

Sparkle Shine
Celebrate!

Penicillin Allergy Label (PAL) IS NOT YOUR FRIEND

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Disclosure

I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation (within the last 12 months).

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Presentation Objectives

Pharmacist Objectives

1. Discuss the cross reactivity between penicillin and cephalosporins
2. Review the classifications of hypersensitivity reactions
3. Analyze the Drug Allergy: 2022 Practice Parameter Update
4. Discuss the implications of using second line agents for surgical prophylaxis
5. Discuss the professional liability of prescribing beta-lactams in patients with PCN allergy

Technician Objectives

1. Recognize differences between true allergic reactions and common medications side effects as reported by patients
2. Identify when allergy information should be clarified or escalated to the pharmacist

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WHY IS (PAL) NOT YOUR FRIEND?

A penicillin-allergy label is usually acquired in childhood

Castells, M. et al. N Engl J Med 2019; 381:2338-51

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Pathogens and Common Syndromes for Which Beta-lactams are Considered the Treatment of Choice

Organism	Examples
Group A Streptococcus	Pharyngitis, skin and soft tissue infections, Cellulitis, erysipelas, pyoderma, necrotizing fasciitis, myositis, acute rheumatic fever, acute glomerulonephritis, pneumonia, postpartum endometritis, toxic shock syndrome, bacteremia
Group B Streptococcus	Endocarditis
Viridans group streptococci and Streptococcus gallolyticus (Duke)	
Listeria monocytogenes	Meningitis
Actinomyces spp	Cervicofacial, pelvic, and respiratory infections
Cutibacterium acnes (formerly Propionibacterium acnes)	Bone and joint and central nervous system shunt infections
Staphylococcus aureus	Skin and soft tissue, bone and joint, and respiratory tract infections
Pasteurella multocida	Skin and soft tissue infections, bacteremia, and respiratory tract infections
Neisseria gonorrhoeae	Urethritis, epididymitis, pharyngitis, conjunctivitis, cervicitis, proctitis, disseminated disease (septic arthritis, endocarditis)
Neisseria meningitidis	Meningitis
Treponema pallidum (syphilis)	Primary syphilis (chancres), secondary syphilis (rash, condylomata lata), tertiary syphilis (aortitis), meningitis

Shenoy E. et al. AJ JAMA 2019;321(2):188-199

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BETA-LACTAM TYPE 1 MEDIATED REACTIONS

Estimated anaphylaxis allergic prevalence

- 0.001% parenteral exposure
- 0.0005% oral exposure

Most common reaction to penicillin is maculopapular rash

Blumenthal KG et al. Lancet 2019; 393:185-98

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IT'S ALL ABOUT THE R1 SIDECHEIN

beta-lactam ring

Acyl side chain

Penicillin structure

Acyl side chain

Cephalosporin structure

Acyl side chain

Monobactam structure

Acyl side chain

Carbapenem structure

Blumenthal KG et al. Lancet 2019; 393:183-98

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Legend:

- Red: Cross-reactivity
- Yellow: No cross-reactivity
- Grey: No data

Blumenthal KG et al. Lancet 2019; 393:183-98

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R1 IDENTICAL SIDE CHAINS

Penicillin G	Amoxicillin	Cefepime	Cefdinir	Aztreonam	Cefoxitin	Cefazolin
Penicillin VK	Ampicillin	Cefotaxime	Cefixime	Ceftazidime		
	Cefaclor	Cefepodoxime				
	Cefadroxil	Ceftriaxone				
	Cefprozil					
	Cephalexin					

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CROSS-REACTIVITY AMONG BETA-LACTAMS

Legend:

- Red: Cross-reactivity
- Yellow: No cross-reactivity
- Grey: No data

Blumenthal KG et al. Lancet 2019; 393:183-98

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Cefazidime

Cefepime

Cefiderocol

Catechol moiety
Additional stability against β -lactamases
Binds to free iron

Zhanet, G. et al. Drugs (2019) 79:271-289

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CLASSIFICATION OF HYPERSENSITIVITY REACTIONS

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CLASSIFICATION OF HYPERSENSITIVITY REACTIONS

Type of reaction	Hypersensitivity	Mediated by	Time of onset	Examples
IgE-mediated	Type I	IgE antibodies	Within 1 hour	Anaphylaxis
Non-IgE-mediated	Type II	Cytotoxic	Hours to days	Hemolytic anemia
Non-IgE-mediated	Type III	Immune complex	7-21 days	Serum sickness
Non-IgE-mediated	Type IV	Cell-mediated	Days to weeks	Maculopapular rash Stevens-Johnson syndrome Toxic epidermal necrolysis

IgE = Immunoglobulin E

Gonzalez-Estrada et al. Cleveland Clinic Journal of Medicine 2015;82(3):295-300

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Immunologically Mediated Mechanisms

Type I, Hypersensitivity IgE-mediated

Type II, Cytotoxic Reaction

Type III, Immune-Complex Reaction

Clinical Phenotype

Allergic Reaction:
Urticaria
Angioedema
Bronchospasm
Cardiovascular collapse
Anaphylaxis

