De-label December: Sulfonamide Antibiotics

Jennifer Hu, MD
UW Infectious Diseases Fellow
December 17, 2024

DISCLOSURES: NONE

DISCLAIMERS: NOT AN ALLERGIST!
ALSO NOT A PHARMACIST.

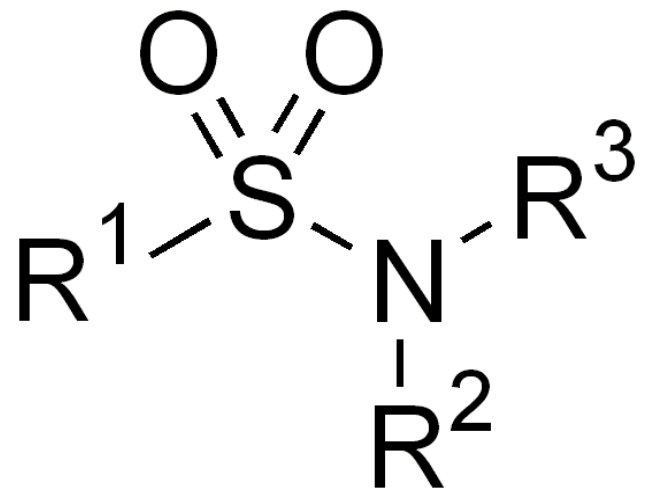
A Case to Contemplate…

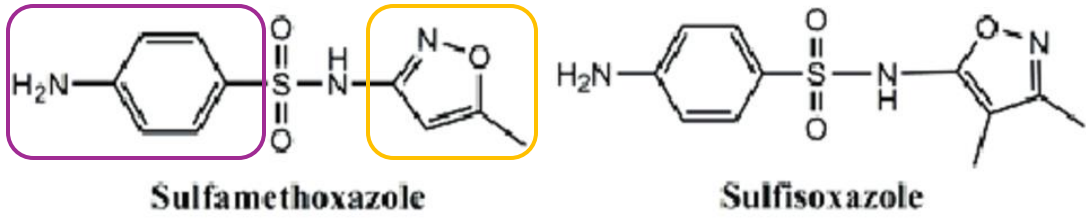
- 57-year-old male without HIV, with reported allergy to TMP/SMX who requires medication for *Pneumocystis* prophylaxis in setting of steroid use. He has G6PD deficiency, and financial difficulties.
  - Reaction occurred >10 years ago.
  - Full body hives, no skin peeling/sloughing, no pustules, no mucosal involvement. No shortness of breath, dyspnea, throat closing. No tongue or lip swelling. Did not require hospitalization nor treatment.
  - There is question about whether the reaction was due to TMP/SMX or another drug.

BEST NEXT STEP?

Sulfonamide Antibiotics

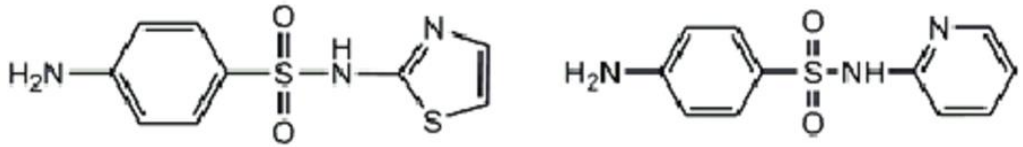
- Sulfonamide moiety (SO2NH2)
- Antimicrobial sulfonamides
  - Arylamine (amine group linked to benzene ring at N4)
  - Aromatic 5-or 6-member ring attached to sulfonamide core
- Presence of these functional groups contribute to hypersensitivity
- Act as analog of para-aminobenzoic acid (cofactor needed for folic acid production)





