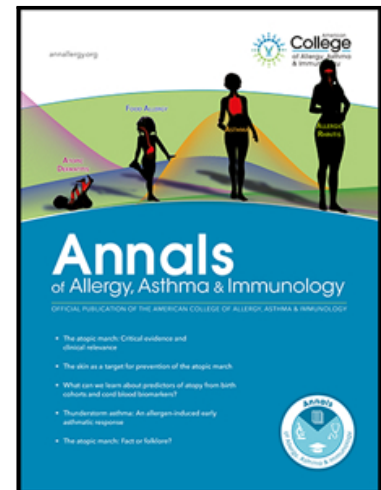


Outcome of trimethoprim-sulfamethoxazole (TMP-SMX) challenge in previously reported sulfa antibiotic allergic patients

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Title: Outcome of trimethoprim-sulfamethoxazole (TMP-SMX) challenge in previously reported sulfa antibiotic allergic patients.

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Key words: trimethoprim-sulfamethoxazole; oral challenge; sulfa allergy; safety

Abbreviations/acronyms

TMP-SMX trimethoprim-sulfamethoxazole

SJS Stevens-Johnson Syndrome

TEN Toxic Epidermal Necrosis

UWMC University of Washington Medical Center

REDCap Research Electronic Data Capture

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Tables: 1

Sulfa antibiotics are the drug of choice for treatment and prophylaxis of several infections. Unfortunately, about 7% of people exposed to them have adverse reactions ranging from mild rash and nausea, to life-threatening reactions like Stevens-Johnson Syndrome/Toxic Epidermal Necrosis (SJS/TEN)^I. Sulfa antibiotics are often avoided in patients with any reported sulfa allergy, irrespective of whether the initial reaction was to an antibiotic or non-antibiotic sulfa drug. This leads to the use of less effective, second-line antibiotics. Desensitization protocols can be used to enable the use of sulfa antibiotics in a patient with a history of reaction to sulfa medications. However, desensitization protocols take hours to days, are expensive, and add logistical hurdles. Desensitization procedures also do not establish tolerance, hence must be repeated whenever therapy is required again.

Direct challenge is the gold standard for establishing allergic status or tolerance to medications^{II}. One study showed that 89.3% of patients with a history of immediate, delayed non-severe, or unknown reactions tolerated direct trimethoprim-sulfamethoxazole (TMP-SMX) oral challenge, and 78.8% of the 52 patients who underwent treatment tolerated it^{III}. All those who failed the challenge had non-severe reactions such as urticaria, skin rash, fever, and pruritus. No individuals had any severe immediate or delayed reactions. Another study systematically re-challenged select patients who had adverse reactions to TMP-SMX while undergoing prophylactic therapy and found that 74% of the 27 patients did not have recurrence of their adverse reaction^{IV}.

With this retrospective cohort study, we demonstrate the safety of direct oral challenge with TMP-SMX in patients sent to our Allergy Clinic for evaluation of a reported sulfa allergy. We include a cohort of patients who were undergoing stem cell transplant for hematological malignancies.

This study was completed with approval from the University of Washington Medical Center (UWMC) Institutional Review Board (STUDY00010440). Patients were identified via the UW Medicine Enterprise Data Warehouse and pharmacy records. REDCap (Research Electronic Data Capture) was used for standardized data collection^V. All patients seen in the UWMC Allergy and Immunology clinic from June 2017- May 2020, had a reported sulfa allergy, and underwent TMX/SMP challenge were included. Patients were excluded if they did not undergo a challenge. Manual chart review was done to abstract patient characteristics (age, gender, race, relevant comorbidities, reported sulfa allergy, types of reaction, and other allergies), reasons for referral (need for prophylaxis, infection where there was lack of alternative antibiotics, anticipated need for sulfa use, or multidrug allergy), and type of challenge (1, 2, or 3 dose). Challenge outcome was determined by reviewing notes from the challenge encounter and following 3 days. Subsequent TMP-SMX use and comfort with potential use after challenge was determined by manual chart review and calling patients. Data was summarized with descriptive statistics.

From June 2017 - May 2020 37 patients underwent direct oral challenge. Three patients reported allergies to non-antibiotic sulfas and were excluded from further analysis. The

remaining 34 patients are described in the Table. The majority of our patients were female (26/76.5%) and white (28/82.4%). None had HIV. Fifteen (44.1%) were undergoing pre-bone marrow transplant evaluation. Many reported allergies to other antibiotics (22/64.5%). Of the 34 patients, 2(5.9%) had no knowledge of their reaction history, 3 (8.8%) had isolated non allergic mild symptoms, 20(58.8%) had a history of non-severe symptoms, and 9(26.5%) had a history of severe immediate symptoms post TMX-SMP exposure (Table). Twenty-three patients had skin prick and intradermal testing for TMP-SMX. Of these, 17 were negative and 4 skin tests had equivocal results. Three patients had reactions during the TMP-SMX challenge - 2 completed the challenge with mild subjective symptoms and one failed due to mild hives, localized rash, and itching (Table). Thus, 33/36 patients (97.13%) tolerated the oral TMP-SMX challenge.