Hemolytic anemia
Thrombocytopenia
Pneumitis

Small-vessel vasculitis
Serum sickness
Arthralgia reaction

Castells, M. et al. N Engl J Med 2019; 381:2338-51

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T-cell-Mediated

Antigen presenting cell

Penicillin hapten-carrier complex

CD4+ or CD8+ cell

TCR

HLA-I

Eosinophil

Interleukin-4

Interleukin-5

Eotaxin

Granzyme B

Granulysin

Perforin

Keratinocyte death

Neutrophil

Neutrophils home to the skin

Interleukin-7

CXCL8

G-CSF

Clinical Phenotype

DRESS, 2-to-8-week delay:
Epidermal edema, fever, lymphadenopathy, eosinophilia, atypical lymphocytosis, and infiltration of skin and internal organs

SJS-TEN, 4-to-28-day delay:
Epidermal necrosis, subepidermal bullae, and involvement of multiple mucous membranes

AGEP, 24-to-48-hour delay:
Fever, neutrophilic leukocytosis, sterile pustules in stratum corneum and epidermis, dermal edema, and infiltration of neutrophils, CD4+ T cells, CD8+ T cells, and some eosinophils

Castells, M. et al. N Engl J Med 2019; 381:2338-51

TCR= T cell receptor

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Drug Reaction With Eosinophilia Systemic Symptoms (DRESS)

- Also called Drug-Induced Hypersensitivity Syndrome (DIHS)
- Characterized by
 - fever ($\geq 38.5^\circ\text{C}$)
 - extensive ($\geq 50\%$ of total body surface area) pruritic morbilliform rash with 8 weeks (most common 2-6 weeks) of culprit drug exposure
- Incidence
 - 1 in 1,000 to 1 in 10,000 depending on the drug culprit
- Associated medications
 - allopurinol, vancomycin, lamotrigine, carbamazepine, and trimethoprim-sulfamethoxazole

Hung, S. et al. Nature Reviews Disease Primers (2024) 10:30

Krochinsky, D. et al. N Engl J Med 2024;391:2340-54

DRESS

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Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)

- Most severe and acute form of SCARs
- Characterized by
 - Widespread blistering cutaneous eruptions
 - Extensive mucosal erosions
- Incidence
 - Stevens-Johnson Syndrome (SJS)
 - 1-13 cases per million per year
 - <10% of epidermal detachment of total body surface area
 - Toxic Epidermal Necrolysis (TEN)
 - 0.4-12 cases per million per year
 - >30% of epidermal detachment of total body surface area
- Associated medications
 - allopurinol, sulfonamides, aromatic anticonvulsants, NSAIDs

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SJS

TEN

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Acute Generalized Exanthematous Pustulosis (AGEP)

- Milder form of SCARs
- Characterized by
 - Massive cell infiltrate consisting of neutrophils in pustules
- Incidence
 - 1-5 cases per million per year
- Associated medications
 - beta-lactam antimicrobials, non-beta-lactam antimicrobials, anticonvulsants, calcium channel blockers, analgesics, hydroxychloroquine

Hung, S. Nature Reviews Disease Primers (2024) 10:30

AGEP

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Practice parameter

Drug allergy: A 2022 practice parameter update [Check for updates](#)

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Consensus-Based Statement 4

We recommend that a proactive effort should be made to de-label patients with reported penicillin allergy, if appropriate

Strength of Recommendation: Strong
Certainty of Evidence: Moderate

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Consensus-Based Statement 4

Patients with an IgE mediated allergy lose their sensitivity over the years
Up to 50% lose sensitivity after 5 years
Up to 80% lose sensitivity after 10 years

Penicillin allergy label is not benign
More likely to receive less effective, more toxic and more expensive antibiotics
Fluoroquinolones, Vancomycin, Clindamycin, Aztreonam

Evaluations for de-labeling of allergy are elective and usually performed when the patient is well

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Consensus-Based Statement 5

We recommend against any testing in patients with a history inconsistent with penicillin allergy

Strength of Recommendation: Strong
Certainty of Evidence: Low

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Consensus-Based Statement 5

Example of inconsistent allergies:
headache, family history, diarrhea
Alternative option:
1-step amoxicillin challenge
Skin testing only detects the presence or absence of penicillin specific IgE antibodies

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Consensus-Based Statement 6

We suggest penicillin skin testing for patients with a history of anaphylaxis or a recent reaction suspected to be IgE mediated

Strength of Recommendation: Conditional
Certainty of Evidence: Low

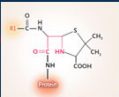
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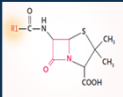
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Consensus-Based Statement 6

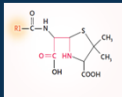
- Example of IgE mediated reaction:
 - Anaphylaxis
 - Immediate onset urticaria
- NPV of PCN skin testing > 95%



