

Nicholas B. Cline, MDThe Allergy, Asthma, and Sinus Center,
Harriman, TN**Amudha Pazhanisamy, DO**Department of Allergy and Clinical
Immunology, Medical Specialty Institute,
Cleveland Clinic, Cleveland, OH**David M. Lang, MD**Department of Allergy and Clinical
Immunology, Medical Specialty Institute,
Cleveland Clinic, Cleveland, OH; Professor,
Cleveland Clinic Lerner College of Medi-
cine of Case Western Reserve University,
Cleveland, OH

Q: Can my patient with a ‘sulfa allergy’ receive celecoxib or other nonantimicrobial sulfonamides?

A: There is no cross-reactivity between antimicrobial sulfonamides and nonantimicrobial sulfonamides. For this reason, patients with a history of immunoglobulin (Ig) E-mediated (allergic or anaphylactic) reaction to a sulfonamide antibiotic can receive nonantimicrobial sulfonamides such as celecoxib, chlorthalidate, furosemide, and others without elevated risk of an IgE-mediated reaction compared with the general population.

■ SULFONAMIDE ALLERGY

Patients with a reported sulfonamide allergy are frequently encountered in clinical practice. A history of “sulfa allergy” is second in frequency to penicillin allergy and is reported in 3% to 6% of the general population.¹⁻⁴ Clarification of allergy status is particularly important because sulfonamide antibiotics remain first-line treatments for certain infections, including *Pneumocystis jirovecii*, *Toxoplasma gondii*, and *Stenotrophomonas maltophilia*.⁵

Adverse reactions to sulfonamides vary from mild and self-limited to potentially life-threatening, and may include any of the 4 hypersensitivity reactions from the Gell and Coombs classification (Table 1).^{1,2} Cutaneous reactions are the most frequent, with maculopapular exanthemas being the most common type.⁶ Cutaneous reactions to sulfonamides have also been reported in up to 30% of patients with human immunodeficiency virus.¹ Drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, and other severe adverse reactions are fortunately less common.⁵

doi:10.3949/ccjm.92a.24054

■ CROSS-REACTIVITY BETWEEN SULFONAMIDES

Table 2 lists commonly prescribed antimicrobial and nonantimicrobial sulfonamides. These drugs all contain an SO_2NH_2 moiety (Figure 1), from which they derive the designation *sulfonamides*. Antimicrobial sulfonamides contain an arylamine group at the N4 position, which accounts for the drugs’ antimicrobial function through competitive inhibition of a structurally similar compound needed for microbial processes. This arylamine group and another nitrogen-containing ring found in antimicrobial sulfonamides are the primary targets, or determinants, for allergic sensitization.^{1,2}

Type I (immediate) hypersensitivity reactions occur when IgE binds and cross-links to a specific antigenic determinant. This results in the activation of mast cells and the release of inflammatory mediators, including histamine, leukotrienes, and others, which can manifest as pruritus, urticaria, angioedema, bronchospasm, vomiting, and hypotension. Thus, molecular structure determines IgE-mediated allergenicity and cross-reactivity. An index reaction to 1 antimicrobial sulfonamide agent precludes future use of other antimicrobial sulfonamides due to interclass cross-reactivity of the shared arylamine group’s allergenic determinant.⁷ A preferred label for this allergy would be *sulfonamide antibiotics*, to indicate that an alternative nonsulfonamide antibiotic should be used. Notably, these type I allergic reactions to sulfonamides are not directed at the SO_2NH_2 group after which the drug class is named.²

Nonantimicrobial sulfonamides include carbonic anhydrase inhibitors, selective cyclooxygenase-2 inhibitors, loop diuretics, sulfonyleureas, thiazide diuretics, triptans, and other agents.² Although product information approved by the US Food and Drug Administration for

