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The role of antibiotic allergies in antimicrobial stewardship in long-term care facilities

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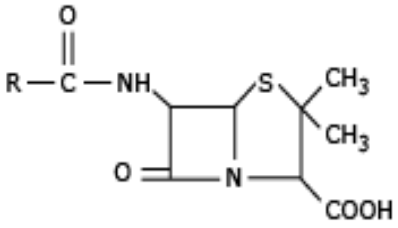
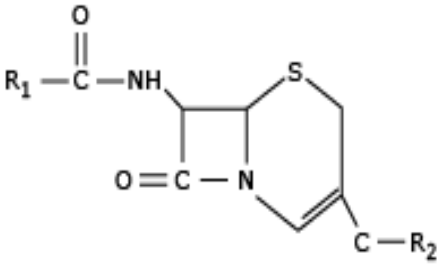
Objectives

- Understand the potential harms of penicillin allergy labels and the relationship with antimicrobial stewardship
- Introduce strategies to optimize treatment of penicillin allergic patients as an antimicrobial stewardship initiative
- Describe processes to de-label patients of a penicillin allergy in long-term care facility patients.

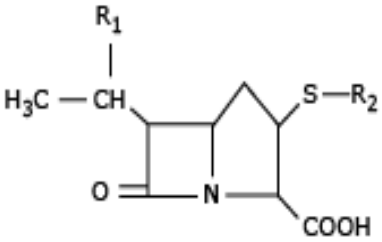
Beta-lactams



Penicillins



Cephalosporins



Carbapenems

- Beta-lactams are the most commonly used antibiotic group in the U.S.
- Core structure is the β-lactam ring with variable side chains at the R site
- Different side chains provide variation in the spectrum of activity and duration of action

FDA Drug Use Review; Pichichero ME et al. Ann Allergy Asthma Immunol 2014;112:404-12.

Drug Related Allergies

- Type 1 – IgE mediated
  - Usually occur within 1 hour of drug exposure, but may occur up to 72 hours afterwards
  - Urticaria, angioedema, bronchospasm, shortness of breath, rash with pruritus, and/or anaphylaxis
- Type 2 – cytotoxic
  - PCN induced hemolytic anemia
- Type 3 – Immune Complex
  - Serum sickness
- Type 4 – Cell mediated (delayed)
  - Contact dermatitis

Pichichero ME et al. Ann Allergy Asthma Immunol 2014;112:404-12.

PCN Allergy – How common

- PCN & other beta-lactams are the most frequent cause of medication-induced anaphylaxis
- Up to 10% of patients report a penicillin allergy
  - Most reports reflect historical childhood events, family history, or non-allergic adverse effects
- Highest rates reported by older and hospitalized patients

Salkind AR et al. JAMA 2001;285:2498-505.; Pichichero ME et al. Ann Allergy Asthma Immunol 2014;112:404-12.

PCN Allergy – Overstated?

- Even with a well documented allergy, hypersensitivity may not persist over time due to loss of anti-PCN IgE antibodies (up to 80% over 10 years)
- 9 out of 10 patients who claim to be allergic to penicillin are not truly allergic when assessed by skin testing
- Preferred beta-lactam therapy is avoided in >50% of patients even when a non-severe prior reaction is reported

Salkind AR et al. JAMA 2001;285:2498-505.; Pichichero ME et al. Ann Allergy Asthma Immunol 2014;112:404-12.
McFadden D et al. Clin Infect Dis 2016;63:904-10.

Beta-lactams are best!

- Surgical Prophylaxis
- Methicillin-susceptible *Staphylococcus aureus*
  - Superior to vancomycin for MSSA bacteremia
- Severe *Pseudomonas* infections
  - Often backbone at many institutions
- Group A streptococcal infections
  - Including invasive necrotizing infections
- Several STIs
  - Syphilis, PID, Gonococcal infections

Blumenthal KG et al. Clin Infect Dis. 2015;61:741-9.

Commonly Prescribed Antibiotics in LTCFs

Antibiotic Prescriptions from Ontario LTCFs

Antibiotic Name	% of Treatment Courses
Fluoroquinolones	28%
Beta-lactams	27%
Nitrofurantoin	15%
SMX-TMP	14%
Macrolides	6%

JAC 2011;66:2856-63.

