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TRANSPLANT INFECTIOUS DISEASE

EDITORIAL

# Sulfa allergy labels and risk of opportunistic infections after solid organ transplantation

Trimethoprim/sulfamethoxazole (TMP-SMX), also known as cotrimoxazole, is widely used after solid organ transplantation (SOT) to prevent opportunistic infections such as *Pneumocystis jirovecii*, *Toxoplasma gondii*, and *Nocardia* infections.[1]

Most experts and guidelines agree that TMP-SMX is the prophylactic agent of choice in SOT recipients, given its effectiveness, low cost, and ease of administration.[2] Alternative prophylactic agents (including atovaquone, dapsone, and inhaled pyrimethamine) are sometimes used instead of TMP-SMX, despite disadvantages such as limited activity (especially against target organisms other than *P. jirovecii*), relative complexity of administration, potential side effects, and higher costs. A common reason for using alternative prophylactic agents after SOT is the presence of a sulfonamide allergy label in the patient's medical record.

In this issue of *Transplant Infectious Diseases*, Al-Shaikhly et al. present the results of a retrospective matched cohort study in which the one-year risk of developing an opportunistic infection due to *P. jirovecii*, *T. gondii*, or *Nocardia* spp. was compared between 1531 SOT recipients carrying a sulfonamide allergy label and an equal number of matched SOT recipients.[3] Not unexpectedly, the presence of a sulfonamide allergy label significantly influenced prescribing practices, with a decreased use of TMP-SMX, and an increased use of alternative prophylactic agents. While the presence of a sulfonamide allergy label was not associated with an increased risk of *P. jirovecii* infection (which occurred in 12 patients with a sulfonamide allergy label vs. 16 control SOT recipients), the authors found it to be associated with a significantly increased risk of both *Toxoplasma* infection (which occurred in 37 vs. 20 SOT recipients, respectively) and *Nocardia* infection (which occurred in 19 vs. 10 SOT recipients, respectively). Even if this increased risk of opportunistic infections did not translate into a significant mortality difference between the study groups, these results are important because the use of alternative prophylactic agents is common in practice, and because both nocardiosis and toxoplasmosis are associated with significant morbidity and mortality after SOT.[4,5]

Al-Shaikhly and colleagues should be congratulated for addressing a clinically important question and including over 1500 SOT recipients with a sulfonamide allergy label, thanks to the availability of coding data from over 100 million patients from 60 healthcare organizations across the United States. Another strength of this study is the use of propensity score matching to compare patients carrying a sulfonamide allergy label with an equal number of control SOT recipients. Limitations of this study include its retrospective nature and the fact it relied on coding data to identify patients labeled as allergic to sulfonamides as well as opportunistic infections. Al-Shaikhly and colleagues were unable to take into account factors that may have increased the individual risk of developing an opportunistic infection (e.g., occurrence and treatment of acute rejection, level of immune suppression, or incidence of cytomegalovirus infection[6]), and were also unable to provide detailed information on the presentation, management, and outcomes of these opportunistic infections.

Interestingly, Al-Shaikhly and colleagues provide evidence supporting the partial but significant effect of TMP-SMX in the prevention of post-transplant nocardiosis. While TMP-SMX has in vitro activity against *Nocardia* spp., and while high-dose TMP-SMX has been the keystone of nocardiosis treatment for decades, there is debate over whether TMP-SMX effectively prevents nocardiosis after SOT when used at "low dose" (i.e., at the dose used for the prevention of *Pneumocystis* infection). In the absence of a randomized trial looking at this specific question, a recent individual participant data meta-analysis provided the strongest evidence so far that TMP-SMX is probably effective at preventing nocardiosis in SOT recipients.[6] In this meta-analysis into which individual data from three case-control studies were obtained (representing 260 SOT recipients with nocardiosis and 519 uninfected controls), TMP-SMX was found to have a partial but significant effect in the prevention of post-transplant nocardiosis.

So, how should SOT recipients who carry a sulfonamide allergy label be managed? It is well known that allergy labels are relatively common and may lead to worse patient outcomes.[7] While the presence of a sulfonamide allergy label may of course reflect a true allergy, available evidence suggests that many patients labeled allergic to sulfonamide experienced non-immune-mediated events such as gastrointestinal upset, cytopenia, or mild serum creatinine rise (which is typically due to benign inhibition of creatinine renal tubular secretion by trimethoprim).[8] Besides, immune-mediated reactions can range from a mild rash to life-threatening severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrosis, or drug reaction eosinophilia and systemic symptoms syndrome.

