What's New in Antibiotic Allergies?

David A. Khan, MD
Program Director, Allergy & Immunology Fellowship Program
Professor of Medicine and Pediatrics
University of Texas Southwestern Medical Center
Dallas, TX

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1

Disclosure

I have no financial interests or relationships to disclose.

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2

Learning Objectives

01

Gain an understanding of the spectrum of antibiotic allergies

02

Be able to identify historical features suggestive of a low likelihood for drug allergy

03

Gain an understanding of updates on beta-lactam allergy and cross-reactivity

04

Review 7 Key Points

3

Key Point 1

Adverse Drug Reactions ≠ Drug Allergy

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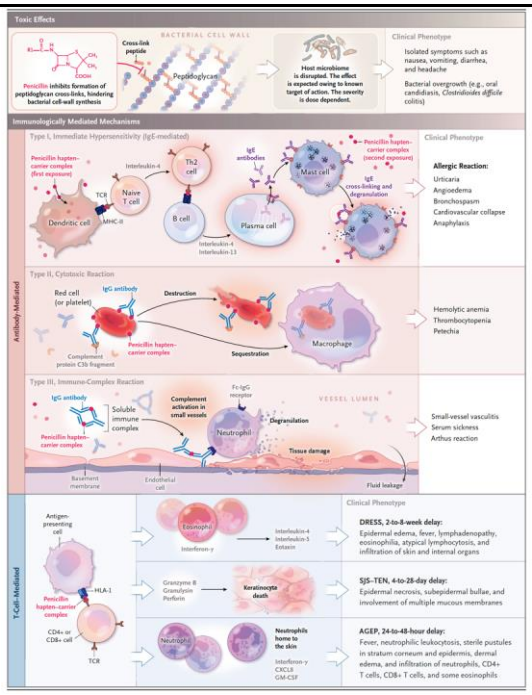
Toxic Effects

Antibody-Mediated

T-Cell Mediated



Thrush

Urticaria/Angioedema/Anaphylaxis

Cytopenias

Serum Sickness-like Reactions

Benign Morbilliform Drug Eruptions

Severe Cutaneous Adverse Reactions

5

Castells MC, Khan DA, Phillips EC. NEJM 2019;381:2338-51

5

Key Point #2

There are Many Different Types of Drug Allergies and Different Types of Drug Rashes Help with Classification & Management

6

Case A

This patient developed this rash 30 minutes after taking amoxicillin

7

Case B

This patient developed a rash **5 days** after taking amoxicillin

8

Which Patient Is at Risk for Anaphylaxis If Amoxicillin Is Administered Again?

A. Patient A
B. Patient B
C. Both A & B
D. Neither

A

B

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TABLE E1. Spectrum of cutaneous drug reactions

Common cutaneous drug reactions
Exanthems
Urticaria
Angioedema
Fixed drug eruption
Pruritus
Acneform
SCARs
DRESS
SJS/TEN
AGEP

Less common cutaneous drug reactions
Acanthosis nigricans
Alopecia
Aphthous stomatitis
Black hairy tongue
Bullous eruptions
Erythema nodosum
Exfoliative dermatitis
Gingival hyperplasia
Lichenoid eruptions
Lupus erythematosus
Phototoxic/photoallergic
Pigmentation
Pityriasis rosea–like eruptions
Psoriasis
Purpura
Vasculitis

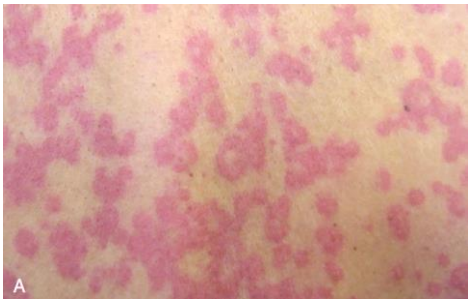
Khan DA. J Allergy Clin Immunol 2012;130:1225-e6.

10

Urticaria & Angioedema

(Case A)

Multiple mechanisms: IgE, pseudoallergic, serum sickness, bradykinin



Urticaria

Angioedema

Joshi SR, Khan DA. Pediatric Allergy: Principles and Practice. 4th ed. 2021

11

IgE Mediated Reactions

Onset

- Usually minutes up to 6 hours after drug exposure
- Requires prior exposure to drug or cross-reacting drug (sensitization)

Symptoms

- Urticaria, flushing, pruritus, angioedema, anaphylaxis

Rash resolves without peeling, or changes in pigmentation

12

Pseudoallergic Reactions

Resemble true IgE allergic reactions but IgE not involved

Pathophysiology

- Non-specific mast cell degranulation
- Activation of MRGPRX2 receptor

Onset usually minutes to hour after exposure (like IgE)

- **May occur with 1st exposure**

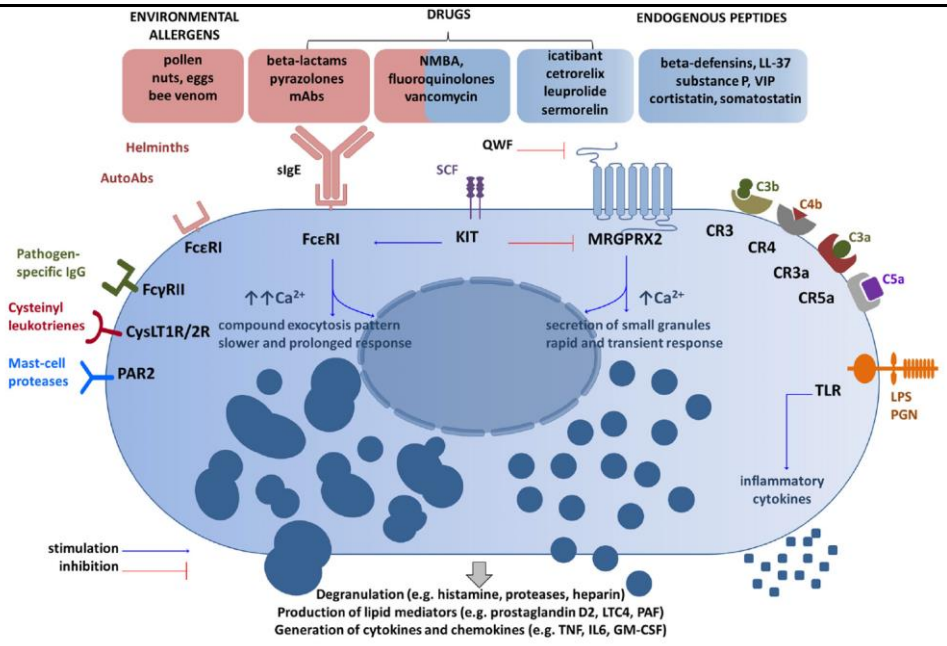
Urticaria, flushing, pruritus, rarely hypotension

Examples

- Opiates, **vancomycin, ciprofloxacin**
- Vancomycin Infusion Reaction (preferred terminology)

Premedication with antihistamines is helpful

13



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Porebski G et al. Front Immunol. 2018;9:3027.