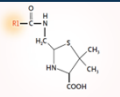
Penicilloic



Penicillin



Penicilloate



Penicillate

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Castells, M. et al. N Engl J Med 2019; 381:2338-51

NPV= negative predictive value

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Consensus-Based Statement 9

We suggest that direct amoxicillin challenge be considered in adults with a history of distant (> 5 years ago) and benign cutaneous reactions

Strength of Recommendation: Conditional
Certainty of Evidence: Low

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Original Article

Comparing Direct Challenge to Penicillin Skin Testing for the Outpatient Evaluation of Penicillin Allergy: A Randomized Controlled Trial

S. Shahzad Mustafa, MD^{1,2}, Kelly Conn, PhD, MPH¹, and Allison Ramsey, MD^{1,3} Rochester, NY

What is already known about this topic? The benefits of penicillin allergy de-labeling are well established. Penicillin skin testing is a proven approach to penicillin allergy de-labeling, but there is emerging data regarding direct challenges without prior skin testing in low-risk individuals.

What does this article add to our knowledge? This article is the first randomized controlled trial comparing penicillin skin testing to a 2-step direct challenge in penicillin-allergic patients with cutaneous-only symptoms.

How does this study impact current management guidelines? This study demonstrates the safety and utility of 2-step direct challenges in low-risk patients with a 30-minute monitoring period as compared with penicillin skin testing for de-labeling of penicillin allergy in the outpatient setting.

Mustafa, S. et al J Allergy Clin Immunol Pract Volume 7, Number 7

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Consensus-Based Statement 10

We suggest that for patients with a history of nonanaphylactic cephalosporin allergy, direct challenges (without prior skin test) to cephalosporins with dis-similar R1 side chains be performed to determine tolerance

Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

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Consensus-Based Statement 11

We suggest that for patients with a history of anaphylaxis to a cephalosporin, a negative cephalosporin skin test should be confirmed prior to administration of a parenteral cephalosporin with a non-identical R1 side chain

Strength of Recommendation: Conditional
Certainty of Evidence: Low

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Consensus-Based Statement 11

If the skin testing is negative, then a drug challenge should be completed to confirm tolerance

Can only perform skin testing with parenteral cephalosporins

- If administering an oral cephalosporin or skin testing is unable to be completed
- Drug challenge (higher risk)
- Empiric induction of tolerance (desensitization) can be performed

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R1 IDENTICAL SIDE CHAINS						
Penicillin G	Amoxicillin	Cefepime	Cefdinir	Aztreonam	Cefoxitin	Cefazolin
Penicillin VK	Ampicillin	Cefotaxime	Cefixime	Ceftazidime		
	Cefaclor	Cefpodoxime				
	Cefadroxil	Ceftriaxone				
	Cefprozil					
	Cephalexin					

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Consensus-Based Statement 12

We suggest that for patients with a history of anaphylaxis to a penicillin, a structurally dissimilar R1 side chain cephalosporin can be administered without testing or additional precautions

Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

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R1 IDENTICAL SIDE CHAINS						
Penicillin G	Amoxicillin	Cefepime	Cefdinir	Aztreonam	Cefoxitin	Cefazolin
Penicillin VK	Ampicillin	Cefotaxime	Cefixime	Ceftazidime		
	Cefaclor	Cefpodoxime				
	Cefadroxil	Ceftriaxone				
	Cefprozil					
	Cephalexin					

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Consensus-Based Statement 13

We suggest that for patients with a history of an unverified (not confirmed) nonanaphylactic penicillin allergy, a cephalosporin can be administered without testing or additional precautions

Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

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Consensus-Based Statement 13

Less than 5% of patients with unverified penicillin allergy are truly allergic
~2% of those who are truly allergic will experience a reaction to cephalosporins

Chance of anaphylaxis is very low with a linked probability of ~0.1%

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Postgraduate Medical Journal (February Suppl. 1971), 64-69.

SESSION III

Chairman: WILLIAM M. M. KIRBY, M.D., University of Washington, Seattle, Washington

Immunologic reactions of humans to cephalosporins

LAWRENCE D. PETZ, M.D.

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Table 2. Allergic reactions to cephalosporin drugs in penicillin-allergic and non-allergic patients

Number of patients	History of penicillin allergy	Number of allergic reactions	% of allergic reactions	Comments
3320	No	84	2.5%	Urticaria (6), rash (11), fever (1)
109	Yes	18	16.5%	
1983	No	21	1%	Anaphylaxis (2), rash or urticaria (4), unspecified (5)
138	Yes	8	5.8%	Anaphylaxis (2), rash or urticaria (5), unspecified (1)
4085	No	61	1.5%	Rash (37), urticaria (12), misc. (12)
203	Yes	11	5.4%	Rash (8), urticaria (1), misc. (2)

Allergic reaction (Any)

- 203/9,838= 2%

Allergic reaction to cephalosporin in patients not allergic to PCN

- 166/9,388= 1.7%

Allergic reaction to cephalosporin in patients with Hx PCN allergy

- 37/450= 8.2%

Anaphylactic reaction Cephalothin

- No PCN Hx 2/1,983= 0.1%
- No PCN Hx & PCN Hx 4/2,121=0.18%
- PCN Hx 2/138= 1.4%

