Managing Beta-Lactam Allergies: How Pharmacists Can Scratch That Itch

UTAH SOCIETY OF HEALTH-SYSTEM PHARMACISTS

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Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Maren Campbell, PharmD:**
    - None
  - **CE Mentor, Lauren Williams, PharmD, BCPS:**
    - None
- Off-Label Uses of Medications
  - None

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Abbreviations

- AE = Adverse Effect
- USD = US Dollar
- SJS = Stevens-Johnson Syndrome
- TEN = Toxic Epidermal Necrolysis
- DRESS = Drug Rash with Eosinophilia and Systemic Symptoms
- EMR = Electronic Medical Record
- CDI = *Clostridioides difficile* Infection
- PST = Penicillin Skin Testing

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Pharmacist Learning Objectives

- **Describe** what constitutes a true beta-lactam allergy and its implications
- **Apply** strategies to assess patients with a labeled beta-lactam allergy
- **Design** a management plan for patients with a beta-lactam allergy
- **Discuss** beta-lactam allergy de-labeling strategies and implications

Technician Learning Objectives

- **Recognize** the impact of labeled beta-lactam allergies on patient care
- **Describe** general assessment strategies for beta-lactam allergies
- **Examine** the different strategies for managing beta-lactam allergies

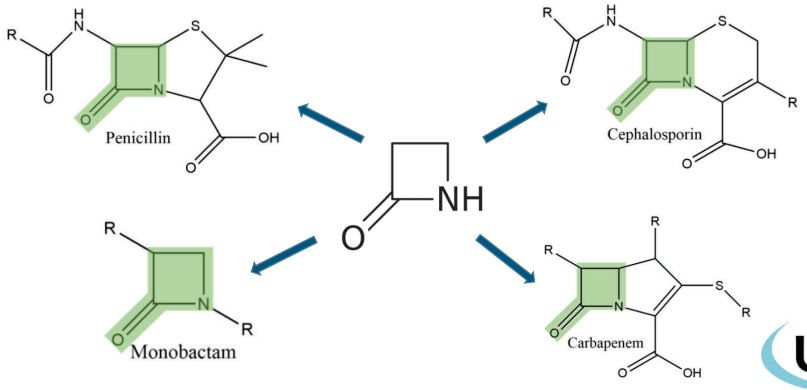
Background

Beta-Lactam Antibiotics in Practice

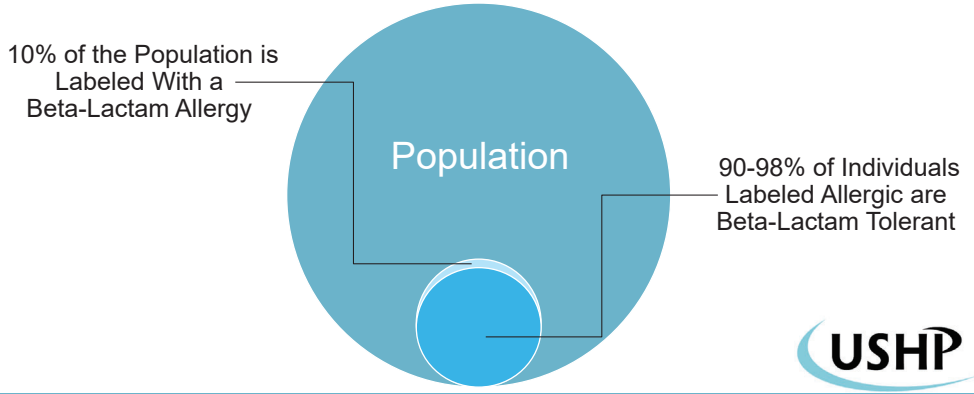
- Beta-lactams are one of the most commonly listed drug allergies
- Annual expenditure for these antibiotics amounts to approximately $15 billion USD
- Beta-lactams make up approximately 65% of the total antibiotics market

andey N, Cascella M. Beta Lactam Antibiotics. StatPearls. Updated September 2021. Available at: https://www.ncbi.nlm.nih.gov/books/NBK545311/

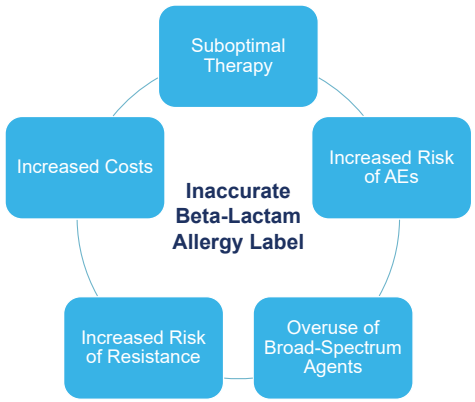
What are Beta-Lactam Antibiotics?