Sulfamethoxazole

Sulfisoxazole



Sulfathiazole

Sulfapyridine

Medications Easily Confused…

Non-antimicrobial sulfonamides	Protease Inhibitors	NOT sulfonamides
Diuretics (furosemide, HCTZ, acetazolamide) Glyburide Celecoxib Sumatriptan	Darunavir Fosamprenavir Tipranavir Simeprevir (HCV protease inhibitor)	Dapsone (sulfone) Sulfites/metabisulfites Medications containing sulfur atoms (amoxicillin, captopril, omperazole) or sulfate ions (albuterol sulfate)
• Do not contain arylamine group or substituted aromatic ring • Exception: sulfasalazine releases sulfapyridine (cross reactive arylamine sulfonamide) when contacting gut flora	• Contain sulfonamide moiety but lack one or both functional groups implicated in hypersensitivity • No cross reaction with antimicrobial sulfonamides	• Sulfites/metabisulfites are used to preserve food/beverage/meds • Sulfite sensitivity is distinct (respiratory reactions in patients with asthma)

No Cross Reactivity Between Sulfonamide Antibiotics and Sulfonamide Non-Antibiotic

- Retrospective cohort study of the General Practice Research Database (UK)
- Population: Patients who have received systemic sulfonamide antibiotic and then a sulfonamide nonantibiotic 60+ days later
- Outcome: Codes for hypersensitivity or allergic reaction within 30 days after receipt of sulfonamide non-antibiotic [and penicillin, as a comparator group]
    - Narrow outcome definition (e.g., urticaria, anaphylactic shock, erythema multiforme, and drug allergy) and a broad definition, which also included asthma, eczema, and unspecified adverse effects of a drug

Strom et al (NEJM 2003)

- Compared to those without prior documented sulfonamide antibiotic allergy, persons with prior documented sulfonamide antibiotic allergy had:
  - HIGHER odds of allergic reaction in 30 days after receiving sulfonamide nonantibiotic
    - Adjusted OR 2.8 (95% CI 2.1-3.7)
  - HIGHER odds of allergic reaction in 30 days after receiving penicillin
    - Adjusted OR 3.8 (95% CI 3.4-4.2)

- Persons with prior documented hypersensitivity to sulfonamide antibiotics had LOWER odds of allergic reaction to sulfonamide non-antibiotic, as compared to penicillin. OR = 0.7 (95% CI 0.5-0.9)

Predisposition to allergic reactions rather than cross reactivity.

Quick Question!

- 63-year-old female with asthma and reported "sulfa" allergy in chart.
  - The terms Bactrim and TMP/SMX do not sound familiar to her
  - You cannot find TMP/SMX in refill/prescription history
  - Recalls that reaction occurred ~10 years ago when she was eating some preserved foods; developed trouble breathing and an asthma attack
  - What do you make of this?

Likely sulfite sensitivity: Can use TMP/SMX

Scope of the Issue?

- Estimated prevalence of allergy to TMP/SMX ~3-8%
- Second most common reported allergy in the health record
- Data from 1980-1990s: high prevalence in persons living with HIV
  - 37-50% with cutaneous reactions (PMID: 7979835)
  - CD4<250 associated with reduced risk of TMP/SMX hypersensitivity (PMID: 8380290)
  - Among those with prior non-life threatening adverse reactions, ~50% tolerated subsequent rechallenge and treatment with TMP/SMX (PMID: 8442919)
  - Allergy literature from 1990s with data supporting oral desensitization (PMID: 8933778)

Why Does This Matter?

- TMP/SMX is an excellent drug!
  - First line for PJP prophylaxis and treatment
    - Retrospective study of 9 French lung transplant centers demonstrated lowest rate of breakthrough PJP with TMP/SMX (4%) compared to atovaquone (7%) or pentamadine (29%)- consistent with studies in non-SOT patients (PMID: 32442112)
  - Prevention of toxoplasmosis
  - Useful for common infections (purulent SSTI, UTI etc)
- Alternate therapies have side effects and are costly

Table: Price for one month supply of medications

TMP/SMX	Atovaquone	Dapsone	Pentamadine
$23	$2190	$39	$119

Price from Cincinnati Children's, 2015

Sulfonamide Allergy Label and the Risk of Opportunistic Infections in Solid Organ Transplant Recipients – A Retrospective Matched Cohort Study

@TheTxIDJournal @TahaATweet

Al-Shaikhly *et al.* ***Transplant Infectious Diseases.*** 2024.