Petz, L. Postgraduate Medical Journal (Feb Suppl. 1977), 64-69

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Consensus-Based Statement 14

We suggest that in patients with a history of an unverified nonanaphylactic cephalosporin allergy, a penicillin can be administered without testing or additional precautions

Strength of Recommendation: Conditional
Certainty of Evidence: Low

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Consensus-Based Statement 15

We suggest that in patients with a history of anaphylaxis to cephalosporins, penicillin skin testing and drug challenge should be performed prior to administration of a penicillin therapy

Strength of Recommendation: Conditional
Certainty of Evidence: Low

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Consensus-Based Statement 16

We suggest against penicillin skin testing in patients with a history of nonanaphylactic cephalosporin allergy prior to administration of a penicillin therapy

Strength of Recommendation: Conditional
Certainty of Evidence: Low

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Consensus-Based Statement 17

We suggest that in patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without testing or additional precautions

Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

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Consensus-Based Statement 17

Overall reported incidence of carbapenem allergy:
0.3% - 3.7%

Exceptions:

- Severe delayed cutaneous reactions (SCARS) to penicillin or cephalosporins
- Stevens-Johnson Syndrome (SJS)
- Toxic Epidermal Necrolysis (TEN)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Acute Generalized Exanthematous Pustulosis (AGEP)
- Do not re-challenge any beta-lactam

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Consensus-Based Statement 18

We suggest in patients with a history of penicillin or cephalosporin allergy, aztreonam may be administered without prior testing unless there is a history of ceftazidime allergy

Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

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R1 IDENTICAL SIDE CHAINS

Penicillin G	Amoxicillin	Cefepime	Cefdinir	Aztreonam	Cefoxitin	Cefazolin
Penicillin VK	Ampicillin	Cefotaxime	Cefixime	Ceftazidime		
	Cefaclor	Cefpodoxime				
	Cefadroxil	Ceftriaxone				
	Cefprozil					
	Cephalexin					

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Consensus-Based Statement 18

- No cross-reactivity for IgE or T-cell mediated hypersensitivity between penicillin or cephalosporins (except ceftazidime) and aztreonam
- Aztreonam is commonly used as an alternative for patients with penicillin/cephalosporin allergy
 - Lacks activity against gram positive bacteria
 - Not as efficacious against gram-negative bacteria
 - Increasing rates of resistance
 - Expensive

Does Not Address:
Severe delayed cutaneous reactions (SCARs) to penicillin or cephalosporins

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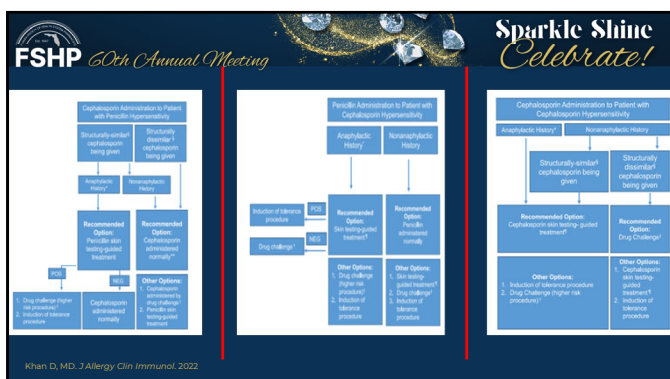
Consensus-Based Statement 19

We recommend that allergist-immunologists collaborate with hospitals and health care systems to implement beta-lactam allergy pathways to improve antibiotics stewardship outcomes

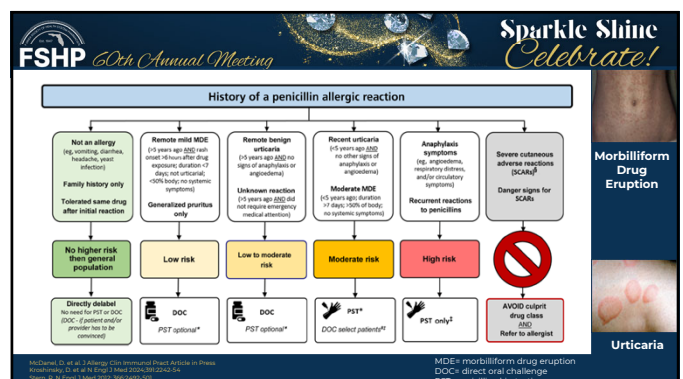
Strength of Recommendation: Strong
Certainty of Evidence: Moderate