The Reality of Beta-Lactam Allergies

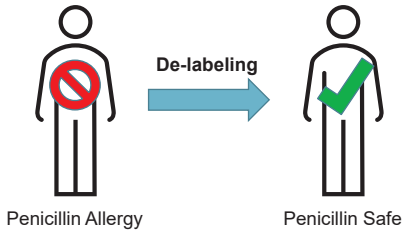


Beta-Lactam Allergies: A Public Health Crisis



What is De-labeling?

- The removal of an identifier or ”label” that indicates a patient is allergic to penicillin or other beta-lactam antibiotics



Brief Overview of De-labeling Benefits

- **Avoid** well-documented public health implications of erroneous labeling
- **Limit** antimicrobial resistance of broader agents
- **Decrease** costs
  - Mill et al. 2016 - *Testing for beta-lactam allergies would cost 9.5x less than treating an in-patient population with an alternative antimicrobial*

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imy S, Ben-Shoshan M, et al. Practical guide for evaluation and management of beta-lactam allergy: position statement from the Canadian Society of Allergy and Clinical Immunology. Allergy, Asthma & Clinical Immunology 020;16(95): https://doi.org/10.1186/s13223-020-00494-2
ll C, Primeau MN, Medoff E, Lejtenyi C, O'Keefe A, Netchiporouk E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in ildren. *JAMA Pediatr.* 2016;170(6):e160033

The Test of Time

Positive Test for Beta-Lactam Allergy

- 10% decrease per year of subsequent positive reaction

"True" allergies (antibody-mediated reactions) lessen over time if beta-lactams are avoided

10 Years Later

- 80-100% patients will test negative for an allergy

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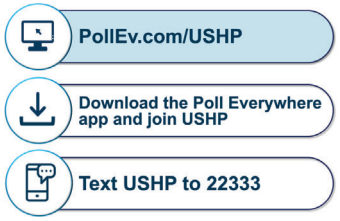
adley N, Lee Y, Weinstein D. Overview of Beta-Lactam Allergy and the Role of the Pharmacist in Management. Allergies 2021;1:128-136

Poll Everywhere – Technician Question

Which of the following is most likely to be a potential consequence of an inaccurate beta-lactam allergy label on a patient's chart?

A. Shortened length of hospital stay
B. Lower risk of adverse effects
C. Increased risk of antimicrobial resistance
D. Conserve supply of broad-spectrum antibiotics



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Evidence for De-labeling Practices

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Moussa et al. 2018

De-labeling of β-lactam allergy reduces intraoperative time and optimizes choice in antibiotic prophylaxis	
Methods	• Risk assessment tool by an allergist, β-lactam skin testing, oral provocation • Appraisal of intraoperative antibiotic choices correlated with time to first incision
Results	• 194 patients labeled with a beta-lactam allergy were evaluated preoperatively • 4 patients diagnosed with β-lactam allergy on skin testing • 146 patients β-lactam challenged → only 5% reacted • Cefazolin was perioperative antibiotic of choice for 77% of patients requiring prophylaxis, with only 5 confirmed β-lactam allergic patients receiving vancomycin • Patients avoiding use of vancomycin saved an average of 22 minutes in operative time
Conclusions	Using this 3-step process enabled almost all β-lactam allergic patients to be de-labeled
Limitations	• Poor patient recall and incomplete data influenced use of penicillin challenges • Did not identify patients referred for evaluation but not skin tested or challenged • Did not assess patients given alternative antibiotics who were not referred for preop eval

oussa Y, Shuster J, et al. De-labeling of β-lactam allergy reduces intraoperative time and optimizes choice in antibiotic prophylaxis. Surgery 2018;164(1):117-123