14

Morbilliform Drug Eruptions

(Case B)

- Most common drug allergic reaction
- Pathophysiology mixed: Often T cell mediated
- Onset variable often within days or longer
- Pruritic, usually starts on trunk and spreads to extremities in a symmetric fashion
- Often resolves with scaling/peeling
- **Does not evolve into anaphylaxis**

15

Acute (Hospital) Days Later (Home)

Morbilliform Drug Eruption

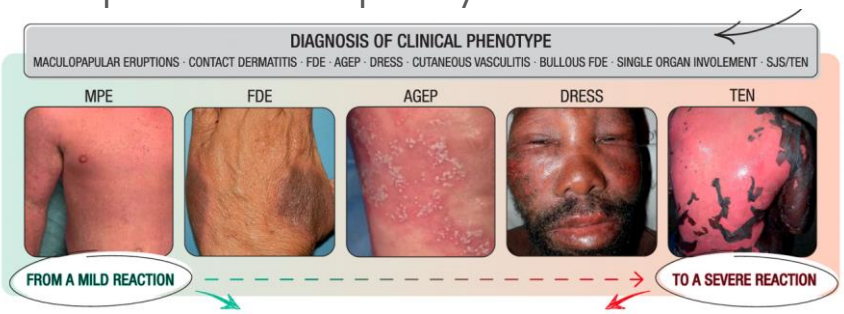
16

Cutaneous Drug Eruptions

17

Severe Cutaneous Adverse Drug Reactions (SCAR)

- SJS/TEN, DRESS, AGEP
- Patients are ill
  - Fever, other systemic symptoms
- Mortality 5 to >30%
- Require multidisciplinary care



Lehloenya RL et al. J Allergy Clin Immunol Pract. 2020;8(9):2878-95..

18

Non-Cutaneous Organ Specific Drug Allergic Reactions

	Clinical Features	Examples of causative agents
Hematologic	hemolytic anemia, thrombocytopenia, granulocytopenia	penicillin, sulfonamides
Hepatic	hepatitis, cholestatic jaundice	sulfonamides, phenothiazines
Pulmonary	pneumonitis, fibrosis	nitrofurantoin, bleomycin, methotrexate
Renal	interstital nephritis, membranous glomerulonephritis	penicillin, sulfonamides, allopurinol

Khan DA, Solensky R. J Allergy Clin Immunol 2010;125(2 Suppl 2):S126-37.

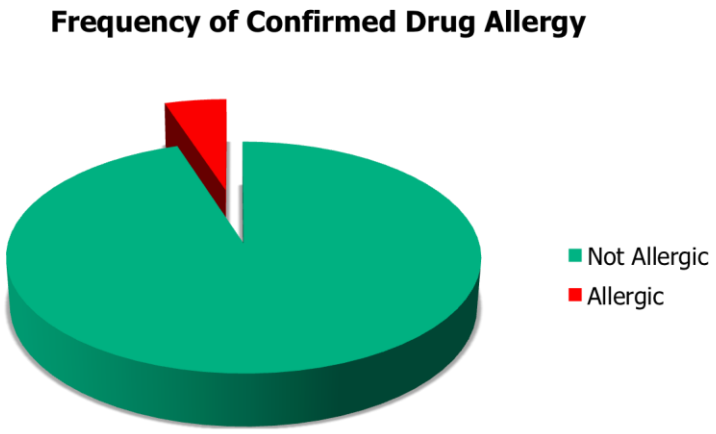
19

The Best Tool in Our Toolbox

History Taking in Drug Allergy

20

Vast Majority of Patients Labeled with a Drug Allergy Are Not Allergic



21

Features Suggestive of **True** Drug Allergy

Objective findings

- Rash
- Wheezing, hypoxia
- Hypotension

Rational temporal relationship to drug

"allergy-prone" drug

Resolution with discontinuation

22

Features **Less Suggestive** of Drug Allergy

- Subjective symptoms only
  - "swelling", pruritus
  - isolated throat symptoms
- High number of listed drug allergies
- Stereotypical reactions
- History of a remote reaction

23

Is This Angioedema?

1

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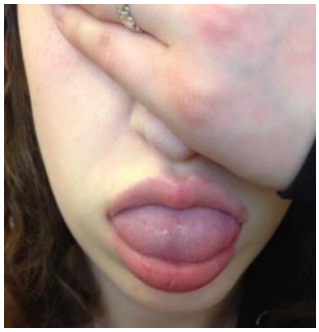

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24

Testing in Drug Allergy

- Genetic Screening
- Skin Testing
- Drug Challenges

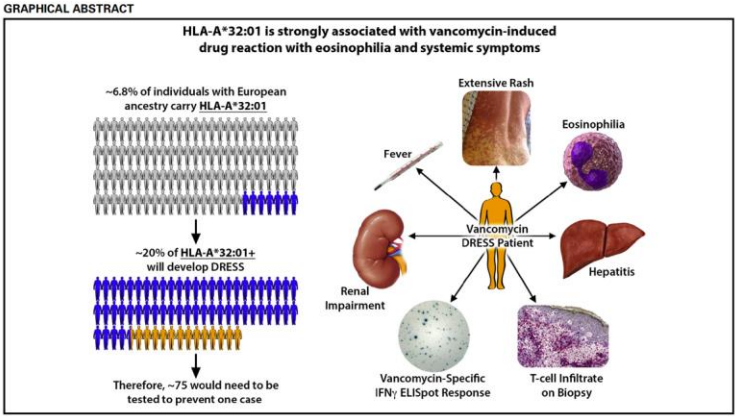
25

HLA-A*32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms

Katherine C. Konvinse, MS,[a] Jason A. Trubiano, MBBS, PhD,[b,c,d] Rebecca Pavlos, PhD,[e] Ian James, PhD,[f] Christian M. Shaffer, BS,[g] Cosmin A. Bejan, PhD,[h] Ryan J. Schutte, PhD,[i] David A. Ostrov, PhD,[i] Mark A. Pilkinton, MD, PhD,[j] Misha Rosenbach, MD,[k] Jeffrey P. Zwerner, MD, PhD,[l] Kristina B. Williams, RN, BSN, CCRP,[j] Jack Bourke, MBBS,[m] Patricia Martinez, MBBS, PhD,[m,n,o] Francois Rwandamuriye, MS,[f] Abha Chopra, PhD,[f] Mark Watson, PhD,[f] Alec J. Redwood, PhD,[f] Katie D. White, MD, PhD,[j] Simon A. Mallal, MBBS,[a,f,j] and Elizabeth J. Phillips, MD[a,f,j,p]

Nashville, Tenn; Heidelberg, Parkville, Nedlands, Murdoch, Perth, and Crawley, Australia; Gainesville, Fla; and Philadelphia, Pa

GRAPHICAL ABSTRACT



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J Allergy Clin Immunol. 2019;144(1):183-92.