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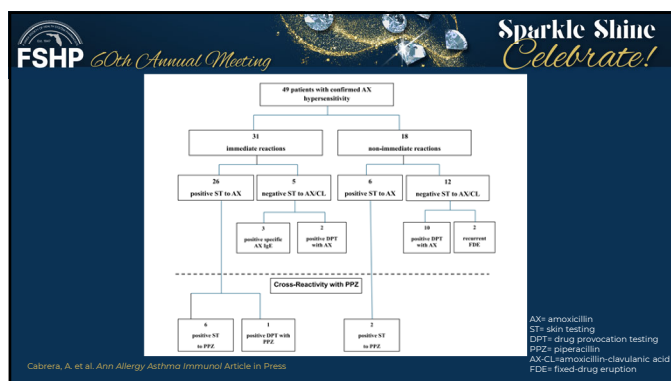
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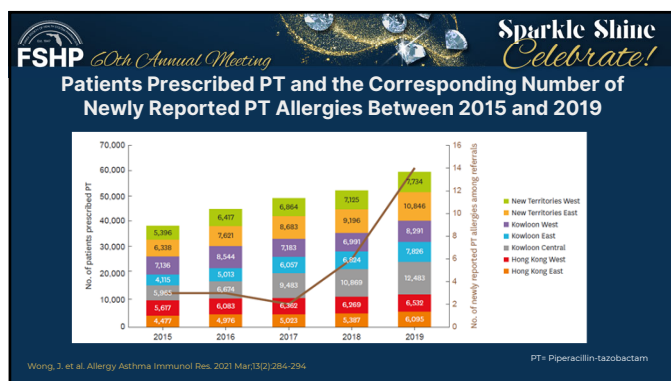
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Authority	Index population	Reaction type	N (patients)	Cross-reactivity between AX/PPZ
Moncada-Salinas et al. ²⁰ 2025	AX allergy	Immediate	28	17.8% (5/28) reacted to PPZ-TZB
Gallardo et al. ¹³ 2021	PPZ-TZB allergy	Immediate	11	18.2% (2/11) were also positive to ampicillins
Copescu et al. ¹⁰ 2021	PPZ-TZB allergy	Mostly non-immediate (80%)	44	18.2% (8/44) positive STs to AX/ampicillin
Casimir-Brown et al. ¹⁹ 2021	PPZ-TZB allergy	Immediate + non-immediate	24	Approximately 33% positive to other penicillins; 18.7% to AX

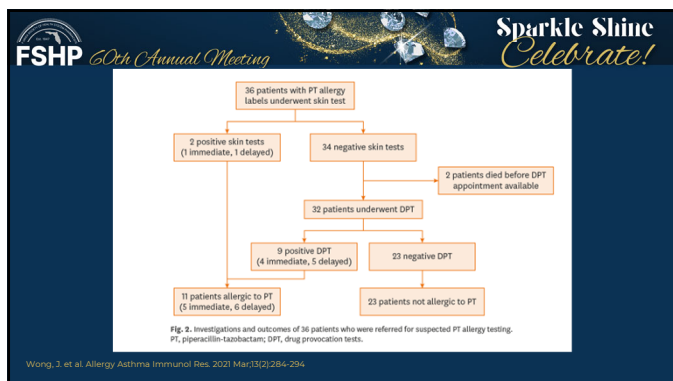
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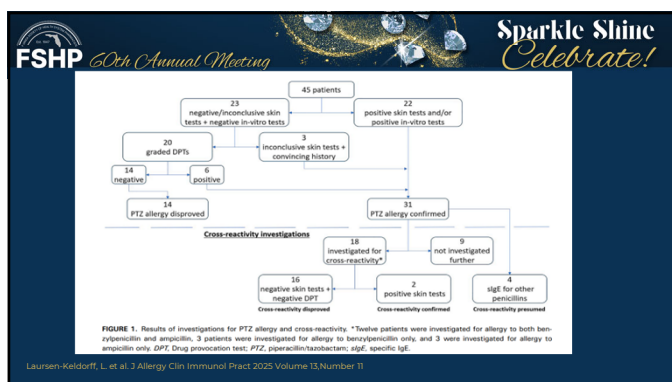
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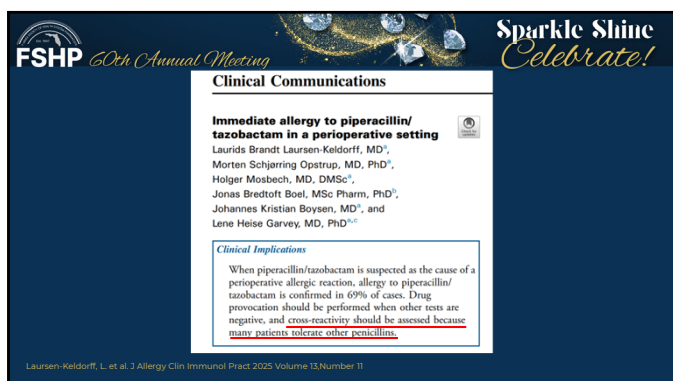
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Primary outcome

Tolerance to piperacillin-tazobactam	Number of patients (%)
Yes	187 (98%)
No	4 (2%)

Subgroup analysis: piperacillin-tazobactam tolerance based on FHA AHS penicillin allergy risk stratification