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Turner et al. 2021

Evaluation of a Pharmacist-Led Penicillin Allergy Assessment Program and Allergy De-labeling in a Tertiary Care Hospital	
Methods	• 2 phase pharmacist-led allergy assessment program at a single center • Hospital outcomes assessed by segmented regression; individual outcomes assessed with propensity score-matching
Results	• 46,416 median admissions per year over 2014-2020 • Allergy histories associated with decreased use of non-penicillin alternatives (rate ratio, 0.87; 95% CI, 0.79-0.97) and high-CDI-risk antibiotics (rate ratio, 0.91; 95% CI, 0.85-0.98) • Penicillin skin testing associated with lower hospital-acquired CDI rates (rate ratio, 0.61; 95% CI, 0.43-0.86)
Conclusions	Pharmacist-led allergy assessments may be associated with reduced high-CDI-risk antibiotics
Limitations	• Penicillin skin testing was used in a small number of patients • Ongoing stewardship efforts during study period may have confounded results • Inherent risk of selection bias

urner N, Wrenn R, Sarubbi C, et al. Evaluation of a Pharmacist-Led Penicillin Allergy Assessment Program and Allergy Delabeling in a Tertiary Care Hospital. Jama Netw Open 2021;4(5):e219820

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Evidence for De-labeling Benefits

Bottom Line: the body of evidence supporting the benefits of de-labeling patients with beta-lactam allergies is continuously growing!

- **Multiple studies looking at pharmacy-led initiatives**

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Pathophysiology

THE MAKING OF A BETA-LACTAM ALLERGY

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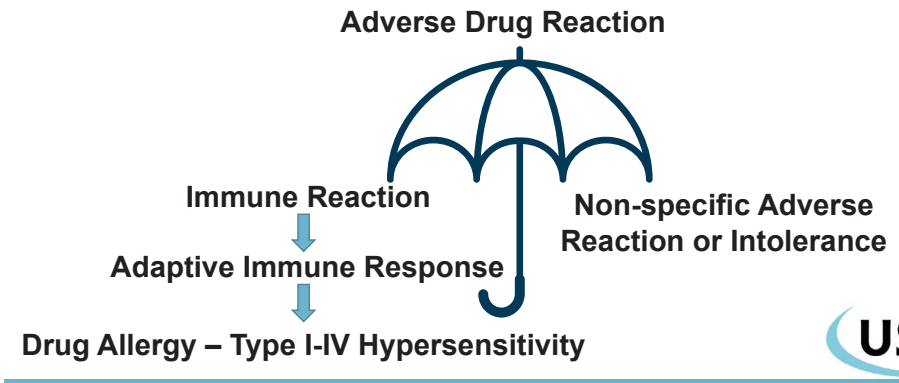
Defining Drug Allergies



Classification of Hypersensitivity Reactions

Hypersensitivity Type	Reaction Type	Time of Onset	Examples
Type I	IgE-mediated	Within 1 hour	Anaphylaxis, urticaria, bronchospasm
Type II	Non-IgE mediated (IgG, IgM) Cytotoxic (FC receptor)	Several hours to days	Hemolytic anemia, blood cell dyscrasia
Type III	Non-IgE mediated IgG, Immune Complex	7-21 days	Serum sickness, vasculitis
Type IV	Non-IgE mediated Cell-mediated	Days to weeks	Maculopapular rash, SJS, TEN, DRESS

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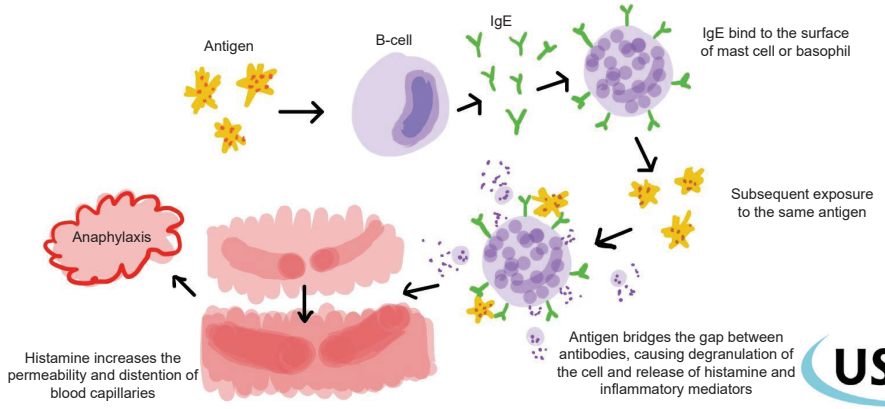
Penicillin allergies most commonly present as Type I or Type IV reactions