Background

Pneumocystitis jerovecii pneumonia (PJP), nocardiosis, and toxoplasmosis can cause significant morbidity among immunocompromised solid organ transplant (SOT) recipients.

Trimethoprim/sulfamethoxazole (TMP-SMX) provides effective prophylaxis against these opportunistic infections.

Does sulfa allergy label (SAL) interfere with optimal care of these patients?

TriNetX US collaborative Network (multicenter electronic health record database) (N= 105 millions patients)

SOT recipients with SAL (N=1,573)

SOT recipients without SAL (controls) (N=65,561)

1:1 Propensity score matching for demographics and co-morbidities

What is the 1-year probability of developing PJP, nocardiosis or toxoplasmosis? ?

Antibiotic prescription practices?

When compared to matched controls, SOT with SAL were approximately:

- **3.9x** more likely to develop nocardiosis
- **1.9x** more likely to develop toxoplasmosis
- **80%** less likely to use TMP or SMX
- **5.5x** more likely to use other prophylactic agents

NO difference in the probability of PJP or mortality

WILEY TRANSPLANT INFECTIOUS DISEASE

The Official Journal of Transplant Infectious Disease

TX NETWORK

Alternative Pneumocystis Pneumonia Prophylaxis in Solid Organ Transplants

@TheTxIDJournal @KevinHeMD

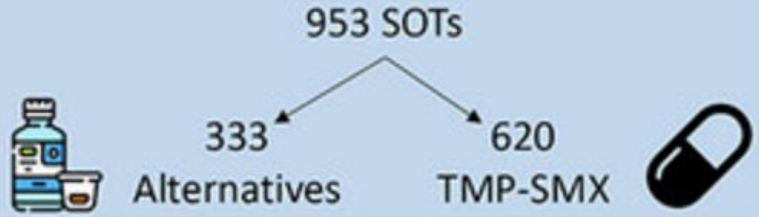
He *et al.* ***Transplant Infectious Diseases.*** 2024.

Background

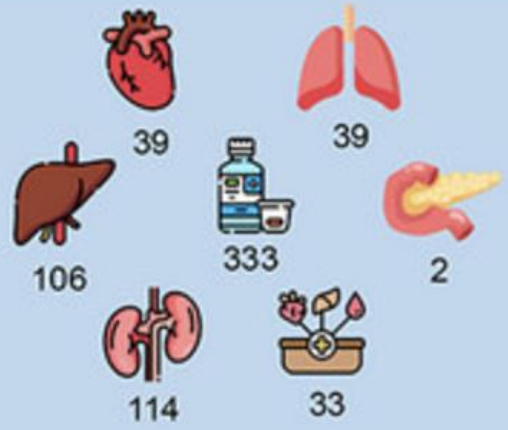
There are limited data to support use of alternatives to trimethoprim-sulfamethoxazole (TMP-SMX) in *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis in solid organ transplant (SOT) recipients.

Methods

Single center, retrospective cohort study of all SOT recipients from 11/13/2020 – 11/13/2022 followed for one year after transplant



Cohort Characteristics



319 recipients (95.8%) received atovaquone and 14 (4.2%) received dapsone

Alternative prophylaxis was started in 76 (22.8%) without initial TMP-SMX trial mostly due to allergy (81.6%)

Hyperkalemia (105, 40.9%) and leukopenia (77, 30.0%) were the most common reasons for TMP-SMX intolerance

Main Findings

79.8% of recipients had adverse effects resolve, but **only 27.3%** resumed TMP-SMX—**85.7% tolerated TMP-SMX after resumption**

Barriers to alternative prophylaxis access included **cost** (25, 7.5%) and **prior authorizations** (26, 7.8%)