Penicillin allergy risk stratification based on the Fraser Health Authority Antimicrobial Stewardship handbook	Number of patients who tolerated piperacillin-tazobactam (%)	Number of patients who did not tolerate piperacillin-tazobactam (%)
Low risk: delayed reactions or poorly described symptoms (n=6)	95 (97%)	3 (3%)
High risk: Of anaphylactic reactions or poorly described symptoms and unstable cardiac or respiratory comorbidity (n=1)	90 (99%)	1 (1%)
Well-documented delayed allergic reactions (n=2)	2 (100%)	0 (0%)

Secondary outcome: proportion of patients with a labeled anaphylactic, allergic or anaphylactoid, like reactions who tolerated piperacillin-tazobactam

Labeled allergic reaction to penicillin	Number of patients (%)
Shortness of breath (throat closing, difficulty breathing) (n=1)	13 (100%)
Anaphylaxis (n=7)	7 (100%)
Angioedema (n=7)	7 (100%)
"Swelling" (n=2)	2 (100%)

Purewal, A. et al. Antimicrobial Stewardship & Healthcare Epidemiology 2026; 6: e68-1-6

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Original Article

Piperacillin-tazobactam tolerability in patients with a labeled penicillin allergy (PIPPEN)

Ameret Purewal Pharm.D., Kieran Shah B.Sc. (Pharm), ACPE, Pharm.D., Sarah N. Stabler B.Sc. (Pharm), ACPE, Pharm.D., Kevin Alta M.D., MSc, MScPhD, and Neel S. Pham D., ACPE, ACPP

Abstract

Background: Piperacillin-tazobactam is a beta-lactam antibiotic with a distinct R1 side chain compared to other penicillins. Therefore, the risk of cross-reactivity should be theoretically low. Despite this, different antimicrobial guidelines recommend against using piperacillin-tazobactam in patients with penicillin allergy. There is limited data available regarding piperacillin-tazobactam use in patients with a penicillin allergy or rate of cross-reactivity. Therefore, the objective of this study was to assess the incidence of cross-reactivity to piperacillin-tazobactam in patients with a labeled penicillin allergy.

Methods: This was a retrospective study of patients admitted to Sunnybrook Hospital (SMBH) between November 17, 2021 to January 10, 2023 receiving piperacillin-tazobactam in patients with prior labeled penicillin allergy. Baseline characteristics and outcomes were collected from electronic medical records (EMRs).

Results: Of the 191 patients included, 98% were found to tolerate one or more doses of piperacillin-tazobactam. This included 97 patients with "low risk allergic reactions", 94 patients with "high risk anaphylactic reactions", and 2 patients with "well-documented delayed reactions". No patients (0%) had documented intolerance to piperacillin-tazobactam post-exposure.

Conclusions: This study suggests that piperacillin-tazobactam has a low rate of cross-reactivity (2%) in patients with a labeled penicillin allergy.

Keywords: piperacillin-tazobactam, penicillin allergy, cross-reactivity, antimicrobial stewardship

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Purewal, A. et al. Antimicrobial Stewardship & Healthcare Epidemiology 2026; 6: e68-1-6

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SURGICAL PROPHYLAXIS

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Clinical Infectious Diseases MAJOR ARTICLE

The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk

Kimberly K. Blumenthal, ^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}

Background: A reported penicillin allergy may compromise receipt of recommended antibiotic prophylaxis intended to prevent surgical site infections (SSIs). Most patients with a reported penicillin allergy or true allergy. We determined the impact of a reported penicillin allergy on the development of SSI.

Methods: In this retrospective cohort study of Massachusetts General Hospital hip arthroplasty, knee arthroplasty, hysterectomy, colon resection, and coronary artery bypass grafting patients from 2010 to 2014, we compared patients with and without a reported penicillin allergy. The primary outcome was an SSI, as defined by the Centers for Disease Control and Prevention's National Healthcare Safety Network. The secondary outcome was postoperative antibiotic use.

Results: Of 10,000 patients who underwent MHA procedures, 922 (11%) reported a penicillin allergy, and 140 (12%) had an SSI. In multivariable logistic regression, patients reporting a penicillin allergy had increased odds (adjusted odds ratio, 1.51; 95% confidence interval, 1.05-2.12) of SSI. Penicillin allergy exposure was associated with antibiotic use (ORs vs 30%: P < .001) and more antibiotics (ORs vs 30%: P < .001), vancomycin (ORs vs 30%: P < .001), and gentamicin (ORs vs 30%: P < .001) compared with those without a reported penicillin allergy. The increased SSI risk was entirely mediated by the patient receipt of an alternative prophylactic antibiotic, between 112 and 124 patients with reported penicillin allergy would need allergy evaluation to prevent 1 SSI.

Conclusions: Patients with a reported penicillin allergy had a 50% increased odds of SSI, attributable to the receipt of oral and intravenous antibiotics. Classification of penicillin allergies as part of routine preoperative care may decrease SSI risk.

