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Single or two-step challenge versus six-step challenge in non-HIV infected patients with a sulfonamide antibiotic allergy label: a retrospective case series

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Clinical implications

Single- or two-step oral TMP-SMX challenges in non-HIV infected patients had similar outcomes compared to a six-step challenge protocol with a reduction in costs.

Antibiotics account for the majority of drug allergy label reports ¹, and sulfonamide antibiotics are the second most commonly reported class of outpatient antibiotic allergy labels ². Sulfonamide antibiotics can cause a variety of hypersensitivity reactions (HSRs) ranging from rare immediate-onset IgE-mediated allergic reactions and much more common delayed-onset benign T-cell-mediated rashes to extremely rare severe cutaneous adverse reactions (SCARs) ³. As a consequence, a sulfonamide antibiotic allergy label limits the use of trimethoprim-sulfamethoxazole (TMP-SMX), the first option for *Pneumocystis jirovecii* pneumonia prophylaxis, and a preferred agent for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). Currently there are no validated diagnostic tests for immunologically-mediated sulfonamide hypersensitivity. There are several protocols that use multiple steps, along with single- or two-step challenge protocols⁴. We aimed to implement a change in our practice, retrospectively evaluating our previous historical use of six-step challenge protocols compared to single- or two-step challenges in non-HIV infected patients with a sulfonamide antibiotic allergy label using a quality improvement study design.

A pre-/post-intervention, quality improvement design study was performed in a study population composed of non-HIV positive patients older than 18-years with self-reported non-severe, delayed-, immediate-, or unknown-onset reactions to TMP-SMX who underwent TMP-SMX graded administration (challenge) at an academic tertiary care center over two periods, January 2017- December 2018 and January 2019- December 2020. We excluded patients with severe delayed onset systemic immune-mediated reactions including SCARs, and drug-induced nephritis or hepatitis. This study was

approved by our institutional review board. Retrospective chart review was performed. We compared the effectiveness and costs of a single- or two-step challenge versus a six-step challenge with TMP-SMX, which was based on Pyle et al. protocol⁵. The post-intervention group (January 2019- December 2020) underwent either a two-dose TMP-SMX (8–40mg; 80–400mg) challenge or a single-dose (80-400 mg) challenge using Krantz et al. study protocol and selection criteria⁶. The patients were monitored for 90 minutes in the clinic after the medication was administered for any immediate reaction. Additionally, the patients were contacted via telephone at 24-hours to follow for potential delayed reactions. Success in the oral challenge was defined as no symptoms during the 24-hour period.

The main outcome measure was the rate of success for a six-step challenge versus a single- or two-step challenge. Secondary outcomes included frequency of adverse drug reaction, type of challenge performed, type of drug hypersensitivity reaction, and estimated post-intervention cost reduction. To estimate the cost reduction, the Current Procedural Terminology (CPT) codes for desensitization (95180) and challenge (95076) were used to obtain the standard Medicare tariffs for Florida. The estimated time for a six-step challenge was 3.5 hours compared to a median time of 1.5 hours for single- or two-step challenges. The tariffs were multiplied for the number of hours in each group and then adjusted to calculate the difference between both interventions.

Patients in the single- or two-step challenge group were contacted via phone to evaluate safety of further TMP-SMX administration up to a year after the challenge. While many antibiotic adverse reactions are intolerances, the term “allergy label” will be

used throughout this manuscript to describe any sulfa antibiotic adverse reaction which may also include intolerances. Statistical analysis was performed in R version 4.0.2 (The R Foundation). Chi-squared tests and Fisher's exact tests were used to compare categorical variables, where appropriate. Significance level was set at $p < 0.05$, all statistical tests were two-sided.

A convenience sample of 52 patients underwent a six-step TMP-SMX challenge in the pre-intervention period and were compared to 26 patients who underwent single-step and 26 who underwent two-step TMP-SMX challenges in the post-intervention period. Most patients were female, white, and >60 years old (Table I). The most common indications for TMP-SMX administration were prophylaxis for *Pneumocystis pneumonia*, and treatment of infections. Most patients reported hypersensitivity reactions that occurred >20 years ago, more frequently in the single-or two-step challenge group (33, 63.5%) than in the 6-step challenge group (28, 53.8%). Rash was the most frequent symptom in both groups during the index reaction, followed by angioedema. The most common timing of reaction was immediate in the single-or-two-step challenge group (27, 51.9%), and delayed in the six-step challenge group (14, 26.9 %) (Table I). Less than 15% of patients in either group reported angioedema.