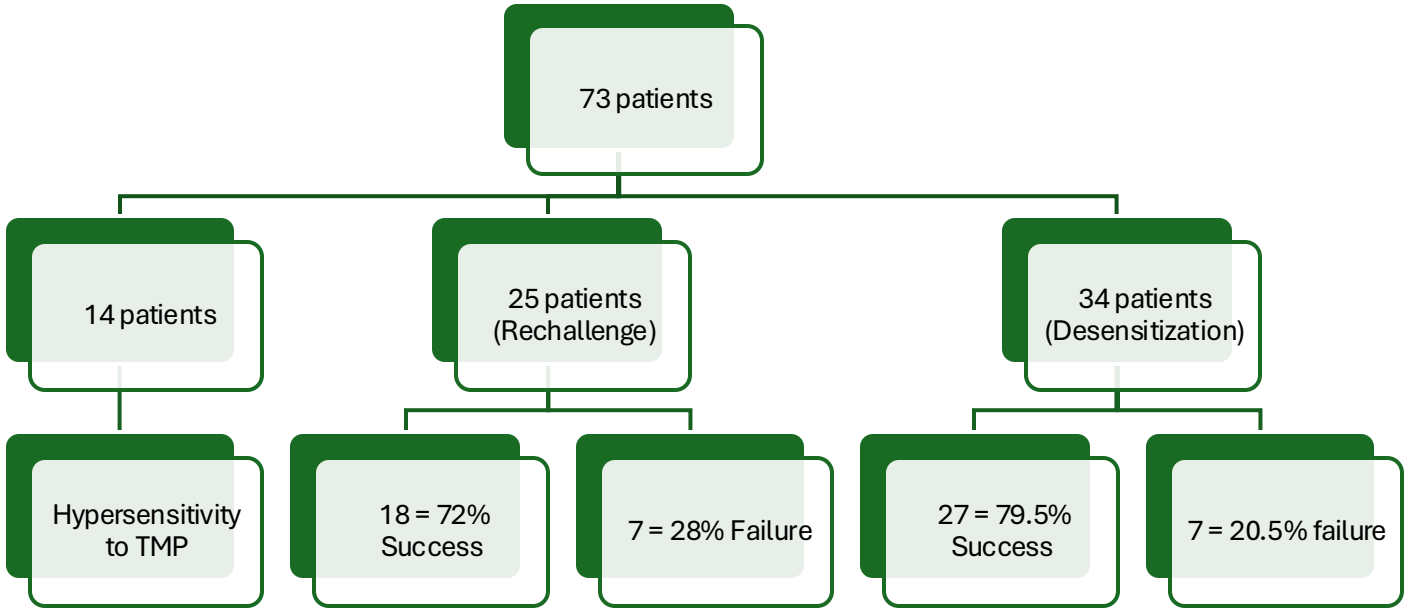
There was one case of breakthrough **toxoplasmosis** and one case of ***Nocardia*** infection

WILEY TRANSPLANT INFECTIOUS DISEASE
The Official Journal of Transplant Infectious Disease
TX NETWORK

The Problem With TMP/SMX Allergy

Is desensitization more effective than rechallenge in preventing hypersensitivity reactions to TMP/SMX?

- Bonfanti et al (2020)
- Population: Persons with HIV and documented TMP/SMX allergy who require PJP prophylaxis
- Intervention: Desensitization versus drug challenge
- Outcome: Development of hypersensitivity reaction in 30 days



Excluded: Serious reactions including exfoliating dermatitis, asthma, anaphylactic shock. Initial manifestation diagnosed as hypersensitivity had to be observed and documented by a physician

PMID: 10721462

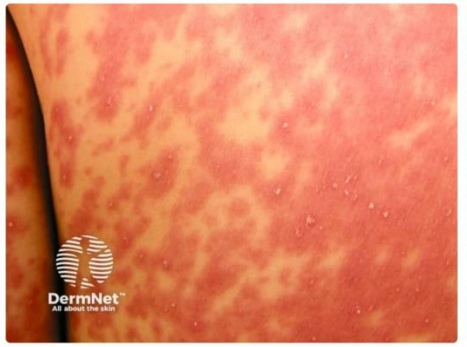
Single and Two dose oral challenges for de-labeling TMP/SMX allergy?