No consensus exists regarding the optimal management of SOT recipients carrying a sulfonamide allergy label, but four points are worth noting.[9] First and foremost, a careful history is essential to guide decision-making. On one side, patients who only experienced benign non-immune-mediated events (e.g., gastrointestinal upset, cytopenia, or mild serum creatinine rise) generally tolerate low-dose TMP-SMX. On the other side, life-long TMP-SMX avoidance should be recommended for patients with a history of severe cutaneous adverse

**TABLE 1** Oral challenge strategy and characteristics of the included patients of recent studies involving delabeling approaches for transplant patients.

| Study | Country | Study design | Inclusion criteria | Exclusion criteria | Oral challenge protocol | Follow-up after oral challenge | No. of the patients who underwent the TMP-SMX challenge | No. of transplant recipients (among all study patients) | Oral challenge success rate (i.e., absence of reaction) | Type of reaction(s) (in case of reaction after the oral challenge) | No. of patients retreated with TMP-SMX after negative testing (and possible reactions) |
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| Urbancic, 2017 | Australia | Retrospective | History of TMP-SMX adverse drug reaction (either immune-mediated or not, or unknown) | History of scar, rash, drug fever, acute interstitial nephritis, or immune complex deposition Not specified | Single-dose challenge (TMP-SMX 40–800 mg) | 2-h observation, and review at 96 h | 27 | 27/27 (all kidney transplant recipients) | 74% (20/27) | All mild | Not specified |
| Krantz, 2020 | USA | Retrospective | History of immediate, non-severe delayed, or unknown reaction to TMP-SMX (or unspecified sulfa antibiotics) | Severely delayed reaction (including SJS, TEN, DRESS, AGEP, hepatitis, or nephritis) | Based on history, either (i) two-dose challenge (TMP-SMX 8–40 mg; 40–800 mg), or (ii) single-dose challenge (40–800 mg) | 2-h observation, and phone call at 24 h | 204 | 17/204 No details available | 94% (191/204) | All mild (three immediate and 10 delayed) | 52 retreated (including 9/52 who developed mild adverse events leading to treatment cessation) |

(Continues)

**TABLE 1** (Continued)

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| Benesch, 2021 | USA | Retrospective | Unspecified sulfa allergy | No challenge | Two-dose challenge in most patients (26/32), followed by single-dose (6/32) and three-dose challenge (2/32) | 3-day follow-up (no details available) | 34 | 15/34 HCT, 4/34 SOT | 91% (31/34) | Either mild (two patients) or moderate (one patient with hives, localized rash, and itching) | 16 retreated (including 1/16 who experienced 'debilitating myalgias and a sense of doom') |
| Rose, 2021 | Australia | Prospective | History of non-severe TMP-SMX or sulfonamide allergy | Severe cutaneous adverse reaction or anaphylaxis | At the discretion of the clinician, either (i) single-dose, (ii) two-dose, or (iii) extended challenge for at least 3 days | 2-h observation, ± phone call if needed | 45 | 17/204 No details available | 96% (43/45) | All mild (one urticarial rash and one maculopapular exanthema) | Not specified |

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug-induced hypersensitivity syndrome; HCT, hematopoietic cell transplantation; post-op, post-operation; SJS, Steven-Johnson syndrome; SOT, solid organ transplantation; TEN, toxic epidermal necrolysis; TMP/SMX, trimethoprim/sulfamethoxazole.

reactions. Second, in contrast to ß-lactam antibiotics, skin testing has not been validated for allergy to sulfonamides. Third, TMP-SMX desensitization (or "temporary induction of tolerance") is not well established and has several limitations; in particular, it is a relatively time-consuming approach that is only effective as long as the patient receives the drug. That said, in a study of 52 SOT recipients with a history of non-anaphylactic sulfonamide allergy, a 3-day desensitization protocol during the index transplant hospitalization was associated with relatively good outcomes, with nearly 80% still on TMP-SMX at 3 months without adverse reaction.[10] Fourth, a growing body of evidence indicates that direct oral TMP-SMX challenge may be a safe and easier-to-implement alternative to desensitization, with similar outcomes. Table 1 summarises evidence regarding the use of direct oral TMP-SMX challenge in transplant recipients. Limitations of these studies include the fact that they were typically conducted in resource-rich centers where both dedicated protocols and experts in antibiotic allergy assessment were available. The development of a simple and practical sulfonamide allergy clinical decision rule (such as SULF-FAST, which is adapted from the penicillin allergy tool PEN-FAST) may enable point-of-care risk assessment of sulfonamide allergy labels and performance of direct oral TMP-SMX challenge when possible. Ideally, TMP-SMX allergy assessment should be done prior to transplantation, because the first months after SOT are associated with a high level of immune suppression and risk of infections. Pre-transplant evaluation is supported by a recent single-center study into which 11/12 SOT recipients who self-reported a sulfonamide allergy were successfully delabeled during their pre-transplant evaluation, with significant cost savings related to the avoidance of expensive alternative prophylactic agents.[9]

In conclusion, Al-Shaikhly and colleagues provided an additional piece of evidence showing that TMP-SMX is an important prophylactic agent after SOT and that patients who carry a sulfonamide allergy label probably have an increased risk of opportunistic infections. Efforts should be made to systematically and carefully reassess sulfonamide allergy labels in these patients, identify delabeling strategies that are both safe and easy to implement in the transplant setting, and eventually use TMP-SMX in as many eligible SOT recipients as possible.

## AUTHOR CONTRIBUTIONS

**Matteo Passerini**: Conceptualization; data curation; methodology; and writing—original draft. **Andrea Lombardi**: Conceptualization; data curation; formal analysis; methodology; and writing—review and editing. **Julien Coussement**: Supervision; validation; and writing—review and editing.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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