Of the 33 patients who tolerated the challenge, at least 16(48.5%) went on to receive TMX-SMP (Table). Eleven (68.8%) received it for prophylaxis and 5 (31.3%) were being treated for an active infection. One of those did not tolerate therapy for infection due to debilitating myalgias and a sense of doom. Of the other 17 patients who passed the challenge, 11 (30.5%) were contacted and confirmed that they did not need TMP-SMX after the challenge procedure. The other 6 (16.7%) could not be contacted or did not recall if they had been prescribed TMX-SMP yet (Table).

Skin test for TMP-SMX is not standardized and the predictive value is unknown, thus it is an unreliable diagnostic method. Hence it is critical to establish tolerance or allergic status through oral challenge.

In our study we observed that oral TMP-SMX challenge was safely completed by all patients regardless of the reaction history and only 1 patient (with a history of itching) failed with mild symptoms. Most patients received a 2 dose challenge. Of those who received therapy post challenge, only one did not tolerate it due to myalgia, not an allergic reaction.

A limitation of this study is that this is a retrospective chart review. There was no standardization in the criteria used to select patients for the challenge or the type of challenge. Some of the patients had a non-antibiotic sulfa allergy, which is known to not cross react with sulfa antibiotics, and so they were extremely low risk. We do not have data on long term tolerability of TMP-SMX for almost half our patients. Generalizability of our study is limited by its small sample size. Still, our study adds to the data that direct oral challenges with or without prior skin testing is a safe way to determine if TMP-SMX can be safely used by patients with a history of an allergy. Since TMP-SMX is the most effective antibiotic for treatment or prophylaxis in a number of situations, this is an important tool for optimizing treatment for our patients. This is particularly important for the cohort of bone marrow transplant patients in this study.

Prospective studies with larger patient populations are needed for generalizing the safety of oral challenges and for risk stratification on which type of patients are likely to tolerate or fail the challenge.

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Table: Patient Characteristics and Trial Outcomes

	1 step challenge (n=6)	2 step challenge (n=26)	3 step challenge (n=2)
Median age	24.5 years	62 years	29.5 years
Sex			
Female	4 (66.7%)	20 (76.9%)	2 (100%)
Male	2 (33.3%)	6 (23%)	0 (0%)
Race			
White	6 (100%)	21 (80.8%)	1 (50%)
Other/Unknown	0	5 (19.2%)	1 (50%)
Comorbidities			
Hematologic malignancy	4	13	0
Pre-bone marrow transplant	3	12	0
Pre-organ transplant evaluation	0	4	0
Post Organ Transplant	0	0	0
HIV	0	0	0
Allergy label			
Sulfa antibiotic	6	26	2
Other antibiotics	3	18	1
Other medications	3	15	0
Median number of drug allergies	2.5	3	1
Reason for referral			
Need for prophylaxis	3	16	0
Treatment of active infection	1	1	1
Anticipate need of use of sulfa	1	0	0
Multi-drug allergy	3	15	1
Most severe reported index reaction			
Unknown	0	2	0
Non-allergic mild symptoms	0	3	0
Non-severe symptoms ¹	3	16	1
Severe immediate symptoms ²	3	5	1
Skin Test Results			
Not done	4	5	2
Negative	2	17	0
Equivocal	0	4	0
Positive	0	0	0
Passed challenge	6	25	2
No reaction	5 (83.3%)	23 (92.0%)	2 (100 %)
Benign Subjective	1 (16.7%)	0	0
Mild	0	1 (3.8%)	0
Moderate ³	0	1 (3.8%)	0
Severe ⁴	0	0	0
Post Challenge TMP-SMX re-trial	5	10	1
Prophylaxis	4	7	0

Treatment of infection	1	3	1
Passed re-trial	5 (100%)	9 (90.0%)	1 (100%)
No TMP-SMX re-trial	1	10	0
Unknown TMP-SMX re-trial status	0	5	1

¹localized rash, subjective shortness of breath (SOB)/throat closing, itching, sneezing/rhinorrhea

²hives, rash with itching/flushing, anaphylaxis

³localized rash/itching, oropharynx itching, swelling outside of throat, cough

⁴generalized hives/flushing, wheezing, anaphylaxis, hypoxia, SOB, angioedema, laryngeal edema, dizziness