Keywords: prophylaxis, antibiotic, healthcare-associated infections, surgical site infections, allergy

Blumenthal, K. et al. Clinical Infectious Diseases 2018; 66(3):329-36

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JAMA Surgery | Original Investigation

Assessment of the Frequency of Dual Allergy to Penicillins and Cefazolin: A Systematic Review and Meta-analysis

Bernardo Sousa Pinto MD, PhD, PhD, Kimberly G. Blumenthal MD, MSc, Lindsay Courtney PhamD, Christian M. Winkler, Jeffrey A. Hersh, PhD, MD

IMPORTANCE: Cefazolin is the preoperative antibiotic of choice because it is safer and more effective than second-line alternatives. Surgical patients without a known penicillin allergy are less likely to prophylactically receive cefazolin and more likely to receive clindamycin or vancomycin, which results in higher rates of surgical site infections.

OBJECTIVE: To examine the incidence of dual allergy to cefazolin and natural penicillins.

DESIGN, SETTING, AND PARTICIPANTS: Dual allergy to cefazolin and a natural penicillin.

MEASUREMENTS AND MAIN RESULTS: Dual allergy to cefazolin and a natural penicillin was identified in 44 participants with a history of penicillin allergy. The frequency of dual allergy was assessed in 10 studies, with a pooled prevalence of 0.1% (95% CI, 0.05% to 0.15%, P = .04). Dual frequency was lower for participants with unconfirmed (0.05%, 95% CI, 0.01% to 0.09%, P = .04) than for those with confirmed penicillin allergy (0.15%, 95% CI, 0.07% to 0.23%, P = .002). These studies exclusively assessed surgical patients (n = 10,000), among whom 2% (95% CI, 0.04% to 0.26%, P = .002) had confirmed allergy to cefazolin. Dual frequency was also assessed for studies of patients with unconfirmed penicillin allergy who had been exposed to penicillin (0.05%, 95% CI, 0.01% to 0.09%, P = .002). Penicillin allergy was confirmed in 10 patients with a history of cefazolin allergy, resulting in a meta-analysis of frequency of 3.7% (95% CI, 0.02% to 0.24%, P = .04). The frequency of penicillin allergy was 4.4% (95% CI, 0.04% to 0.24%, P = .002) for the 10 studies that exclusively assessed surgical patients allergy to cefazolin.

CONCLUSIONS AND RELEVANCE: These findings suggest that most patients with a penicillin allergy history may safely receive cefazolin. The exception is patients with confirmed penicillin allergy along with natural additional units is warranted.

Sousa-Pinto, B. et al. JAMA Surg 2021;156(4):1-10

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R1 IDENTICAL SIDE CHAINS

Penicillin G	Ampicillin	Cefepime	Cefdinir	Aztreonam	Cefazolin	Cefazolin
Penicillin VK	Ampicillin	Cefotaxime	Cefixime	Ceftazidime		
	Cefaclor	Cefepodoxime				
	Cefadroxil	Ceftriaxone				
	Cefprozil					
	Cephalexin					

Patients with a history of anaphylaxis to penicillin, a non-cross-reactive cephalosporin (e.g., cefazolin) can be administered routinely without prior testing

Khan D, MD. J Allergy Clin Immunol 2022

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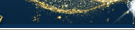
[illegible]

**PROFESSIONAL LIABILITY WHEN PRESCRIBING
BETA-LACTAMS FOR PATIENTS WITH PENICILLIN
ALLERGY**



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Contents lists available at ScienceDirect

Annals of Pharmacotherapy

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Reviews

Systematic review of professional liability when prescribing
β-lactams for patients with a known penicillin allergy

Meghan N. Jeffers, PharmD^a; Elizabeth A. Hall-Lipsy, JD, MPH^b; S. Travis King, PharmD, BCPS (AQ-ID)^c; John D. Cleary, PharmD, FCCP, BCPS (AQ-ID)^d

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^c Department of Pharmacy, Ochsner Medical Center, New Orleans, Louisiana
^d St Dominic Hospital, Department of Pharmacy, Jackson, Mississippi

Objective

- To describe medical negligence and malpractice cases in which a patient with a known penicillin allergy received a beta lactam and experienced an adverse reaction related to the beta-lactam



RESULTS

- 78 court opinions identified
 - 27 cases excluded because allergy not due to beta-lactam
 - 15 cases excluded because patients did not have a preexisting PCN allergy
 - 5 cases excluded because patients did not receive a beta-lactam
 - 3 cases excluded because they did not experience an allergic reaction
 - 1 case excluded because patient was not human

Jeffrey, M. et al Ann Allergy Asthma Immunol 121 (2018) 530-536



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RESULTS

- 27 unique cases in systematic review
- Earliest case in 1959
- Most recent 2013
- 15 cases had published legal outcomes
- 12 cases with unknown outcomes

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RESULTS

- Plaintiffs (patients) in 3 of 10 cases (30%) who received a penicillin-based antibiotic prevailed or settled
8 unknown trial outcome (5 PCN, 2 Ampicillin, 1 Amoxicillin)
- Plaintiff (patient) in 1 of 4 cases (25%) who received a cephalosporin prevailed
3 unknown trial outcome (2 Cephalexin, 1 Cefazolin)
- Plaintiff (patient) in the 1 case who received a carbapenem (Ertapenem) did not prevail
1 unknown trial outcome (Imipenem)