26

Antibiotic Skin Testing

Indications

- Most commonly used for high risk patient histories
  - e.g. Anaphylaxis
- **Not useful for noncutaneous organ-specific reactions (e.g. AIN, cytopenias, drug-induced liver injury)**

Specific antibiotics

- Proven accuracy for penicillin
- May be useful to predict tolerance to cephalosporins with disparate R1 groups
- Not helpful for sulfonamides, macrolides, fluoroquinolones, vancomycin etc.

27

Drug Challenges

Most common method used to determine tolerance to a drug

Used in patients with low-risk drug allergy histories

- Reaction > 5-10 years ago
- Benign skin rashes
- Unknown/vague reactions

28

Practice parameter

Drug allergy: A 2022 practice parameter update

David A. Khan, MD,[a] Aleena Banerji, MD,[b] Kimberly G. Blumenthal, MD, MSc,[b] Elizabeth J. Phillips, MD,[c,d] Roland Solensky, MD,[e] Andrew A. White, MD,[f] Jonathan A. Bernstein, MD,[g] Derek K. Chu, MD, PhD,[h,i,j] Anne K. Ellis, MD,[k] David B. K. Golden, MD,[l] Matthew J. Greenhawt, MD,[m] Caroline C. Horner, MD,[n] Dennis Ledford, MD,[o,p] Jay A. Lieberman, MD,[q] John Oppenheimer, MD,[r] Matthew A. Rank, MD,[s] Marcus S. Shaker, MD, MSc,[t] David R. Stukus, MD,[u,v] Dana Wallace, MD,[w] and Julie Wang, MD[x]

Dallas, Tex; Boston, Mass; Murdoch, Australia; Nashville and Memphis, Tenn; Corvallis, Ore; San Diego, Calif; Cincinnati and Columbus, Ohio; Hamilton and Kingston, Ontario, Canada; Baltimore, Md; Aurora, Colo; St Louis, Mo; Tampa and Fort Lauderdale, Fla; Rutgers, NJ; Scottsdale, Ariz; Lebanon, NH; and New York, NY

https://www.jacionline.org/article/S0091-6749(22)01186-1/fulltext

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

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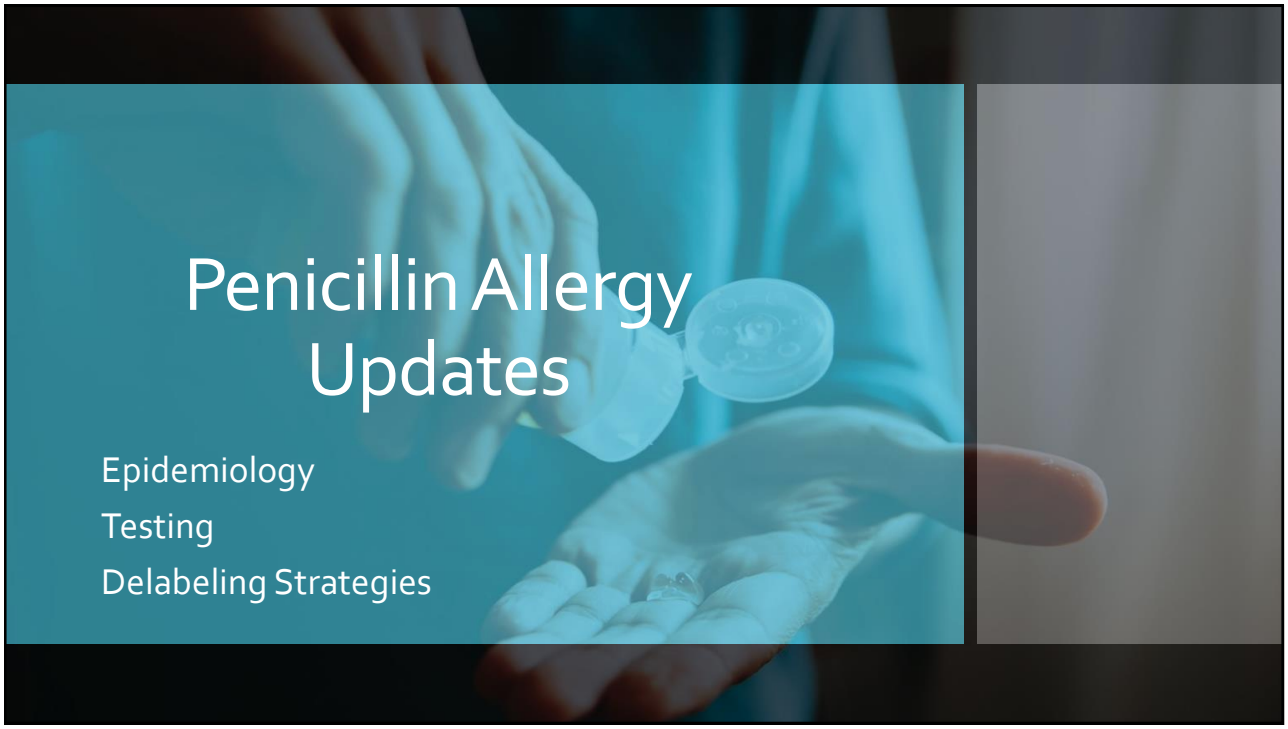
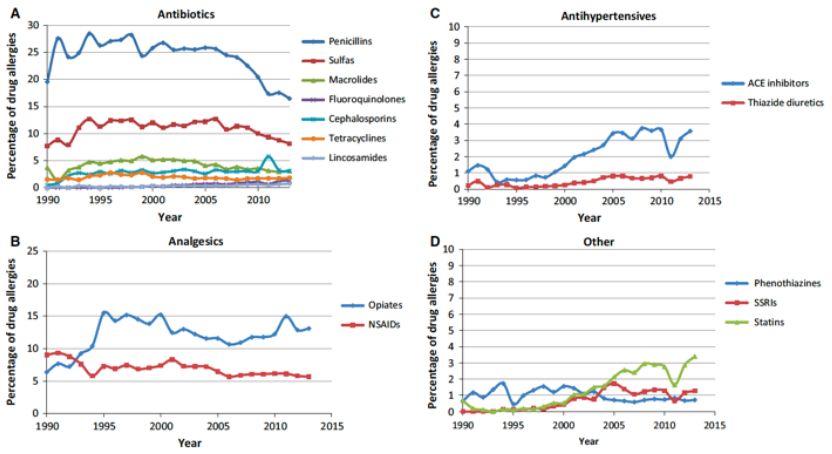