Beta-lactams are safe(r)!

- Fluoroquinolones
  - QTc prolongation
  - Tendinitis/tendon rupture
  - Hypo/Hyperglycemia
  - CNS toxicities including insomnia and hallucinations, particularly in elderly
  - Drug interactions
- Beta—lactams
  - Generally well tolerated!
  - Main side effects: GI upset, rash
- Macrolides
  - QTc prolongation
  - Drug interactions (less with azithro)
  - GI
- SMX-TMP
  - Drug interactions
  - Hyperkalemia
  - Decreased tolerance in elderly

Implications of PCN "Allergy"

- Increased adverse effects
- Longer hospital stays, more readmissions
  - Two days longer in a study of geriatric inpatients, less likely to be discharged home
  - 30,000 hospital days/65 million in expenditures
- Development of MDR infections
  - 23.4% increase in *C. difficile* infection
  - 14.1% more MRSA
  - 30.1% increased VRE
- 50% increased odds of surgical site infection

MacFadden DR et al. Clin Infect Dis. 2016;63:904-10.
Macy E et al. J Allergy Clin Immunol 2014;133:790-6.
Baman, N. JACI 2012; 389
Blumenthal K, Clin Infect Dis 2018

Implications of PCN "Allergy"

- Increased usage of broad-spectrum antibiotics
  - FQ, Clindamycin, Vancomycin
- Increased antibiotic costs
  - 63% higher than those without reported allergy
- Antibiotic regimens deviate from standard of care (as defined by national guidelines, protocols or ID consults) in ~40% of patients with a reported PCN allergy

MacLaughlin EJ et al. Arch Fam Med 2009;9:722-6.; Charneski L et al. Pharmacother 2011;31:742-7.; Macy E. er al. J Allergy Clin Immunol 2014;133:790-6.

PCN Allergy - Documentation

- Allergy history documentation is poor
  - Often lack documentation of nature and severity of reaction
  - One retrospective cohort found only 39.8% of records had a specific allergen identified and only 22.7% had reaction characteristics identified
- Appropriate history can improve classification of mild versus life-threatening reactions
- Rechallange with beta—lactams is more likely when allergic reactions are well documented

Shah N. PLoS One 2016;11(3):e0150514.

PCN Allergy - Documentation

- Allergy records are rarely updated to demonstrate tolerance
  - ONLY 18% of patients with a documented penicillin allergy who received a penicillin antibiotic without incident had their records updated at UMMC
  - Rarely updated to indicate tolerance of other beta-lactams
- Algorithms to guide penicillin allergy histories can improve documentation

Oliver WD. JACI In Practice 2017;5:184-6.
Staicu ML. ID Week 2016

Conducting a Drug Allergy History

- *What is the name of the medication?*
- *How long ago did the reaction occur?*
- *Which systems were involved in the reaction, and what were the characteristics?*
- *When during the course did the reaction occur?*
- *Why was the medication prescribed?*

J Allergy Clin Immunol 2010;125(2):S126-37

Conducting a Drug Allergy History

- *Was the patient taking concurrent medications at the time of the reaction?*
- *What was the therapeutic management required secondary to the reaction?*
- *Had the patient taken the same or a cross-reacting medication before the reaction?*
- *Has the patient been exposed to the same or similar medication since the reaction?*