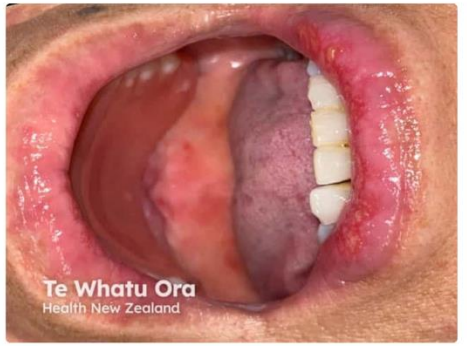
- Krantz et al (2019)
- Single center, retrospective cohort study
- Population: Patients with "sulfa antibiotic allergy" labels without severe delayed immune mediated reactions (SJS, TEN, DRESS, AGEP, drug induced nephritis or hepatitis). Total 204 patients, 195 without HIV.
- Outcome: Safety and outcome of single or two dose TMP/SMX oral challenges, tolerance of future TMP/SMX treatment

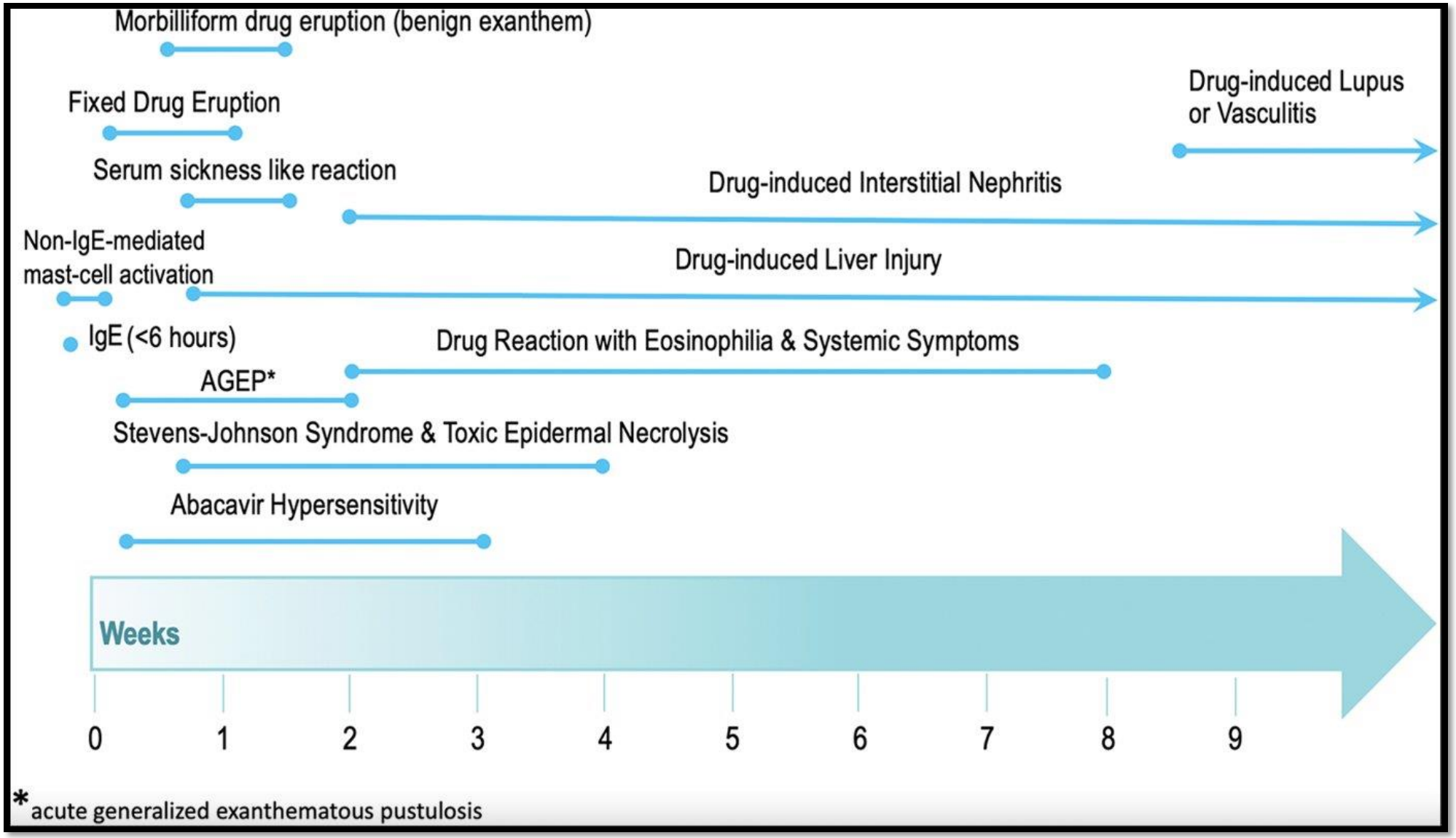
PMCID: PMC6960372

A Reminder: SJS-TEN, AGEP = SCAR!