30

Drug Allergies in a Boston EHR



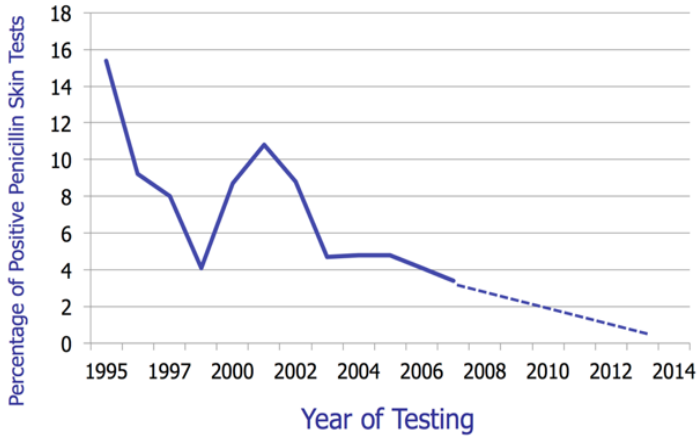
N=1.76 million

Penicillin Allergy=12.8%

Zhou L et al. Allergy 2016; 71: 1305–1313.

31

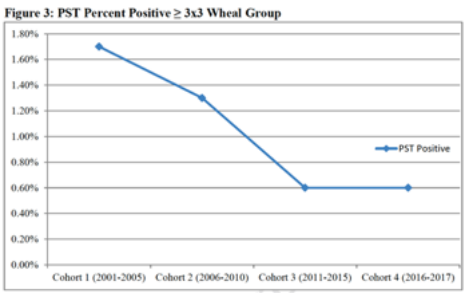
Decline in Positive Penicillin Skin Tests (Kaiser)

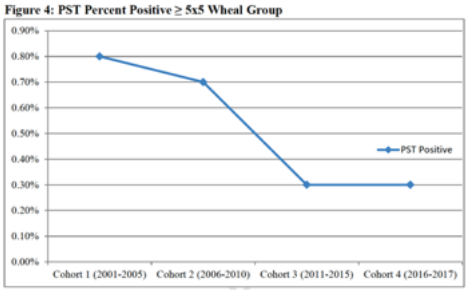


Khan DA. Allergy Asthma Proc. 2020;41(2):82-89.

32

Low Rate (<1%) of Positive Skin Tests Since 2000 (Mayo Clinic)





N=30,883

Voelker D et al. J Allergy Clin Immunol Pract. 2020;8(6):1980-1986.e1987.

33

Key Point #3

Most Patients Who Really Were Allergic to Penicillin in the Past, Lose Their Allergy Over Time

34

Why Penicillin Allergy Labels Matter

Castells MC, Khan DA, Phillips EC. NEJM 2019

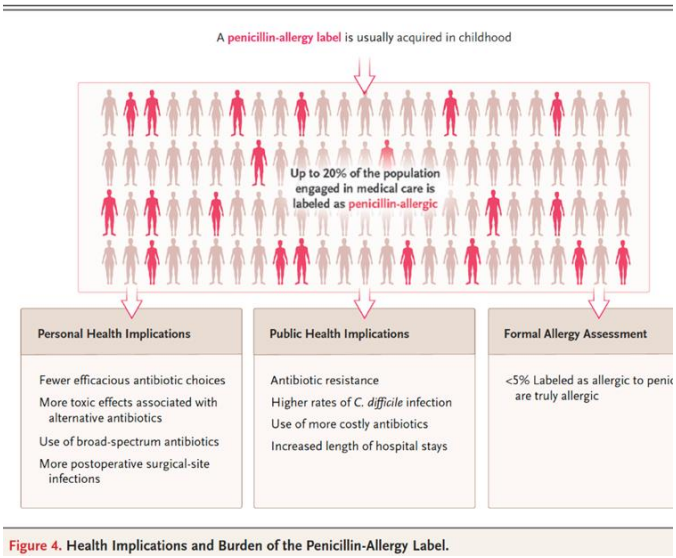


Figure 4. Health Implications and Burden of the Penicillin-Allergy Label.

35

Proactive Penicillin Allergy Delabeling

PRACTICE CHANGER

Consensus Based Statement

- We recommend that a proactive effort should be made to delabel a penicillin allergy, if appropriate.

Strength of Recommendation

- Strong

Certainty of Evidence

- Moderate

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

36

No Need to Test Patients with Invalid Histories of Penicillin Allergy

Consensus Based Statement

- We **recommend against testing in patients with a history inconsistent with penicillin allergy** (such as headache or family history of penicillin allergy), but a 1-step amoxicillin challenge may be offered to patients who are anxious or request additional reassurance to accept the removal of a penicillin allergy label.

Strength of Recommendation

- Strong

Certainty of Evidence

- Moderate

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

37

PARADIGM SHIFT

Penicillin Skin Testing Not Required for Most Children

Consensus Based Statement

- We **recommend <u>against</u> penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction** (such as morbilliform drug eruptions and urticaria).

Strength of Recommendation

- Strong

Certainty of Evidence

- Moderate

38

Direct Amoxicillin Challenges Safe in Children with Penicillin Allergy Label

Original Article

The Safety of the Direct Drug Provocation Test in Beta-Lactam Hypersensitivity in Children: A Systematic Review and Meta-Analysis

Witchaya Srisuwatchari, MD[a], Phichayut Phinyo, MD, PhD[b,c,d], Anca Mirela Chiriac, MD, PhD[e,f], Surasak Saokaew, PharmD, PhD, BPHCP, FACP, FCPA[g], and Prapasri Kulalert, MD, PhD[h,i] *Bangkok, Chiang Mai, Phayao, and Pathum Thani, Thailand; and Montpellier, France*

- 5% Challenges positive
- <1% are immediate reactions
- 4% delayed rash
- Risk of anaphylaxis < 1 in 8000 challenge

Srisuwatchari W et al. J Allergy Clin Immunol Pract. 2023;11(2):506-18.

39

Direct Amoxicillin Challenge May Be Considered for Low Risk Patients Labeled with Penicillin Allergy

PRACTICE CHANGER

Consensus Based Statement

- We suggest that **direct amoxicillin challenge be considered in adults** with a history of distant and benign cutaneous reactions (such as morbilliform drug eruptions and urticaria).