J Allergy Clin Immunol 2010;125(2):S126-37

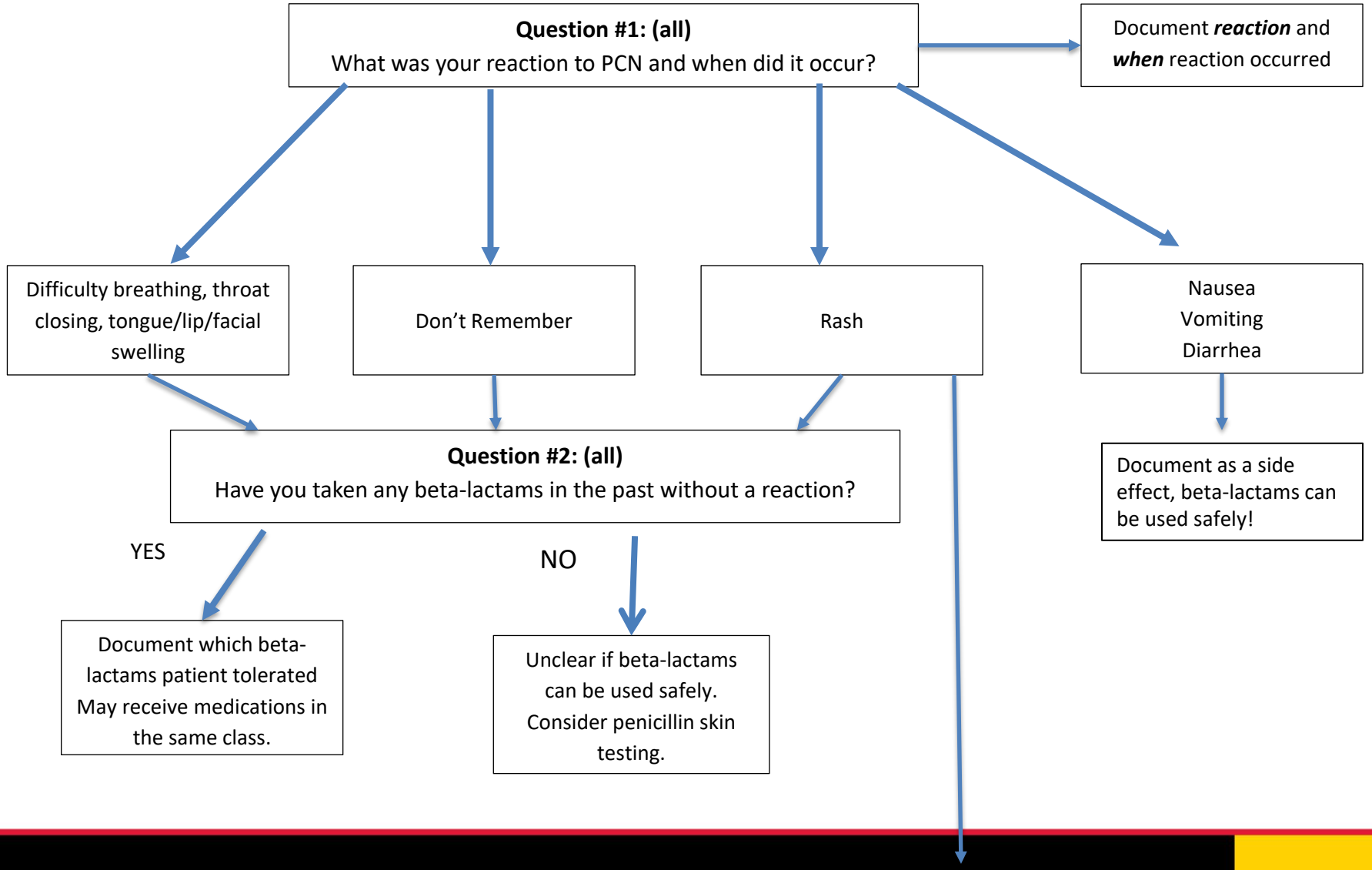
Conducting a Drug Allergy History

- *Has the patient experienced symtpoms similar to the reaction in the absence of drug treatment?*