TABLE 1
Gell and Coombs classification of hypersensitivity reactions

Type	Hypersensitivity reaction	Immune mechanism	Description
I	Immediate hypersensitivity	Immunoglobulin E-mediated reaction driven by immunoglobulin E bound to mast cells or basophils or both	Engagement of immunoglobulin E with its appropriate antigen leads to degranulation and release of histamine, leukotrienes, and other inflammatory mediators (eg, anaphylaxis)
II	Cytotoxic antibody	Antigen-antibody interaction	Local production of anaphylatoxin (C5a) and recruitment of polymorphonuclear leukocytes lead to release of hydrolytic neutrophil enzymes and subsequent tissue injury (eg, immune cytopenia)
III	Immune complex	Immunoglobulin G and M antibodies bind to antigen	Antigen-antibody complexes deposit in the glomerular basement membrane, pulmonary basement membrane, or both, leading to tissue injury and organ damage (eg, serum sickness reaction)
IV	Delayed hypersensitivity	Cell-mediated immune response	T cells are activated by an antigen-presenting cell; when antigen is presented again, memory T cells activate leukocytes (macrophages, neutrophils, eosinophils), leading to an inflammatory response with possible tissue injury via reactive oxygen species, lysosomal enzymes, and inflammatory cytokines (eg, tuberculin skin test, Rhus dermatitis, Stevens-Johnson syndrome or toxic epidermal necrolysis)

nonantimicrobial sulfonamides may include warnings about possible cross-reaction with antimicrobial sulfonamides,¹ these drugs do not need to be withheld. Nonantimicrobial sulfonamides lack an arylamine group at the N4 position, so they do not cross-react with antimicrobial sulfonamides. For example, a patient with a history consistent with IgE-mediated reaction to the antimicrobial sulfonamide trimethoprim-sulfamethoxazole can receive celecoxib, chlorthalidate, furosemide, or other nonantimicrobial sulfonamides, as indicated.

Antimicrobial sulfonamide metabolites are most likely responsible for non-IgE-mediated reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.^{1,2,6} Because nonantimicrobial sulfonamides lack an arylamine group, they do not produce similar metabolites, which is the reason they do not cross-react in patients who have had non-IgE-mediated reactions to antimicrobial sulfonamides.

Patients who have had IgE-mediated or non-IgE-mediated reactions to antimicrobial sulfonamides may also receive medications or other agents that contain sulfates or sulfites, such as morphine sulfate, ferrous sulfate, potassium metabisulfite, and sodium bisulfite, as

these are not sulfonamides. The same recommendation applies for dapsone, a sulfone, which also does not need to be withheld.

■ EVALUATION AND MANAGEMENT OF SULFONAMIDE ALLERGY

Sulfonamide allergy management depends on the type of reaction and the underlying immune mechanism. Patients who report a severe delayed immune-mediated reaction (eg, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome or toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug-induced nephritis or hepatitis) should subsequently avoid the culprit drug, as this can be regarded as a contraindication to future use.^{4,8-11} However, patients with more benign reactions or a suspected IgE-mediated allergy may be candidates for reevaluation.

Lack of validated testing

Clinical history combined with immediate hypersensitivity skin or in vitro testing can be used to confirm or rule out IgE-mediated allergic potential to penicillin;

TABLE 2
Commonly prescribed antimicrobial and nonantimicrobial sulfonamides

Antimicrobial	Nonantimicrobial	
	Class	Examples
Sulfacetamide	Carbonic anhydrase inhibitors	Acetazolamide
Sulfadiazine	Cyclooxygenase-2 inhibitors	Celecoxib
Sulfamerazine	Loop diuretics	Bumetanide
Sulfamethoxazole		Furosemide
Sulfanilamide		Torsemide
Sulfapyridine	Sulfonylureas	Glipizide
Sulfasalazine		Glyburide
Sulfathiazole	Thiazide diuretics	Hydrochlorothiazide
		Chlorthalidone
	Triptans	Rizatriptan
		Sumatriptan
	Miscellaneous	Diazoxide
		Tamsulosin
		Zonisamide
		Metolazone
		Probenecid

in vitro testing is generally not recommended based on poor sensitivity.⁴ In contrast to penicillin, neither skin nor in vitro testing for sulfonamide allergy has been validated.^{4,8} The reference standard to establish allergic potential vs tolerance is drug provocation, or direct oral challenge (DOC) with a test dose of the culprit drug.