Strength of Recommendation

- Conditional

Certainty of Evidence

- Low

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

40

41

JAMA Internal Medicine | Original Investigation

Development and Validation of a Penicillin Allergy Clinical Decision Rule

Jason A. Trubiano, MBBS, PhD; Sara Vogrin, MBBS, MBiostat; Kyra Y. L. Chua, MBBS, PhD; Jack Bourke, MBBS; James Yun, MBBS, PhD; Abby Douglas, MBBS; Cosby A. Stone, MD; Roger Yu, MD; Lauren Groenendijk, MD; Natasha E. Holmes, MBBS, PhD; Elizabeth J. Phillips, MD

Figure. PEN-FAST Penicillin Allergy Clinical Decision Rule

PEN	Penicillin allergy reported by patient	☐ *If yes, proceed with assessment*
F	*Five years or less since reaction*[a]	☐ 2 points
A	Anaphylaxis or angioedema	☐ 2 points
OR		
S	Severe cutaneous adverse reaction[b]	
T	*Treatment required for reaction*[a]	☐ 1 point
		☐ Total points

Interpretation	
Points	
0	**Very low risk** of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)
1-2	**Low risk** of positive penicillin allergy test 5% (1 in 20 patients)
3	**Moderate risk** of positive penicillin allergy test 20% (1 in 5 patients)
4-5	**High risk** of positive penicillin allergy test 50% (1 in 2 patients)

PEN-FAST Score=0, NPV of 99.4%
PEN-FAST Score=3, NPV of 96.3%

PEN-FAST Score < 3 excluded severe allergies

JAMA Intern Med. 2020;180(5):745-52.

42

JAMA Internal Medicine | Original Investigation

Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy
The PALACE Randomized Clinical Trial

Ana Maria Copaescu, MD; Sara Vogrin, MBiostat; Fiona James, BBiomedSci; Kyra Y. L. Chua, PhD; Morgan T. Rose, MBBS; Joseph De Luca, MBBS; Jamie Waldron, MD; Andrew Awad, MD; Jack Godsell, MBBS; Elise Mitri, BPharm; Belinda Lambros, MAdvNursPrac; Abby Douglas, PhD; Rabea Youcef Khoudja, MD; Ghislaine A. C. Isabwe, MD; Genevieve Genest, MD; Michael Fein, MD; Cristine Radojicic, MD; Ann Collier, MD; Patricia Lugar, MD; Cosby Stone, MD; Moshe Ben-Shoshan, MD; Nicholas A. Turner, MD; Natasha E. Holmes, PhD; Elizabeth J. Phillips, MD; Jason A. Trubiano, PhD

JAMA Intern Med. 2023;183(9):944-52.

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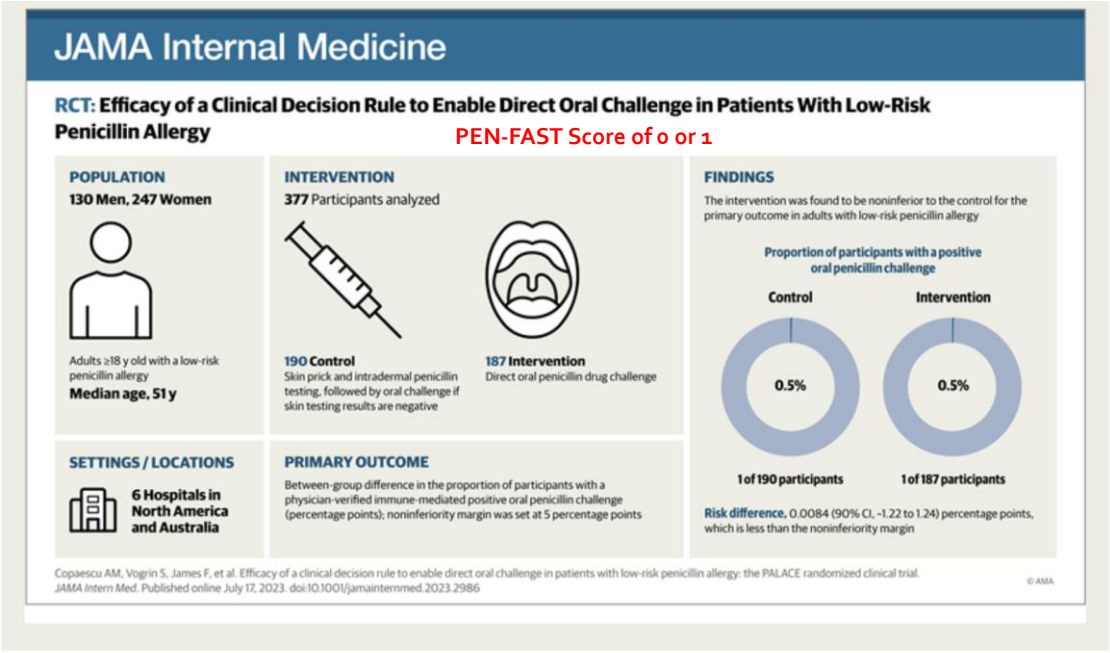


JAMA Intern Med. 2023;183(9):944-52.