Type I Reaction



Type I Reaction Symptoms

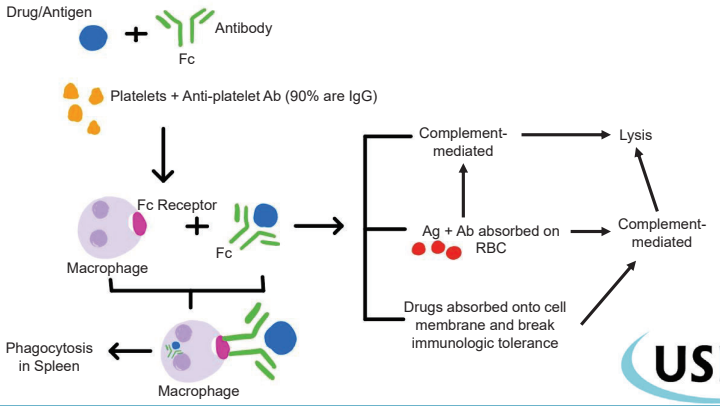
- Urticaria
- Flushing
- Dyspnea
- Bronchospasm
- Gastrointestinal Upset
- Altered Mental Status
- Angioedema
- Hypotension
- Tachycardia

Immediate in Nature
< 1 Hour Onset

Relatively Rare

adley N, Lee Y, Weinstein D. Overview of Beta-Lactam Allergy and the Role of the Pharmacist in Management. Allergies 2021;1:128-136

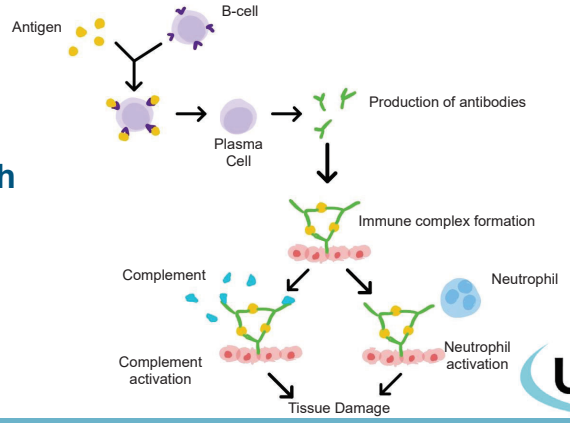
Type II Reaction



abpedia.net. Chapter 12: Type II Hypersensitivity Reaction and ADCC (Cytotoxic reaction). Available at: https://labpedia.net/elementary-immunology/chapter-12-type-ii-hypersensitivity-reaction/

Type III Reaction

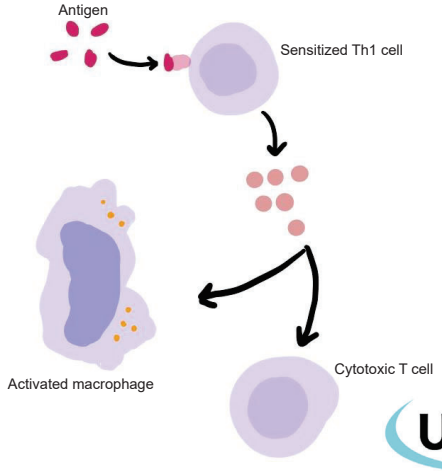
Not usually associated with beta-lactam exposure



ainKart.com. Type III Hypersensitivity Reactions. Available at: https://www.brainkart.com/article/Type-III-(Immune-Complex)-Hypersensitivity_17976/

Type IV Reaction

Delayed in Nature, Onset of Days to Weeks



iseth S, Jones L, et al. Type IV Hypersensitivity Reaction. Updated September 2020. Available at: https://www.lecturio.com/concepts/type-iv-hypersensitivity-reaction/

Risk Factors For Beta-Lactam Allergy

Brief Summary of Evidence*	
Apter et al. 2008	• Family history of penicillin allergy • IL-4 gene single nucleotide polymorphism
Nicoletti et al. 2021	• HLA-DRB1*10:01 predisposed patients to an immediate hypersensitivity reaction
Park et al. 2007	• Greater risk of penicillin allergy in females
Kelkar et al. 2001	• Greater risk of beta-lactam allergy in those with a history of prior reaction to penicillin

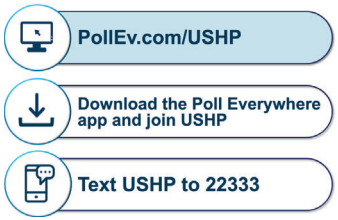
***Risk factors for beta-lactam allergies not fully elucidated**

pter A, Schelleman H, Walker A, et al. Clinical and genetic risk factors of self-reported penicillin allergy. J Allergy Clin Immunol 2008;122:152–158
icoletti P, Carr D, et al. Beta-lactam-induced immediate hypersensitivity reactions: A genome-wide association study of a deeply phenotyped cohort. J Allergy Clin Immunol 2021;147:1830–1837.e15
ark M, Matesic D, et al. Female sex as a risk factor for penicillin allergy. Ann Allergy Asthma Immunol 2007;99:54-58
elkar P, Li J. Cephalosporin allergy. N Engl J Med 2001;345:804-809

Poll Everywhere – Pharmacist Question

Which symptom is least likely to be attributed to a Type I hypersensitivity reaction?