Jeffres, M. et al Ann Allergy Asthma Immunol 121 (2018) 530-536

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KILLEEN v REINHART, 1979

Killeen in 1971 who was 6 months pregnant, presented to her obstetrician with asthma attack. She received an unknown medication, which did not alleviate her symptoms

She was admitted to obstetrics ward and started to deteriorate quickly. She was given cephalothin (1st Generation cephalosporin) for possible pulmonary infection. Killeen dies within 24 hours. The immediate cause of death was bronchial pneumonia

Anaphylactic shock secondary to cephalothin was ruled out

Jeffres, M. et al Ann Allergy Asthma Immunol 121 (2018) 530-536

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KILLEEN v REINHART, 1979

Three physicians were initially sued and settled before trial for \$265,000

Trial proceeded against hospital that Killeen should have been placed on internal medicine ward not the obstetrics ward

Trial resulted in verdict against hospital for \$650,000

Hospital appealed and results from new trial were not publicly published

Jeffres, M. et al Ann Allergy Asthma Immunol 121 (2018) 530-536

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Studies on the Epidemiology of Adverse Drug Reactions

IV. The Relationship of Cephalothin and Penicillin Allergy

Robert Phillips, MD, Joseph B. Johnson, MD, PhD, and Jonathan B. Craig, MD

Seven patients with allergic reactions to cephalothin were studied. Four of these occurred in 51 consecutive patients receiving cephalothin. The majority of the patients with cephalothin reactions had a previous history of penicillin allergy and were found to have positive skin tests with penicilloyl-polylysine (PPL). Allergic reactions to cephalothin occurred at a higher rate in Negro women than in Negro men or white persons. A history of atopic disease was more common in patients with allergic reactions to cephalothin than in persons given cephalothin without reactions. Cephalothin must be used with caution in the treatment of patients with a history of allergic reactions to penicillin or with positive skin tests to PPL, and cannot be considered as a uniformly safe substitute for penicillin in such patients.

Chemical structures shown: Penicillin G, 6-AMINO-PENICILLANIC ACID, Cephalothin, 7-AMINO-CEPHALOSPORANIC ACID.

Thoburn, R. et al JAMA, Oct 24, 1966, Vol 198, No 4

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DISCUSSION

- The most common scenario in which the plaintiff (patient) prevailed was in the setting of receiving PCN itself or, amoxicillin, or ampicillin despite a known documented allergy to PCN
- Cross-reactivity between PCN and cephalosporins is not a class effect but attributable to similarities in R1 side-chain

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SUMMARY

- Penicillin allergies are not benign allergies as they can have severe impacts on patient care
- Be proactive and investigate penicillin allergy
- A cephalosporin with a different R1 side chain may be given to a patient with a penicillin allergy without a drug challenge
- Carbapenems can be administered without skin testing or drug challenges to patients with penicillin/cephalosporin allergies
 - Exception:
 - severe delayed cutaneous reactions
- Consult Allergist if needed

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Penicillin Allergy Learning Module (PALM)

7:00am Registration and Breakfast
 7:30am Session 1: Penicillin Allergy: A Review of the Literature
 8:00am Session 2: Penicillin Allergy: A Review of the Literature
 8:30am Session 3: Penicillin Allergy: A Review of the Literature
 9:00am Session 4: Penicillin Allergy: A Review of the Literature
 9:30am Session 5: Penicillin Allergy: A Review of the Literature
 10:00am Session 6: Penicillin Allergy: A Review of the Literature
 10:30am Session 7: Penicillin Allergy: A Review of the Literature
 11:00am Session 8: Penicillin Allergy: A Review of the Literature
 11:30am Session 9: Penicillin Allergy: A Review of the Literature
 12:00pm Session 10: Penicillin Allergy: A Review of the Literature
 12:30pm Session 11: Penicillin Allergy: A Review of the Literature
 1:00pm Session 12: Penicillin Allergy: A Review of the Literature
 1:30pm Session 13: Penicillin Allergy: A Review of the Literature
 2:00pm Session 14: Penicillin Allergy: A Review of the Literature
 2:30pm Session 15: Penicillin Allergy: A Review of the Literature
 3:00pm Session 16: Penicillin Allergy: A Review of the Literature
 3:30pm Session 17: Penicillin Allergy: A Review of the Literature
 4:00pm Session 18: Penicillin Allergy: A Review of the Literature
 4:30pm Session 19: Penicillin Allergy: A Review of the Literature
 5:00pm Session 20: Penicillin Allergy: A Review of the Literature

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QUESTIONS?

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Penicillin Allergy Label (PAL) IS NOT YOUR FRIEND

Kevin L. Epps PharmD, BCPS, BCIDP
 EPPS.KEVIN@MAYO.EDU

Thank you!

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