics in those with a history of reactions to penicillins than those with a history of reactions to sulfonamide antibiotics.⁴⁸ These results were found to be robust, using both narrower and broader definitions of criteria for inclusion and classification of these presumed allergic reactions.

Another study specifically designed to evaluate potential cross-reactivity among different sulfonamides was recently published. This prospective observational study of 94 hospitalized adults with reported sulfa allergy noted that 40 of these patients (43%) had been taking a nonantimicrobial sulfonamide as outpatients for a median duration of 6.2 years, and 9 patients (10%) received nonantimicrobial sulfonamides as inpatients, all without adverse reaction.⁴⁹ In most of these cases, furosemide was the specific nonantimicrobial sulfonamide that was tolerated.

The theoretical basis for these differences in cross-reactivity or cross-allergenicity among sulfonamides of various classes has been reviewed in detail by Cribb et al.²⁴ Important chemical, structural, metabolic, and immunologic determinants vary significantly among sulfonamides of antimicrobial, diuretic, hypoglycemic, and antihypertensive categories, which may account for these differences.

Antimicrobial Sulfonamide Allergy in HIV Infection

Until the advent of HAART, this was the most common of the clinical situations involving sulfa allergy. Fortunately, now there is much more effective HIV treatment available,

and the number of patients with severely depressed CD4 T-lymphocyte cell counts has markedly decreased and therefore so has the need for PCP prophylaxis in patients at elevated risk for sulfonamide allergy. Alternate prophylaxis and/or treatment options have included trimethoprim-dapsone (also sometimes problematic in sulfonamide allergy), pentamidine, atovaquone, clindamycin-primaquine, and trimetrexate-leucovorin.⁵⁰

Sulfasalazine Allergy in Inflammatory Bowel Disease and Rheumatic Diseases

Another clinical situation that had been similarly challenging is the use of sulfasalazine for inflammatory bowel disease. Sulfasalazine is a sulfonamide prodrug activated in the gut by cleaving the presumed inactive sulfapyridine moiety away from the active therapeutic salicylate, 5-aminosalicylic acid. Sulfonamide allergy had frequently complicated this treatment, but different preparations of 5-aminosalicylic acid itself have become available and may be preferable for use.⁵¹ Additionally, new immunomodulatory therapies have also recently been developed, which has improved treatment options and overall management of this condition. Before these developments, protocols had been published that were effective in allowing many patients to eventually tolerate the use of sulfasalazine but have since become of largely historical interest.^{52,53} Sulfasalazine has been used in a variety of other conditions, including psoriasis, lupus, and rheumatoid arthritis, and patients with these conditions have also been desensitized as necessary.⁵⁴ However, here too, sulfasalazine may often now be replaced by other more effective and better-tolerated agents.

Nonantimicrobial Sulfonamide Allergy in Patients Needing Diuresis

Most of the potent loop diuretics are sulfonamides, which may cause allergic reactions,^{55,56} albeit less commonly than the antimicrobial sulfonamides. This situation is further complicated by the fact that many of the less potent diuretics (including thiazides, spironolactone, and carbonic anhydrase inhibitors such as acetazolamide) also contain sulfur moieties of various types, with poorly understood risks of cross-allergenicity.

In addition to the recent study by Strom et al,⁴⁸ 2 other significant studies of risks of cross-reactivity of nonantimicrobial sulfonamides in patients with medical record–documented sulfa allergy have been published. In the article by Hemstreet et al, 24 sulfa-allergic patients had received furosemide as outpatients and 9 as inpatients, all of which was tolerated without adverse reaction.⁴⁹ Finally, another study of 34 patients with reported sulfa allergy and intracranial hypertension treated with furosemide and/or acetazolamide revealed no documented severe adverse reactions due to those medications. No reactions occurred in those receiving furosemide, although of those receiving acetazolamide 7% had urticaria and 56% had known predictable adverse effects of

the acetazolamide itself (eg, paresthesias, gastrointestinal symptoms).⁵⁷

Currently, ethacrynic acid is notable as the only loop diuretic that is not a sulfonamide. During a recent period of ethacrynic acid unavailability, however, reports were published detailing a graded-dose challenge to torsemide⁵⁵ and furosemide desensitization protocols^{56,58} in patients with sulfonamide sensitivity and presumed unable to otherwise tolerate alternative agents.