In the absence of validated diagnostic testing, counseling for a reported “sulfa allergy” historically led to a recommendation of future sulfonamide drug avoidance. When a sulfonamide drug was clearly indicated, without an equally efficacious antibiotic that could be used, desensitization was performed to induce temporary tolerance.⁴ This enabled administration of a sulfonamide antibiotic to treat an acute infection, but it did not clarify whether an allergic or anaphylactic potential was present. Although effective, these protocols were lengthy, costly, and at times impractical—especially for patients needing intermittent therapy, as serial desensitization was required for temporary tolerance for each antibiotic course.⁸

DOC for low-risk patients

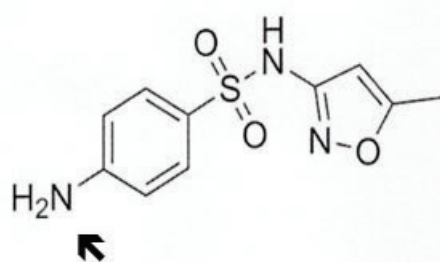
Fortunately, guidance on the approach to sulfonamide allergy has evolved to reflect more recent data showing the safety and efficacy of performing DOC in properly selected low-risk patients. A simplified algorithm for reassessment, as opposed to avoidance or desensitization, which implies a presumption of lifelong

IgE-mediated potential, enables allergy “delabeling” based on history-guided DOC as standard of care.

We have learned that rates of true or persistent type I hypersensitivity to sulfonamide antibiotics are lower than previously thought.⁴ Accordingly, the 2022 Drug Allergy Practice Parameter update⁴ recommends a 1-step DOC to trimethoprim-sulfamethoxazole for low-risk patients, defined as those with a history of benign cutaneous reaction (eg, morbilliform or urticarial rash), unknown or remote history, or nonsevere delayed (> 36 hours) reaction to a sulfonamide antibiotic. As an added precaution for patients with a reaction history within the previous 5 years, which makes them higher risk, a 2-step DOC, starting with 10% of the target dose, is recommended.

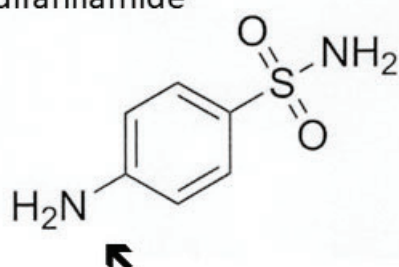
This protocol is an extension of the widely accepted PEN-FAST (penicillin allergy reported by patient, five years or less since reaction, anaphylaxis or angioedema, severe cutaneous adverse reaction, and treatment required for reaction) clinical decision tool that has been used to identify patients with reported penicillin allergy who are appropriate for DOC rather than immediate hypersensitivity skin testing, which recent data suggest has poor positive predictive value in low-risk patients.¹¹ Preliminary data for the SULF-FAST clinical decision tool have been promising, with high

Sulfamethoxazole

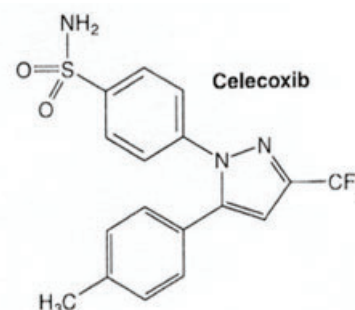


N4 position

Sulfanilamide



N4 position



Chlorothiazide

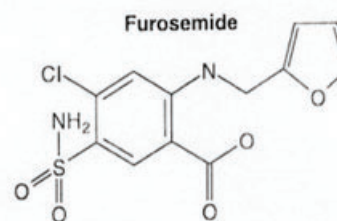
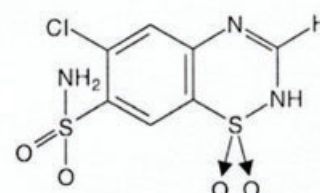


Figure 1. Chemical structures of antimicrobial and nonantimicrobial sulfonamides. Interclass reactivity and nonreactivity between antimicrobial and nonantimicrobial sulfonamides are shown. All sulfonamides contain an SO_2NH_2 moiety. Antimicrobial sulfonamides (eg, sulfamethoxazole and sulfanilamide) contain an arylamine group at the N4 position (arrow), which serves as the primary target for immunoglobulin E-mediated sensitization. Nonantimicrobial sulfonamides (eg, celecoxib, chlorothiazide, and furosemide) lack the arylamine group at the N4 position. For this reason, these drugs do not cross-react with antimicrobial sulfonamides.

specificity and negative predictive value; however, further validation is required before it is implemented more widely.¹²

Delabeling patients

Earlier studies were directed at delabeling patients with greater need for sulfonamide antibiotics, such as trimethoprim-sulfamethoxazole for *P jirovecii* prophylaxis in immunosuppressed populations, including patients with cancer, human immunodeficiency virus, or acquired immunodeficiency syndrome in whom the benefit of DOC outweighed the risk.¹³ More recent data have shown similar levels of DOC safety and tolerance in the general population.^{8,10,12} Proactive delabeling

for “sulfa allergy” is not yet the standard of care as it is for penicillin. However, when there is an explicit need for sulfonamide antibiotic therapy, including anticipated immunosuppression due to a future organ transplant,¹⁰ delabeling via DOC can be performed for both immunocompromised and immunocompetent patients categorized as low risk.⁴