44

Simple Low-Risk Definition

Reaction History

- Rash only
- Unknown
- Childhood

Time Since Reaction

- >5-10 years

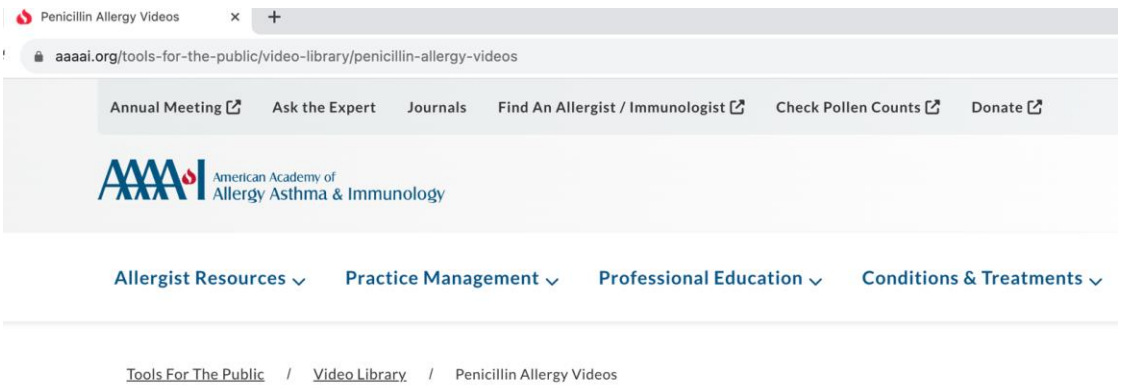
45

Other Populations to Delabel

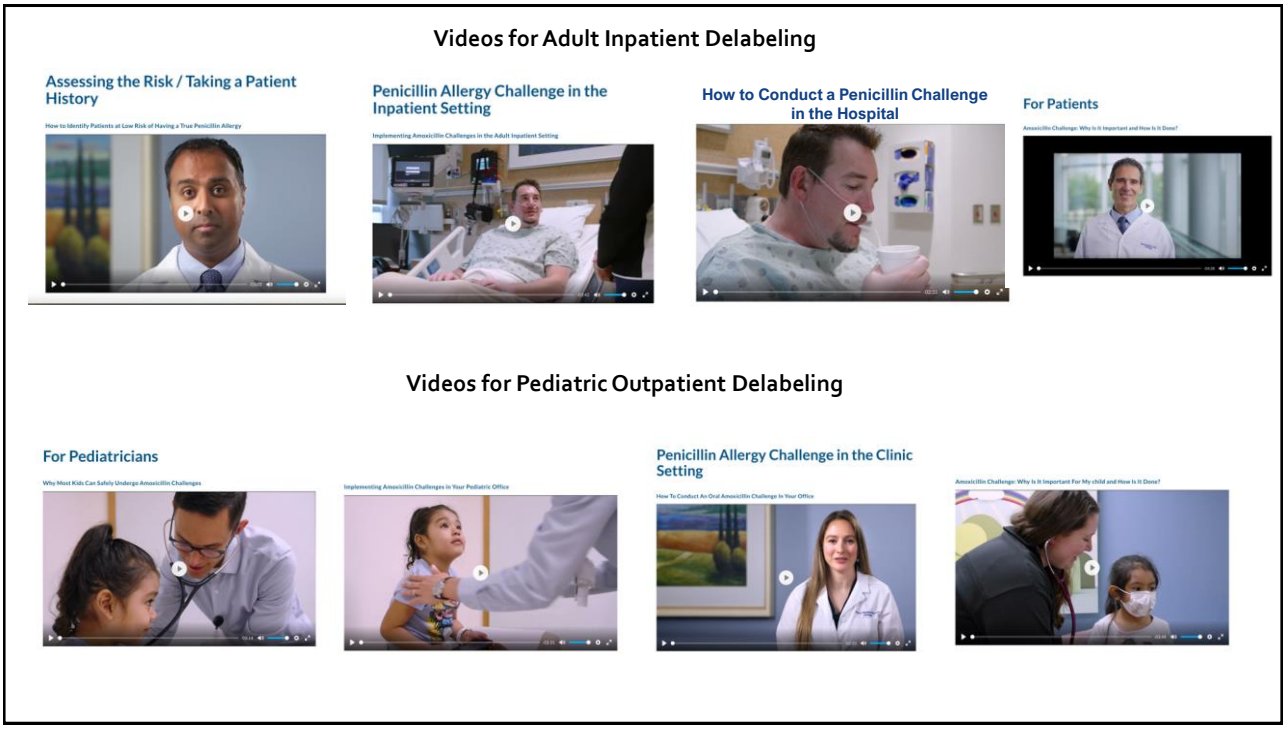
- ICU patients
- Pregnant patients

Koo G et al. J Allergy Clin Immunol Pract. 2022 Jun;10(6):1660-3 e2.
Mak R et al. J Allergy Clin Immunol Pract 2022 Vol. 10 Issue 7 Pages 1919-1921 e1

46


Penicillin Allergy Videos
aaaai.org/tools-for-the-public/video-library/penicillin-allergy-videos
Annual Meeting
Ask the Expert
Journals
Find An Allergist / Immunologist
Check Pollen Counts
Donate
American Academy of Allergy Asthma & Immunology
Allergist Resources
Practice Management
Professional Education
Conditions & Treatments
Tools For The Public / Video Library / Penicillin Allergy Videos
Penicillin Allergy Videos
A Penicillin Allergy Direct Challenge can be conducted safely in both the in-patient and clinic settings by physicians and other health care providers. This video series takes an in depth look at how and when to conduct the challenge in both settings as well as for adults and children.

47

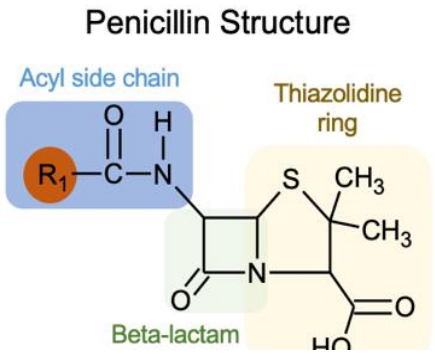

Videos for Adult Inpatient Delabeling
Assessing the Risk / Taking a Patient History
Penicillin Allergy Challenge in the Inpatient Setting
How to Conduct a Penicillin Challenge in the Hospital
For Patients
Videos for Pediatric Outpatient Delabeling
For Pediatricians
Penicillin Allergy Challenge in the Clinic Setting

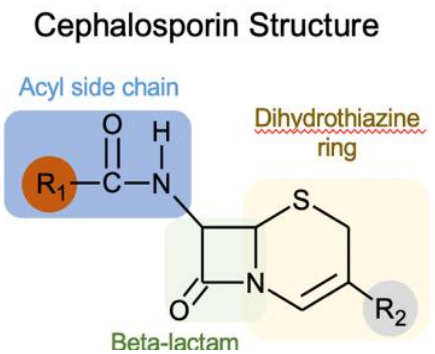
48

In a Patient Who Developed Hives After Taking Penicillin, What Is the Risk of Reacting to a Cephalosporin?

A. 25%
B. 10%
C. 5%
D. <1%

Penicillin Allergy and Cross-Reactivity with Beta-Lactams





Penicillin and Cephalosporin Cross-Reactivity

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

51

Key Point #4

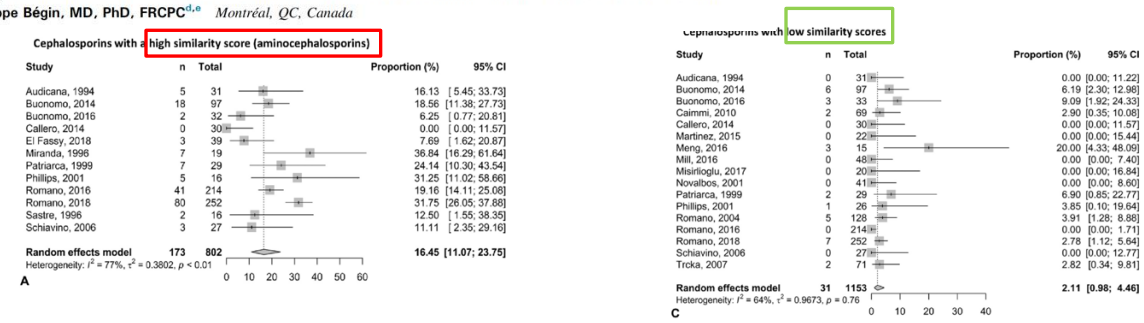
Most All Patients Labeled as Penicillin Allergic Can Take Cephalosporins

52

Original Article

Cross-Reactivity to Cephalosporins and Carbapenems in Penicillin-Allergic Patients: Two Systematic Reviews and Meta-Analyses

Matthieu Picard, MD, FRCPC[a], Geneviève Robitaille, PhD[b], Fatiha Karam, PhD[b], Jean-Marc Daigle, MSc[b], François Bédard, MSc[c], Éric Biron, PhD[c], Mélanie R. Tardif, PhD[b], Jonathan Lacombe-Barrios, MD, FRCPC[d], and Philippe Bégin, MD, PhD, FRCPC[d,e] *Montréal, QC, Canada*



If proven allergy to aminopenicillin risk of positive skin test to:

aminocephalosporin is **16%**

unrelated cephalosporin is **2%**

Picard M, et al. J Allergy Clin Immunol Pract. 2019;7(8):2722-38 e5.