- Stevens Johnsons – Toxic Epidermal Necrolysis (SJS-TEN)
  - Typically systemic prodromal symptoms
  - Tender/painful red rash trunk -> face, limbs (rarely affecting scalp, palms, or soles)
  - Nikolysky sign
- Acute Generalized Examthematous Pustolosis (AGEP)
  - Starts on face or armpits/groin -> spreads
  - Red skin studded with pinhead-sized sterile pustules
  - 20% patients have oral lesions







PMID: 36122788

Table: Criteria for single versus two dose TMP/SMX challenge

Type	Criteria	Dose	Follow Up
1 Step	Nonsevere delayed reactions without multiple features consistent with IgE-mediated reaction Nonsevere immediate (eg, isolated urticaria, maculopapular exanthem, or gastrointestinal symptoms) reaction (onset <1 h) ≥5 y ago Nonsevere accelerated reaction (onset >1 h to 36 h) ≥5 y ago Unknown, remote history	TMP-SMX 80-400 mg 2-h observation in clinic after full dose	24-h phone call after full dose
2 Step	Nonsevere immediate reaction (onset <1 h) within the past 5 y Nonsevere accelerated reaction (onset >1 h but <36 h) within the past 5 y Anaphylaxis at any time point in the past; multiple (≥2) features potential compatible with IgE-mediated reaction at any time point in the past: * Urticaria * Angioedema * Shortness of breath * Hypotension Significant patient anxiety surrounding single-dose challenge	TMP-SMX 8-40 mg Observe for 1 hour TMP-SMX 80-400 mg Observe for 2 hours	24-h phone call after second, full dose

Table: Outcomes for single versus two dose TMP/SMX challenge in patients without HIV

	Single dose	**Two dose**
Oral Challenge Success Rate	165/173 (95.4%)	19/22 (86.3%)
Patients retreated with TMP/SMX after negative testing	38 (23.0%)	10 (52.6%)
Clinical manifestation of suspected drug hypersensitivity when patient retreated	6 (15.7%) - 3 delayed - 3 non-allergic	3 (30%) - 1 delayed - 2 non-allergic

- **Index History:** 13% with history of immediate hypersensitivity failed oral challenge, compared to 8.5% non-severe delayed history or unknown history (p = 0.03)
- **Nature of Initial Label:** 11% with history of TMP/SMX allergy label failed oral challenge, compared to 1% with unspecified sulfa allergy (p = 0.03)
- **Time since reaction:** Reduced risk of challenge failure with longer time since reaction, adjusted OR 0.88/year (95% CI 0.80-0.97)

A New Risk Score: SULF-FAST?

SULF-FAST Score (2023)

- <5 years since reaction (2 points)
- Anaphylaxis or angioedema or severe cutaneous adverse reaction (2 points)
- Treatment required (1 point)

Score <3 with low allergy risk <5%, scores >3 had risk >20%

Unclear how many of these were patients living with HIV

In US cohort, AUC 0.67, sensitivity of 38.5%, specificity of 89.5%, NPV 95.5% (performed better in Australian cohort, with AUC 0.86). [PMID: 37273210]

Has been used to identify patients for delabeling in the inpatient setting [Mitri 2024]

Drug Allergy: A 2022 Practice Parameter Update

- "We suggest that for patients with a history of benign cutaneous reactions (eg, MDE, urticaria) to sulfonamide antibiotics that occurred >5 years ago, a 1-step drug challenge with TMP-SMX be performed when there is a need to delabel a sulfonamide antibiotic allergy."