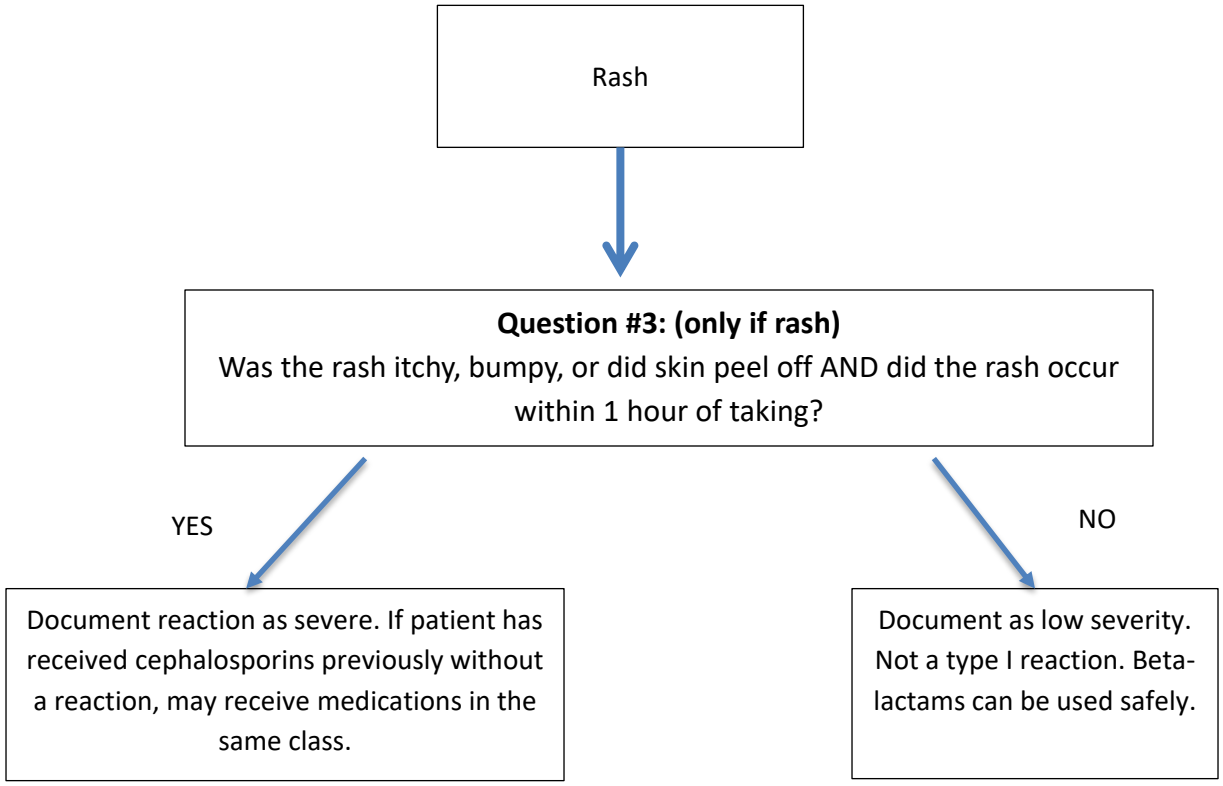
- *Does the patient have an underlying condition that favors reactions to certain medications?*

J Allergy Clin Immunol 2010;125(2):S126-37

PCN Allergy - Documentation



PCN Allergy Documentation



Pharmacist Allergy Interviews on FQ Use

Table 2. Primary and Secondary Outcomes.

	Control Group (n = 43)	Prospective Group (n = 37)	*P* Value
Duration of fluoroquinolone, mean days (SD)	3.7 (2.2)	2.7 (1.7)	0.027
Duration of fluoroquinolones, mean hours (SD)	88.4 (52.2)	64.2 (42.0)	0.027
Length of stay, median days (IQR)	6 (3-9)	5 (4-8)	0.73
Patient switched to β-lactam antibiotic, n (%)	N/A	18 (49)	
Ceftriaxone, n (%)	N/A	16 (43)	
Cefdinir, n (%)	N/A	1 (3)	
Cefepime, n (%)	N/A	1 (3)	
Reason for switch from FQ to β-lactam, n (%)	N/A		
Pharmacy recommendation		17 (94)	
Physician switch without intervention		1 (6)	
Pharmacy recommendations accepted, n (percentage recommendations)	N/A	17/18 (94)	
Adverse reaction after switch to β-lactam, n	N/A	0	

Abbreviations: FQ, fluoroquinolone; IQR, interquartile range.

PCN Allergy & Cross-Reactivity

- Cross-reactivity in penicillin-allergic patients is related to side chains
- For first generation cephalosporins, the risk of cross-reactivity is higher (used to be documented in the literature as 8%, newer reports suggest 2%), but risk of cross-reactivity with 2^{nd}, 3^{rd}, 4^{th} generation cephalosporins is negligible
- 1 patient of 300 with a reported PCN allergy had a reaction to cefazolin given for surgical ppx in large retrospective review

Kellkar PS et a. N Engl J Med 2001;345:804-9.; Kula B et al. Clin Infect Dis 2014;59:1113-22. Goodman EJ. J Clin Anesth 2001;13:561-4.