Sulfonylurea Allergy in Diabetes

Some of the oral hypoglycemic agents used in type 2 diabetes mellitus are nonantimicrobial sulfonamides, although these are chemically classified as sulfonylureas. These medications occasionally cause adverse reactions with presumed immunologic mechanisms, most commonly various dermatologic drug eruptions such as urticaria, photosensitive rash, and leukocytoclastic vasculitis. The symptoms usually associated with drugs of this category are rather different from those often seen with the sulfonylarylamines, as described previously. Apart from a few isolated case reports, little of the published medical literature addresses issues of possible cross-reactivity between these 2 distinct categories of medications. There may, however, be some distinct patterns of cross-allergenicity *within* the sulfonylurea group itself.⁵⁹

Management of sulfonylurea allergy in diabetic patients has become less challenging in recent years because numerous other agents of different classes and mechanisms have been developed. New treatment paradigms have since shifted these medications away from their previously central role, given their less favorable overall risk-to-benefit ratio. Achieving glycemic control using parenteral insulin presents another effective management alternative in these diabetic patients, although insulin itself may also be immunogenic.⁶⁰ Historical rates of insulin allergy have markedly declined with the advent of recombinant human products, synthetic insulin lispro,⁶¹ and insulin pump therapy,⁶² compared with the prior use of bovine and porcine sources.⁶³

Celecoxib and Sulfonamide Allergy

Some controversy remains with regard to issues of possible cross-reactivity between antimicrobial sulfonamides and the (nonsulfonylarylamine) sulfonamide celecoxib, although the bulk of evidence to date suggests that this is probably unlikely.⁶⁴ A prospective pilot study of 28 patients with a history of reactions to antimicrobial sulfonamides and indications for treatment with celecoxib were all challenged with this medication, initially a small test dose and followed by a full dose, after extensive allergy investigation.⁶⁵ All patients initially tolerated the celecoxib uneventfully, including all 6 patients with positive in vivo or in vitro sulfamethoxazole allergy test results. Later follow-up documented that 5 patients had discontinued this therapy for a variety of reasons, including lack of efficacy or physician preference. Only 1 of these, however, had discontinued therapy specifically because of adverse

effects, gastrointestinal symptoms that resulted in discontinuation after 12 days.⁶⁵

In a large meta-analysis of more than 11,000 patients from 14 double-blinded trials of celecoxib used for arthritis, the rate of allergic reactions specifically to celecoxib was not statistically different from placebo or active alternate therapy (other nonsteroidal anti-inflammatory drugs).⁶⁶ Although sulfonamide allergy was part of the exclusion criteria for those trials, 135 of the 11,008 patients studied deviated from the protocol in that regard. Subgroup analysis of those patients with a history of allergic sulfonamide reactions, as expected, had a higher rate of dermatologic reactions than that of the group as a whole. However, the 3- to 6-fold elevation found in this rate was again not statistically different among those challenged with celecoxib, other nonsteroidal anti-inflammatory drugs, or placebo.⁶⁶

Although a large retrospective review of postmarketing safety surveillance reports (from the Food and Drug Administration Adverse Events Reporting System) for several of the selective cyclooxygenase-2 inhibitors did not specifically study possible cross-reactivity issues among different classes of sulfonamides, it documented significant increases of reported SJS above baseline rates in patients using medications of the coxib class.⁶⁷ Compared with an expected background rate of 1.9 cases per million annually, calculated rates were 5.7 per million in celecoxib users (based on 19 reported cases in the first 2 years of marketing) and 21% of these cases had also reported sulfa allergy.⁶⁷ Since comparison data from appropriate control groups are not available in studies of this nature, which are spontaneous reports of rare adverse events, risks of possible cross-reactivity cannot be calculated or directly inferred. Nevertheless, until these issues are further clarified, it remains prudent to consider structurally distinct alternatives in this situation.