53

Risk of Cephalosporin Cross-Reactivity in Unverified Penicillin Allergy

- <5% of patients with an unverified penicillin allergy are truly allergic
- ~2% of those who are truly allergic will experience a reaction to a cephalosporin
- the chance of a reaction is very low with a linked probability of approximately 0.1%
  - (0.05x0.02=0.001).

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

54

PRACTICE CHANGER

Cephalosporin Administration with Non-Anaphylactic Penicillin Allergy History

Consensus Based Statement

- We suggest that for patients with an **unverified non-anaphylactic penicillin allergy, a cephalosporin can be administered without testing** or additional precautions.

Strength of Recommendation

- Conditional

Certainty of Evidence

- Moderate

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

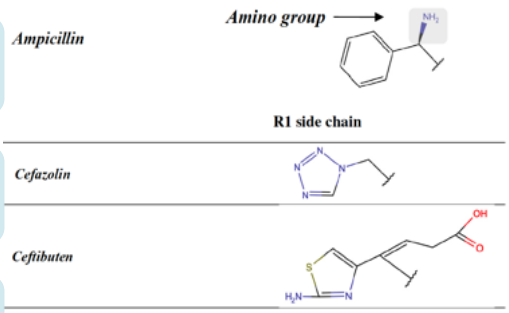
55

Original Article

Tolerability of Cefazolin and Ceftibuten in Patients with IgE-Mediated Aminopenicillin Allergy

Antonino Romano, MD[a], Rocco Luigi Valluzzi, MD[b], Cristiano Caruso, MD[c], Alessandra Zaffiro, MD[d], Donato Quaratino, MD[d], and Francesco Gaeta, MD, PhD[c] *Catania, Vatican City, and Rome, Italy*

131 subjects	• 98.5% aminopenicillin allergy, **78% with anaphylaxis**
130/131 had negative cefazolin/ceftibuten skin tests	• 1 subject (outlier) had positive skin tests to all PCN reagents, cephalosporins and carbapenems
129/130 agreed to cefazolin/ceftibuten challenges	• **All 129 had negative challenges**



Cefazolin and ceftibuten R1 groups disparate from aminopenicillins

J Allergy Clin Immunol Pract. 2020;8(6):1989-93.e2.

56

PRACTICE CHANGER

Cephalosporin Administration with Anaphylactic Penicillin Allergy History

Consensus Based Statement

- We suggest that for patients with a history of **anaphylaxis to penicillin, a non-cross–reactive cephalosporin can be administered without prior testing**.

Strength of Recommendation

- Conditional

Certainty of Evidence

- Moderate

Cefazolin ok even for anaphylactic penicillin allergy history

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

57

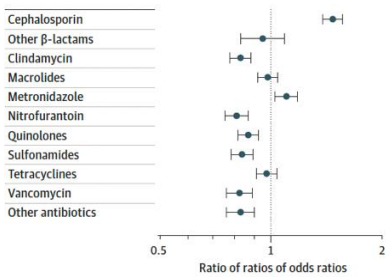
JAMA Network | Open

Original Investigation | Allergy

Association Between Removal of a Warning Against Cephalosporin Use in Patients With Penicillin Allergy and Antibiotic Prescribing

Eric Macy, MD, MS; Thomas A. McCormick, PhD; John L. Adams, PhD; William W. Crawford, MD; Myngoc T. Nguyen, MD; Liem Hoang, PharmD, MS; Victoria Eng, MD; Anna C. Davis, PhD; Elizabeth A. McGlynn, PhD

Figure. Multinomial Logistic Regression of Changes in Antibiotic Use Among Patients With Penicillin Allergies



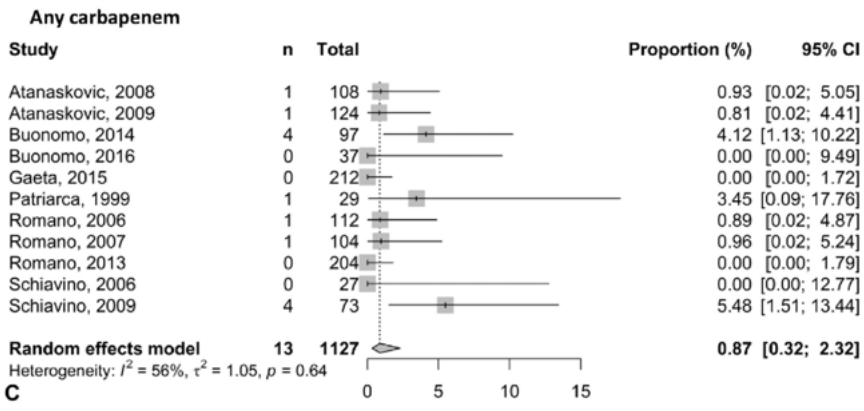
No significant differences in the rates of anaphylaxis, allergies to new antibiotic classes, antibiotic treatment failure, all-cause mortality, hospital days, and new infections after the change.

Macy E et al. JAMA Netw Open. 2021;4(4):e218367.

58

Penicillin Allergy & Carbapenems

In Proven Penicillin Allergy
Risk of Reacting to Carbapenem < 1%



Picard M, et al. JACI In Practice. 2019;7(8):2722-38.e5.

59

Carbapenem Administration with Penicillin Allergy History

PRACTICE CHANGER

Consensus Based Statement

- We recommend that in **patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without prior testing.**

Strength of Recommendation

- Strong

Certainty of Evidence

- Moderate

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

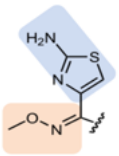
60

Key Point #5

A Patient Allergic to One Cephalosporin Can Usually Take Other Cephalosporins That Are Structurally Different

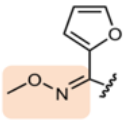
61

Group 1



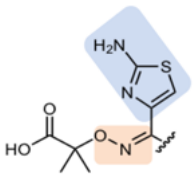
Ceftriaxone, Cefotaxime, Cefepime
Cefpodoxime, Cefditoren

Group 2



Cefuroxime

Group 3



Ceftazidime, aztreonam

62

Khan DA et al. J Allergy Clin Immunol 2019;7(7):2105-14.