THE BOTTOM LINE

Sulfonamide allergy is commonly encountered and is clinically important. Patients with a history of severe cutaneous or other serious delayed-type reaction (eg, drug reaction with eosinophilia and systemic symptoms or Stevens-Johnson syndrome) to an anti-

crobial sulfonamide should be cautioned to maintain lifelong avoidance. Patients with a history of recent IgE-mediated (allergic or anaphylactic) reaction should empirically avoid all antimicrobial sulfonamides based on the risk of cross-reaction; however, nonantimicrobial sulfonamides do not need to be avoided. In addition, a 1- or 2-step DOC can be considered for properly selected low-risk patients. The allergy label should accurately reflect the restrictions above rather

than broadly implicating all sulfonamides, as there is no evidence of cross-reactivity between antimicrobial and nonantimicrobial sulfonamides.

DISCLOSURES

Dr. Lang has disclosed consulting for Astra Zeneca, Celldex Therapeutics, Genentech, and Novartis, and teaching and speaking for Sanofi Regeneron. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. Brackett CC, Singh H, Block JH. Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulfonamide functional group. *Pharmacotherapy* 2004; 24(7):856–870. doi:10.1592/phco.24.9.856.36106
2. Wulf NR, Matuszewski KA. Sulfonamide cross-reactivity: is there evidence to support broad cross-allergenicity? *Am J Health Syst Pharm* 2013; 70(17):1483–1494. doi:10.2146/ajhp120291
3. Strom BL, Schinnar R, Apter AJ, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003; 349(17):1628–1635. doi:10.1056/NEJMoa022963
4. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: a 2022 practice parameter update. *J Allergy Clin Immunol* 2022; 150(6):1333–1393. doi:10.1016/j.jaci.2022.08.028
5. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. *CMAJ* 2011; 183(16):1851–1858. doi:10.1503/cmaj.111152
6. Khan DA, Knowles SR, Shear NH. Sulfonamide hypersensitivity: fact and fiction. *J Allergy Clin Immunol Pract* 2019; 7(7):2116–2123. doi:10.1016/j.jaip.2019.05.034
7. Hemstreet BA, Page RL 2nd. Sulfonamide allergies and outcomes related to use of potentially cross-reactive drugs in hospitalized patients. *Pharmacotherapy* 2006; 26(4):551–557. doi:10.1592/phco.26.4.551
8. Krantz MS, Stone CA Jr, Abreo A, Phillips EJ. Oral challenge with trimethoprim-sulfamethoxazole in patients with “sulfa” antibiotic allergy. *J Allergy Clin Immunol Pract* 2020; 8(2):757–760.e4. doi:10.1016/j.jaip.2019.07.003
9. Rose M, Vogrin S, Chua KYL, et al. The safety and efficacy of direct oral challenge in trimethoprim-sulfamethoxazole antibiotic allergy. *J Allergy Clin Immunol Pract* 2021; 9(10):3847–3849. doi:10.1016/j.jaip.2021.05.046
10. Krantz MS, Stone CA Jr, Abreo A, Phillips EJ. Reply to “The safety and efficacy of direct oral challenge in trimethoprim-sulfamethoxazole antibiotic allergy”. *J Allergy Clin Immunol Pract* 2021; 9(10):3849–3850. doi:10.1016/j.jaip.2021.07.027
11. Kuder MM, McDonnell JC, Weller K, Li M, Wang X, Lang DM. Relationship of reaction history to positive penicillin skin tests. *J Allergy Clin Immunol Pract* 2023; 11(6):1869–1875. doi:10.1016/j.jaip.2023.03.007
12. Waldron JL, Rose M, Vogrin S, et al. Development and validation of a sulfa antibiotic allergy clinical decision rule. *JAMA Netw Open* 2023; 6(6):e2316776. doi:10.1001/jamanetworkopen.2023.16776
13. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; 105(4):259–273. doi:10.1016/j.anai.2010.08.002

Address: David M. Lang, MD, Department of Allergy and Clinical Immunology, Medical Specialty Institute, CF10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; langd@ccf.org