Out of 52 patients in the single- or two-step challenge group, 26 (50%) underwent a two-step challenge. The success rates of single- or two-step, and six-step challenges were similar (96.1% and 90.4%, respectively; $P = .43$) (Table I). We were able to obtain a follow-up antibiotic use on 25 single-dose and 25 two-dose challenge patients; a total of

15 of them received a subsequent therapeutic course of TMP-SMX by 12-30-2020, and all of them tolerated the course. The estimated post-intervention cost reduction of a single-or two-step challenge was \$13,332 compared to the six-step challenge group, \$256.38 less per patient and this would have been \$128.19 less per patient if all had single-step challenges. In addition, patients in the single-step challenge spent two hours less in the clinic compared to the six-step challenge group.

In this cohort, the implementation of these single- or two-step challenge protocols with TMP-SMX showed similar outcomes to our historical six-step challenges. These results are similar to those reported by Krantz et al. in a retrospective study where 89% of patients with TMP-SMX allergy label and 98.9% of patients with an unspecified sulfonamide antibiotic allergy label could receive a single or two-step TMP-SMX challenge ⁶.

In both groups, the majority of patients reported HSRs occurring over 20 years ago. Frameworks for selecting patients that are appropriate for TMP-SMX challenge, such as Krantz et al., currently exclude patients with severe delayed reactions. There is no data available on the safety and efficacy of TMP-SMX challenge in patients with severe delayed reactions; therefore, a decision to use a challenge as diagnostic or de-labeling tool in these patients should weigh the potentially much higher risks of this intervention against the need to perform it. However, while Krantz et al. also reported that a small amount of patients with a history of remote anaphylaxis were less likely to react than patients with more recent reactions, they suggested a desensitization protocol is a

reasonable approach for any patient with a history compatible with anaphylaxis within the last five years ^{6, 7}.

The risk and benefits of the intervention should be carefully considered prior to making the decision to use a challenge as a diagnostic or de-labeling tool ⁸. Benesch et al. reported the safety and high success rates of a direct single-step TMP-SMX challenge, with success rates comparable to the present study ⁹. These results may not be generalized to patients with TMP-SMX non-severe delayed hypersensitivity reactions elsewhere. Further prospective research is needed to assess the efficacy of this intervention in different patient populations and specific clinical scenarios.

The results of our study add to the existing evidence that there is no difference between single-, two- or six-step challenges when the index reaction is a non-severe delayed reaction, using a cohort of exclusively non-HIV positive patients, which addresses a previously described gap in knowledge ⁴. The limitations of this study include its retrospective nature, the small sample size in a single center, and the difficulty we encountered identifying patients who received a subsequent therapeutic course of TMP-SMX after evaluation. Additionally, less patients in the single- or two-step challenge group reported “rash” compared to the six-step challenge group. Finally, patients were not observed for two to five days after the challenge due to time and space constraints; delayed-onset T-cell mediated hypersensitivity reactions are ideally observed after 2-5 days following a challenge.

In this cohort, the implementation of validated single- or two-step TMP-SMX challenge protocols showed similar success rates than with a six-step challenge, without an increase in adverse drug reactions and lower associated costs.

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Table I. Patient characteristics undergoing single-, two-, and six-step TMP-SMX challenges

Variable	Single-step challenge (n=26)	Two-step challenge (n=26)	Six-step challenge (n=52)	P value
Female sex, n (%)	20 (76.9)	19 (73)	45 (86.5)	.23
Age >60 years, n (%)	16 (61.5)	14 (53.8)	31 (60)	.76
Race				.2
White	25 (96.2)	24 (92.3)	44 (84.6)	
Black	1 (3.8)	1 (3.8)	4 (7.7)	
Ethnicity				
Hispanic or Latino	0	0	1 (1.9)	
Other	0	1 (3.8)	3 (5.7)	
Time since index reaction				.08
< 2 years	2 (7.7)	3 (13)	6 (11.5)	
2-4 years	0	0	4 (7.7)	
5-9 years	1 (3.8)	4 (17.4)	4 (7.7)	
10-19 years	5 (19.2)	1 (4.3)	10 (19.2)	
20-29 year	3 (11.5)	6 (26.1)	9 (17.3)	
>30 years	15 (57.7)	9 (39.1)	19 (36.5)	
Index reaction history				<.01
Immediate	12 (46.1)	15 (57.7)	2 (3.8)	
Delayed	3 (11.6)	4 (15.3)	14 (26.9)	
Unknown	11 (42.3)	7 (27)	36 (69.2)	
Index reaction symptoms				
Rash	8 (30.1)	9 (36)	29 (55.7)	.04
Urticaria	8 (30.1)	7 (28)	15 (28.8)	.17
Angioedema	0	3 (12)	5 (9.6)	.48
Successful challenge outcome	25 (96.1)	25 (96.1)	47 (90.4)	.43
Subsequent TMP-SMX use	7 (26.9)	8 (30.7)	37 (71.1)	<.01

TMP-SMX: Trimethoprim-Sulfamethoxazole

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