62

Identical R1 Side Chains:

Penicillins and Cephalosporins

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

	Cefazolin (1st)	Cefaclor (2nd)	Cefadroxil (1st)	Cefepime (4th)	Cefotaxime (3rd)	Cefoxitin(2nd)	Cefprozil (2nd)	Ceftazidime (3rd)	Ceftriaxone (3rd)	Cephalexin (1st)	Amoxicillin	Ampicillin	Aztreonam
Cefazolin (1st)	-												
Cefaclor (2nd)		-								X		X	
Cefadroxil (1st)			-				X			X	X		
Cefepime (4th)				-	X				X				
Cefotaxime (3rd)				X	-				X				
Cefoxitin(2nd)						-							
Cefprozil (2nd)			X				-				X		
Ceftazidime (3rd)								-					X
Ceftriaxone (3rd)				X	X				-				
Cephalexin (1st)		X	X							-		X	
Amoxicillin			X				X				-		
Ampicillin		X								X		-	
Aztreonam								X					-

63

Key Point #6

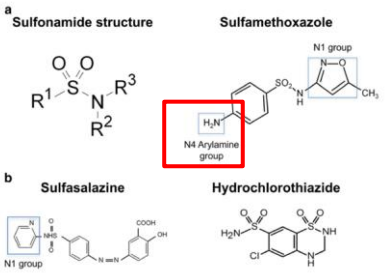
Patients Allergic to Sulfonamide Antibiotics Can Take Other "Sulfa" and Sulfonamide Non-antibiotic Medications

64

Sulfonamide Allergy

65

Sulfonamide Antibiotics Are Structurally Different than Non-Antimicrobial Sulfonamides



Antimicrobial sulfonamides			
Sulfamethoxazole	Sulfamerazine	Sulfamethizole	Sulfamoxole
Sulfacetamide	Sulfanilamide	Sulfamerazine	Sulfadiazine
Sulfamethazine	Sulfisoxazole	Sulfapyridine	Sulfasalazine (metabolized to sulfapyridine)
Non-antimicrobial sulfonamides			
Tamulosin	Ibutilide	Sotalol	Topiramate
Acetazolamide	Methazolamide	Dorzoalamide	Celecoxib
Furosemide	Bumetanide	Metalozone	Torsemide
Hydrochlorothiazide	Chlorthalidone	Glimepiride	Glyburide
Glipizide	Naratriptan	Sumatriptan	Probenecid

Chow TG, Khan DA. Clin Rev Allergy Immunol. 2022;62(3):400-12.

66

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Absence of Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics

Brian L. Strom, M.D., M.P.H., Rita Schinnar, M.P.A., Andrea J. Apter, M.D., David J. Margolis, M.D., Ph.D., Ebbing Lautenbach, M.D., M.P.H., M.S.C.E., Sean Hennessy, Pharm.D., Ph.D., Warren B. Bilker, Ph.D., and Dan Pettitt, D.V.M.

N Engl J Med. 2003;349(17):1628-35.

67

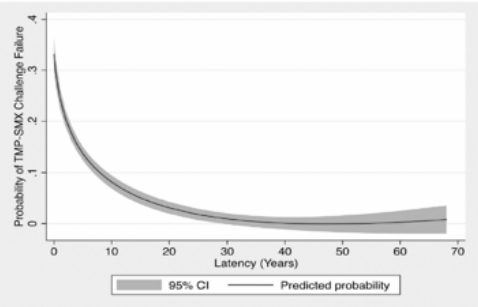
1 or 2 Step Sulfonamide Challenges

195 non-HIV patients with sulfonamide allergy history
- 173 underwent 1-step challenge
  - Low risk histories
  - > 5yrs from reaction
  - **95% passed**
- 22 underwent 2-step challenge
  - Higher risk history
  - 86% passed

J Allergy Clin Immunol Pract. 2020;8(2):757-60.e4.

Oral challenge with trimethoprim-sulfamethoxazole in patients with "sulfa" antibiotic allergy

Matthew S. Krantz, MD[a,*], Cosby A. Stone, Jr., MD, MPH[b,*], Andrew Abreo, MD[b], and Elizabeth J. Phillips, MD[b,c,d,e,f]



Mayo Clinic study of 52 patients showed 96% passed challenge
J Allergy Clin Immunol Pract. 2022;10(4):1107-9.

68

PRACTICE CHANGER

1-Step Sulfonamide Challenge When Delabeling Is Needed

Consensus Based Statement

- We suggest that **for patients with a history of benign cutaneous reactions** (e.g. morbilliform drug eruption, urticaria) **to sulfonamide antibiotics that occurred > 5 years ago, a 1-step drug challenge with trimethoprim-sulfamethoxazole be performed when there is a need to delabel a sulfonamide antibiotic allergy**.

Strength of Recommendation

- Conditional

Certainty of Evidence

- Low

Khan DA et al. J Allergy Clin Immunol 2022;150(6):1333-93.

69

Key Point #7

When There Is No Alternative A Drug Desensitization May Be Considered But It Is Not Permanent

70

Drug Desensitizations

Indicated for patients with:

- High likelihood or confirmed drug allergy
- In need of culprit drug where no alternative therapy exists

Many Rapid Drug Desensitizations

- Antibiotics
- Chemotherapeutics, monoclonal Abs
- Aspirin
- Others

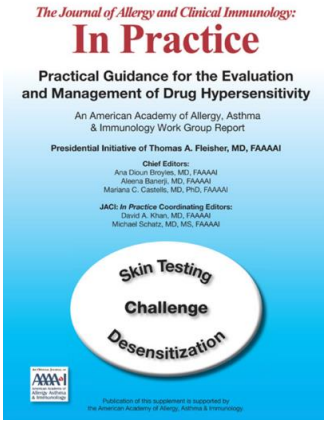
71

Table 2. Three-Bag, 12-Step Intravenous Penicillin Desensitization Protocol.*

Step	Bag	Rate	Time†	Volume Infused	Dose Administered	Cumulative Dose
		ml/hr	*min*	*ml*	*units*	
1	1	2.0	15	0.50	200.0	200.0
2	1	5.0	15	1.25	500.0	700.0
3	1	10.0	15	2.50	1,000.0	1,700.0
4	1	20.0	15	5.00	2,000.0	3,700.0
5	2	5.0	15	1.25	5,000.0	8,700.0
6	2	10.0	15	2.50	10,000.0	18,700.0
7	2	20.0	15	5.00	20,000.0	38,700.0
8	2	40.0	15	10.00	40,000.0	78,700.0
9	3	10.0	15	2.50	98,032.5	176,732.5
10	3	20.0	15	5.00	196,065.0	372,797.5
11	3	40.0	15	10.00	392,130.0	764,927.5
12	3	80.0	61.875	82.50	3,235,072.5	4,000,000.0

Castells M, Khan DA, Phillips EJ. Penicillin Allergy. N Engl J Med. 2019;381(24):2338-51.

72



Other Drug Allergy Resources

73

There are many types of antibiotic reactions, cutaneous features can help determine testing/management/prognosis

Most patients labeled with antibiotic allergy are not allergic

The label of penicillin allergy is associated with adverse health outcomes and can be removed through testing in >98% cases

Antibiotic challenges can be performed to prove tolerance, even by non-allergists

Summary

74