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Reply to "The safety and efficacy of direct oral challenge in trimethoprim-sulfamethoxazole antibiotic allergy"



To the Editor:

We thank Rose et al for their correspondence¹ to our article, "Oral challenge with trimethoprim-sulfamethoxazole in patients with "sulfa" antibiotic allergy,"² in the *Journal of Allergy and Clinical Immunology: In Practice*.

In the 2 years since our article's publication, our experience with direct trimethoprim-sulfamethoxazole (TMP-SMX) oral challenge has successfully continued and we have had increasing referrals for non-HIV immunocompromised hosts. The most common clinical phenotype encountered remains a nonsevere delayed rash for which most tolerate a single-dose TMP-SMX challenge, and for those who experience symptoms, they are mild and self-limited. We agree that the success of this approach mirrors that of penicillin allergy delabeling, and that support for and safety of TMP-SMX allergy assessment by direct oral challenge has emerged and should

be considered standard of care for immunocompromised hosts or those who are expected to enter an immunocompromised state, such as a future solid organ transplant recipient.³ This is evidenced by other reported TMP-SMX direct oral challenge cohorts⁴ and inclusion of TMP-SMX direct oral challenge as an available tool in addition to desensitization, especially for low-risk individuals, in guidelines for the evaluation and management of sulfa antibiotic allergy.⁵ Direct TMP-SMX oral challenge provides information to prove or disprove the presence of true sulfa antibiotic allergy and is also more time efficient and less technically challenging than desensitization. This is particularly important in patients who might require episodic treatment with TMP-SMX that could necessitate multiple desensitizations. There is now broad awareness regarding the importance of penicillin allergy delabeling. Sulfa antibiotic allergy label evaluation should start with awareness by subspecialists about patients for whom TMP-SMX will have high utility. The role of the allergist or immunologist is to maximize patient benefit and minimize patient harm (Figure 1). Although risk stratification and history-guided TMP-SMX delabeling by one- or two-dose challenge is moving toward a guideline-based practice, important caveats about and distinctions from penicillin allergy delabeling demand specific attention. First, immediate reactions to TMP-SMX are rare and there is no validated skin-testing approach. Second, there is no immunologic cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides. Finally, for severe treatment limiting hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms and Stevens-Johnson syndrome and toxic epidermal necrolysis, TMP-SMX is still one of the top five drugs implicated,⁶ and these patients should practice lifelong avoidance of sulfa antibiotics. In the future, functional assays and genetic (human

Highest Risk	High Risk History	Moderate Risk History	Low Risk History
Severe delayed symptoms at any point in the past: - Stevens-Johnson syndrome (SJS) - Toxic epidermal necrolysis (TEN) - Drug rash with eosinophilia and systemic symptoms (DRESS) - Acute generalized exanthematous pustulosis (AGEP) - Generalized bullous fixed drug eruption - Drug induced nephritis - Drug induced hepatitis	Recent anaphylaxis (< 5 years) HIV-positive with detectable viral load and/or CD4+ lymphocytopenia	Recent immediate symptoms (< 5 years) Remote anaphylaxis (> 5 years)	Delayed non-severe symptoms - Maculopapular rash - Single non-mucosal fixed drug eruption Remote immediate symptoms (> 5 years)
Strict lifelong avoidance	Consider TMP-SMX skin testing for recent anaphylaxis ^a Consider two dose TMP-SMX challenge for recent anaphylaxis ^b versus desensitization for HIV-positive patients	Two dose TMP-SMX challenge ^c	Single dose TMP-SMX challenge ^c

FIGURE 1. Risk stratification of prior trimethoprim-sulfamethoxazole adverse reactions.

leukocyte antigen) associations with severe and durable TMP-SMX hypersensitivity may serve as additional tools for risk stratification, diagnosis, and causality assessment.⁷ Like penicillin allergy labels, the presence of either a remote and ill-remembered reaction or a mild delayed rash is predictive of negative testing. Pragmatically in clinical practice, the vast majority of sulfa allergy labels are low risk and result in delabeling. The role of the allergist or immunologist increasingly will follow a model of shared patient decision-making to integrate TMP-SMX allergy label risk stratification and ultimately delabeling into high-yield programs such as infectious diseases, hematology and oncology, and transplant to optimize efficacy, safety, and antibiotic stewardship.

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Conflicts of interest: E.J. Phillips receives royalties from UpToDate and consulting fees from Janssen, Vertex, Biocryst, and Regeneron. She is codirector of IIID Pty Ltd, which holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity, and has a patent pending for Detection of Human Leukocyte Antigen-A*32:01 in connection with Diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms without any financial remuneration and not directly related to the submitted work. The funders had no role in any aspect of the manuscript. The rest of the authors declare that they have no relevant conflicts of interest.

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