PCN Allergy & Cross-Reactivity

Groups of Beta-lactam Antibiotics That Share Identical R_1-Group Side Chains				
Amoxicillin	Ampicllin	Ceftriaxone	Cefoxitin	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephalothin	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime		
	Cephradine	Ceftizoxime		
	Loracarbef			

Each column represents a group with identical R_1 side chains

- In the subset of patients with a history of true anaphylaxis to penicillin, cross reactivity with cephalosporins ~40% - almost exclusively associated with cephalosporins with shared chemical side chains

Annals of allergy, asthma, & immunology 2010;105:259-73.

Management of Reported Type 1 PCN Allergy

- Desensitization
- Graded Challenges
- Direct Oral Challenges
- Penicillin skin testing

Desensitization

- Requires inpatient admission – not practical for LTCF
- Time consuming
  - Pharmacy preparation
  - Nursing monitoring
- Requires exquisite compliance with antibiotic administration times
- Effects are not sustained

Graded Challenges

- Not intended to induce drug tolerance
- Demonstrates that administration of a specific drug will not result in an immediate reaction
- Give 1%, then 10%, then 100% of therapeutic doses at 30 minute intervals
- Recommended for inpatient setting

Annals of allergy, asthma, & immunology 2010;105:259-73.

Direct Oral Challenges

- Administer 250-500 mg dose of amoxicillin and observe for 1 hour after dose
- Reserved for patients with a low suspicion for true anaphylactic allergy (e.g., history of mild childhood rash, non-urticarial rash, adverse events such as nausea or vomiting)
- Could be done in select patients in an outpatient or LTCF setting with appropriate monitoring and access to emergency resources

Antimicrobial Stewardship Guidelines

- Penicillin skin testing is now recommended
- “In patients with a history of B-lactam allergy, we suggest that ASPs promote allergy assessments and PCN skin testing when appropriate”
- Largely unstudied as primary ASP intervention
- Weak recommendation, low-quality evidence

Barlam TF, et al. Clin Infect Dis 2016;62:e51-77.

PCN Skin testing (PST)

- PCN & other beta-lactams spontaneously breakdown into reactive intermediates that bind with circulating carrier proteins forming haptens – these serve as the reactive allergenic major and minor determinants for skin testing
- Major determinant – benzylpenicilloyl polylysine accounts for 90% of PCN intermediates
- PST antigens react with IgE antibodies, if present, and the interaction results in a skin wheal, flare, or bleb at the injection site

Unger NR et al. Pharmacother 2013;33:856-67.

PCN Skin Testing

- When performed in the appropriate setting with proper technique and reagents, the skin test has a negative predictive value of 97-99% and a positive predictive value of 50%
- Patients with a negative skin test are at no greater risk of experiencing an allergic reaction to a beta-lactam than the general population

Unger NR et al. Pharmacother 2013;33:856. del Real GA et al. Ann Allergy Asthma Immunol 2007:98:355. Sullivan TJ et al. J Allergy Clin Immunol 1981;68:171. Sogn DD et al. Arch Intern Med 1992;152:1025.

Who to test?

- Patients that based on history likely experienced an IgE-mediated allergic reaction
- Patients known to be extremely hypersensitive to penicillin (e.g., systemic or anaphylactic reactions) should not be skin tested
- Ensure patient has not been receiving any histamine blockers (H1 – diphenhydramine and H2 – ranitidine and famotidine) within last 24 hours!!

Step 1: Preparation

Mark arm for each reagent – Prepen, PCN G, Histamine (+ control), Normal Saline (-control)

Step 2: Skin Prick

- Place 1 drop of reagent onto forearm and puncture the skin at the drop site with the Duotip device using a slight twisting motion. Use a new duotip for each reagent. Be conservative with the amount of PrePen you use. Wait 15 min, then observe

Step 2 Interpretation

- Positive - presence of a wheal with surrounding erythema ≥3 mm in diameter compared to negative control
- Equivocal – <3 mm wheal with little or no erythema and no itching
- Negative – Absence of wheal <3 mm compared with negative control
- Invalid – no reaction to positive control (histamine)
- If skin prick test positive → do not advance to intradermal test, do not give a beta-lactam
- Equivocal or negative skin prick tests → move on to intradermal test

Step 3: Intradermal testing

- Using a TB syringe, inject 0.02 mL of the reagent(PrePen, PCN G, normal saline) to create a small bleb ~3 mm in diameter on the forearm. Repeat blebs for PrePen and PCN G at least 2 cm apart if enough reagent.
- Draw tight circles around the blebs
- Wait 15 minutes and observe
- Same interpretation criteria as for skin prick test

Patient Education Materials

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Penicillin Allergy Testing

You have been tested to see if you are allergic to the antibiotic penicillin.