Sulfone Allergy

Dapsone is another sulfur-containing medication, but chemically and pharmacologically it is a sulfone (diaminodiphenylsulfone) not a sulfonamide. This drug is most commonly used to treat neutrophilic dermatoses such as dermatitis herpetiformis. It is also used in the treatment of leprosy and as second-line prophylaxis for PCP and malaria. Hypersensitivity to dapsone (or the sulfone syndrome) occurs, characterized by symptoms similar to those seen in sulfonamide reactions (such as fever and rash, sometimes accompanied by hepatitis, lymphadenopathy, and/or hemolytic anemia) and can be even more severe.⁶⁸ Relative risks of possible cross-reactivity with sulfonamide antibiotics remain poorly understood.

Although dapsone is often better tolerated than sulfamethoxazole in patients with HIV infection,⁶⁹ one study showed "possibly related" cross-allergenicity in 5 of 75 patients (7%) with a history of prior reactions to trimethoprim-sulfamethoxazole.⁷⁰ This may be confounded by the high frequency of adverse reactions to dapsone itself, however. Other studies involving HIV infection have documented

much higher rates of presumed cross-reactivity, such as in 9 of 23 patients (39%)⁷¹ and 13 of 60 patients (22%).⁷² Blum and colleagues published a randomized, direct crossover PCP prophylaxis trial of 86 patients with HIV in which those reacting to trimethoprim-sulfamethoxazole were crossed over to dapsone and vice versa. Only approximately half of each group was able to tolerate the other medication, although their definition of drug toxicity was not specifically limited to presumed allergic mechanisms.⁷³ Drug desensitization protocols have also been published for dapsone.^{74,75}

CONCLUSION

Immunologic reactions to sulfonamides and related medications continue to challenge both patients and physicians. Use of the term *sulfa allergy* is imprecise, incorrect, and often misleading and should be abandoned. Recognition of the distinct categories of sulfonylarylamines (antimicrobial sulfonamides), nonarylamine (nonantimicrobial) sulfonamides, and sulfones is important. Complex and not yet fully elucidated immunochemical relationships exist among these groups. Most sulfonylarylamine (and sulfone) reactions probably result from multifactorial immunologic and toxic metabolic mechanisms. Sulfonamide reactions are far more common in untreated HIV disease (and especially in active AIDS) than in the general population. With the advent of HAART, rates now appear to be declining. Finally, sulfonamide allergy remains a clinical diagnosis, without the availability of routine confirmatory testing. If medically acceptable alternatives are not available, consideration may be given to test dosing or drug hyposensitization protocols. These decisions depend on the specific clinical situation and may be best made in consultation with an expert in drug allergy.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

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CME Examination

1–5, Dibbern Jr DA, Montanaro A. 2008;100:91–100.

CME Test Questions

1. Most so-called sulfa antibiotics are members of which chemical class?
 - a. sulfonylarylamines
 - b. sulfonylureas
 - c. sulfhydryls
 - d. sulfites
 - e. sulfates
2. Absolute or relative contraindications to graded drug challenges and drug hyposensitization protocols include all of the following, *except*:
 - a. angiotensin-converting enzyme inhibitors
 - b. β -blocker eye drops
 - c. calcium channel blockers
 - d. history of desquamation
 - e. poorly controlled comorbid illness
3. Which group of medications is the most common cause of drug allergy?
 - a. antimicrobial sulfonamides
 - b. diuretic sulfonamides
 - c. β -lactams
 - d. tetracyclines
 - e. sulfones
4. Most adverse drug reactions to sulfonamides can *best* be classified as:
 - a. Gell and Coombs type 1 reactions
 - b. Gell and Coombs type 2 reactions
 - c. Gell and Coombs type 3 reactions
 - d. Gell and Coombs type 4 reactions

-
- e. multifactorial immune-mediated toxic metabolic reactions
5. Which of the following loop diuretics is *not* a sulfonamide?
- a. furosemide
 - b. bumetanide

- c. torsemide
- d. ethacrynic acid
- e. none of the above, *all* loop diuretics are sulfonamides

Answers on page 111