PMID: 36122788

Case

- 44-year-old woman with a Klebsiella UTI; based on susceptibilities, the only PO antibiotic option is TMP/SMX. She is hesitant about IV therapy.
  - Allergy was approximately 3 years ago when she took TMP/SMX for a skin infection
  - Had fever, rash, liver function test changes, and kidney injury
  - No shortness of breath, angioedema, but required treatment with steroids and required stopping TMP/SMX

Strict Avoidance
SJS?
TEN?
DRESS?
AGEP?
Drug induced nephritis?
Drug induced hepatitis?

AVOID

Return to Initial Case

- 57-year-old male without HIV, with reported allergy to TMP/SMX who requires medication for *Pneumocystis* prophylaxis in setting of steroid use.
- He has G6PD deficiency, and financial difficulties.
  - Reaction occurred >10 years ago.
  - Recalls full body hives, no skin peeling/sloughing, no pustules, no mucosal involvement. No shortness of breath, dyspnea, throat closing. No tongue or lip swelling. Did not require hospitalization nor treatment.
  - There is question about whether the reaction was due to TMP/SMX or another drug.

Strict Avoidance
SJS?
TEN?
DRESS?
AGEP?
Drug induced nephritis?
Drug induced hepatitis?

SULF-FAST
Recent reaction (<5 years)?
Angioedema/Anaphylaxis/SCAR?
Treatment required?

Single Dose Oral Challenge

Take Home Points

- Accurate documentation of allergies matters!
  - Not all "sulfa allergies" are created equal
- If TMP/SMX is first line, ask yourself, can I really not use it?
  - Make sure there are no features of severe delayed immune-mediated reactions
  - Potentially higher risk if patient with HIV and CD4>250
- The SULF-FAST score can be used to identify persons at low risk for true hypersensitivity reactions (unclear how many persons with HIV were included)
- In persons with low risk sulfonamide allergies consider 1-step or 2-step challenge protocols for de-labeling. Involve your allergy colleagues if unsure!

References

- 1. Al-Shaikhly, T., Al-Obaydi, S., Craig, T. J. & Henao, M. P. Sulfonamide allergy label and the risk of opportunistic infections in solid organ transplant recipients – A retrospective matched cohort study. *Transplant Infectious Dis* **26**, e14355 (2024).
- 2. Carr, A., Penny, R. & Cooper, D. A. Efficacy and safety of rechallenge with low-dose trimethoprim-sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* **7**, 65–71 (1993).
- 3. Carr, A., Swanson, C., Penny, R. & Cooper, D. A. Clinical and laboratory markers of hypersensitivity to trimethoprim-sulfamethoxazole in patients with Pneumocystis carinii pneumonia and AIDS. *J Infect Dis* **167**, 180–185 (1993).
- 4. Delbove, A. *et al*. Pneumocystis pneumonia after lung transplantation: A retrospective multicenter study. *Respir Med* **169**, 106019 (2020).
- 5. He, K. D. *et al*. Alternative Pneumocystis Pneumonia Prophylaxis in Solid Organ Transplants. *Transplant Infectious Dis* e14410 (2024) doi:10.1111/tid.14410.
- 6. Jung, A. C. & Paauw, D. S. Management of adverse reactions to trimethoprim-sulfamethoxazole in human immunodeficiency virus-infected patients. *Arch Intern Med* **154**, 2402–2406 (1994).
- 7. Khan, D. A. *et al*. Drug allergy: A 2022 practice parameter update. *J Allergy Clin Immunol* **150**, 1333–1393 (2022).
- 8. Passerini, M. *et al*. Trimethoprim-sulfamethoxazole significantly reduces the risk of nocardiosis in solid organ transplant recipients: systematic review and individual patient data meta-analysis. *Clin Microbiol Infect* **30**, 170–177 (2024).
- 9. Rose, M. *et al*. The safety and efficacy of direct oral challenge in trimethoprim-sulfamethoxazole antibiotic allergy. *J Allergy Clin Immunol Pract* **9**, 3847–3849 (2021).
- 10. Waldron, J. L. *et al*. Development and Validation of a Sulfa Antibiotic Allergy Clinical Decision Rule. *JAMA Netw Open* **6**, e2316776 (2023).