- Many people think they are allergic to penicillin. In fact, lots of people do not have a true allergy.
- It is important to know the facts. The doctors will have more drugs to treat an infection if you do not have a true allergy.
- Reasons why you may think you have an allergy:
  - You had a rash that was not due to the antibiotic. For example it may have been due to your illness.
  - Many people outgrow their allergies.
  - Reactions such as a stomach ache or loose bowels are **not** a true allergy.

How the test works:

- Skin Prick Test: The doctor will scratch / prick the skin on your arm with a small amount of penicillin. This will help them decide if you have a true allergy. If this part of the test is positive you have a penicillin allergy.
- Intradermal Test: If your skin prick test was negative, your doctor will then make a few small injections into your arm just under the skin.
- The entire test takes less than 1 hour.
- The test is safe and you will be watched by the staff during the test.

Test results:

- If both parts of the test are negative, then you **do not** have a true penicillin allergy. This means you can take penicillin and related antibiotics.
- If either part of the test is positive, then you are allergic. You should **not** take penicillin and related antibiotics.

If you have questions contact your primary care doctor.

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Patient Name: _____

Date of Penicillin Skin Testing:_____

On the above stated date, you received a penicillin allergy skin test and the results were negative / positive.
Circle One

Physician Signature: _____

Contact Number: 1-888-210-0511

☐ A negative result indicates you may safely receive beta-lactam antibiotics. Please note that no reagent, test, or combination of tests will completely assure that a reaction to penicillin therapy will not occur.

☐ A positive result confirms an IgE-mediated allergy to penicillin

☐ Other: _____

Name of antibiotic received in the hospital (if applicable):

_____

Show this card to your doctors and nurses

Models for Allergy Evaluation and PST

- Allergy (when available)
- Infectious Diseases Consultants
- Pharmacist-managed (state law dependent)
- Other physician specialties
- Outpatient
- Peri-operative

Final Step: De-Label!

- After allergy evaluations, the electronic health record should be updated and this information should be communicated to other healthcare providers (e.g., pharmacies)
- Delete the allergy, add qualifying comments such as “penicillin skin test negative” or “tolerated amoxicillin/clavulanate”

	Low Risk	Medium Risk	High Risk
History	• Reactions that are unlikely allergic (e.g., GI symptoms) • Pruritis without rash • Remote (>10 y) unknown reactions • Family history of penicillin allergy	• Urticaria or other pruritic rash • Reactions with features of IgE such as itching, flushing but not anaphylaxis	• Anaphylactic symptoms • Recurrent reactions • Reactions to multiple beta-lactams
Action	Direct oral challenge with amoxicillin	Skin test followed by amoxicillin challenge if skin test negative	Allergy referral

Shenoy ES et al. JAMA 2019;321:188-199.

Clinical Review & Education

JAMA | Review

Evaluation and Management of Penicillin Allergy
A Review

Erica S. Shenoy, MD, PhD; Eric Macy, MD, MS; Theresa Rowe, DO, MS; Kimberly G. Blumenthal, MD, MSc

A
Page 1

Toolkit A

Penicillin Allergy History

Date of reaction: _____

Route of last administration: ☐ Oral ☐ Intr

B
Page 1

Toolkit B

Direct Oral Amoxicillin Challenge for Low-Risk Patients

Table S2. Cephalosporin cross-reactivity, by R1 groups*

Common amino R1 group	Common methoxyimino R1 group
Ampicillin Amoxicilin Cefaclor Cephalexin Cefadroxil	Ceftriaxone Cefotaxime Cefuroxime Cefepime Ceftazidime Cefpodoxime

*Beta-lactam antibiotics have shared beta-lactam rings and may have R1 (6/7 position) and/or R2 (3 position) side chains that can be structurally identical or similar. Cross reactivity appears highest for beta-lactams that share identical R1 side chains. More comprehensive cephalosporin cross-reactivity matrices[2] may be used if avoiding identical and similar structures at both side chain locations is desired.

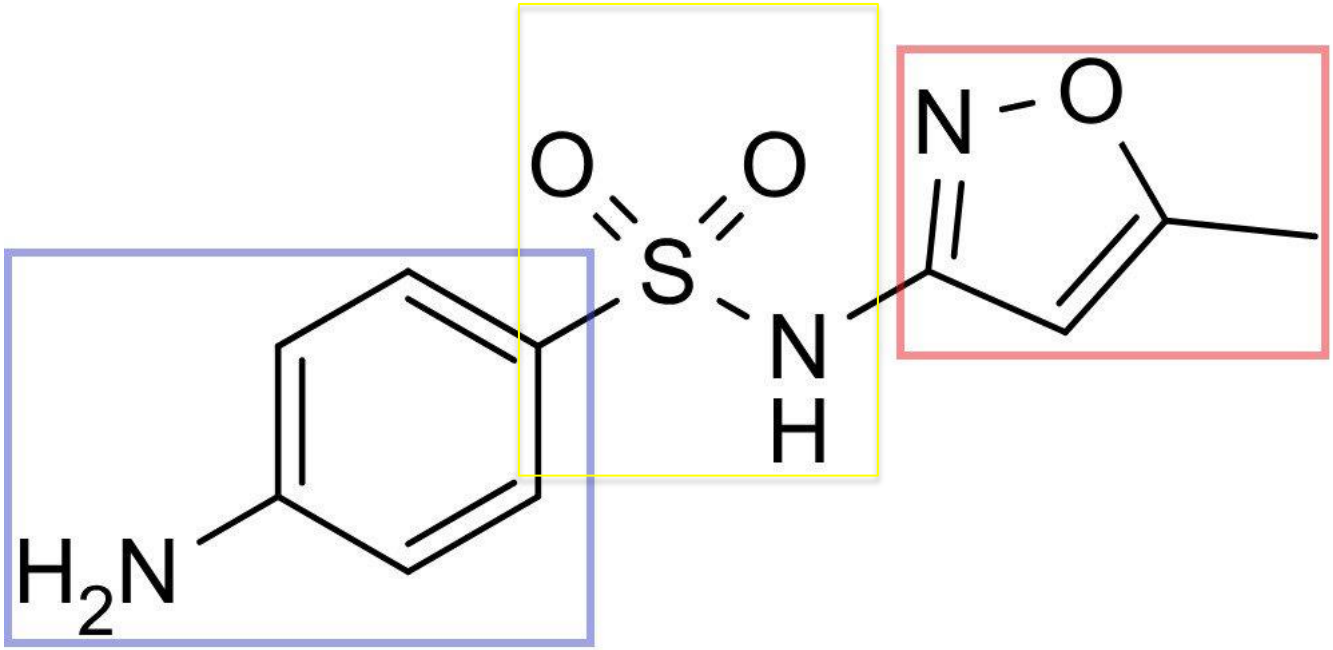
Shenoy ES et al. JAMA 2019;321:188-199.

Sulfonamide Allergy

- 3-6% of the general population allergic to sulfonamides (synthetic derivatives of sulfanilamide)

- Structurally defined by the sulfonamide moiety and further divided into antibacterials and nonantibacterials

SMX-TMP



Sulfonamide Cross-Reactivity: Fact or Fiction?

- Comprehensive literature review identified nine case reports supporting possible cross-reactivity
- However, adequate patient testing not completed to firmly establish cross-reactivity
- Lack of convincing evidence of broad cross-reactivity between sulfonamide antibacterials and nonantibacterials
- Hypersensitivity between sulfonamides due to predisposition to allergic reactions rather than cross-reactivitiy

Am J Health-Syst Pharm 2013;70:1483-94
Ann Pharmacother 2005;39:290-301
N Engl J Med 2003;349:1628-35

Take Home Points

- 50-80% of older adults in LTCFs receive at least 1 antibiotic course per year
- Prevalence of reported penicillin allergy increases with age
- Older adults are more likely to suffer from adverse effects associated with the use of non-beta lactam alternative antibiotics
- Penicillin allergy evaluation could have significant benefits for older adults in LTCFs