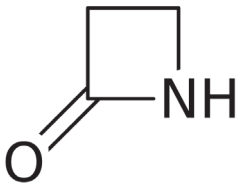
A. Tachycardia
B. Mild headache
C. Urticaria
D. Angioedema



Cross-Reactivity

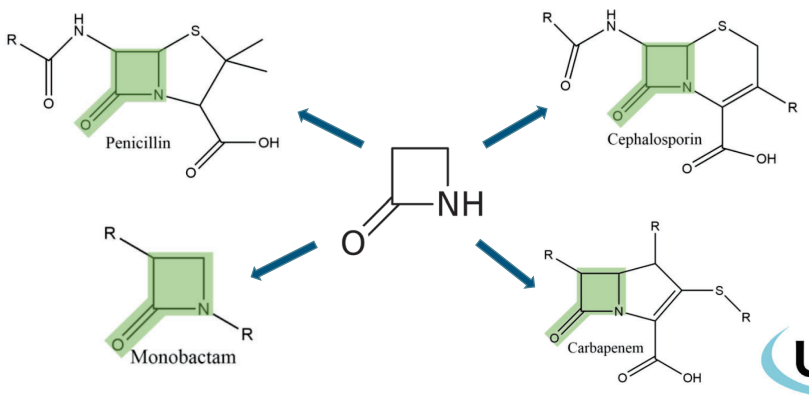
IS THIS A REAL CONCERN?

Beta-Lactam Antibiotic Structure

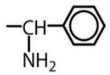
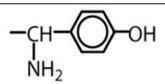
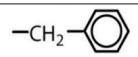
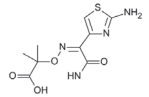


Antibiotic backbone is a highly reactive beta-lactam ring

Beta-Lactam Antibiotic Structures



Probable Cross-Reactivities: Side Chains

Beta-Lactam	R1 Side Chain Structure	Structurally Similar Antibiotics
Ampicillin		Cephalexin (1st generation) Cefaclor (1st generation)
Amoxicillin		Cefadroxil (2nd generation) Cefprozil (2nd generation)
Penicillin G		Penicillin VK Cefoxitin (2nd generation)
Aztreonam		Ceftazidime (3rd generation)

Structurally Similar

Rate of Cross-Reactivity

Beta-Lactam	Rate of Cross-Reactivity with Penicillins
1st Generation Cephalosporins	~2%
Later Generation Cephalosporins	≤1%
Carbapenems	≤1%
Monobactams	none

Structure Similarity & Cross-Reactivity

- Common core structure +/- similar side chains = risk for cross-reactivity
- Similarities of R1 side chains in cephalosporins have shown to be the most important predictor of cross-reactivity compared to the beta-lactam ring

Early studies: Penicillin cross-reactivity with cephalosporins as high as 10%

Now: Likely <2%; earlier rate considered high due to contamination in early manufacturing processes

- **With the true incidence of penicillin allergy being low, the risk of cross-reactivity becomes even more limited**
- **Pearl: extensive cross-reactivity charts available in literature!**

Assessment Tools

Allergy Assessment Toolkit

- Thorough clinical history
- Direct oral challenge/provocation
- Penicillin skin testing

~90% of patients labeled as allergic can be de-labeled through a detailed allergy assessment or testing

Thorough Clinical History

- Appropriate questions should evaluate the following factors:
  - Specific agent causing the reaction
  - Type and severity of reaction
  - Timing of reaction
  - Previous tolerability of other beta-lactam agents

What was the name of the antibiotic?

Describe the nature of the reaction

How long after taking the antibiotic did the reaction develop?

How did you treat the reaction?

When did this reaction occur?

Have you ever been prescribed another beta-lactam antibiotic?

Utilizing Clinical Histories

- **Stratification of allergy risk criteria not universal or standardized**
- General classification (Canadian Society of Allergy and Clinical Immunology)
  - **Low risk**: offending drug taken again without issue, avoidance without exposure, other intolerance (diarrhea, nausea, vomiting, headache, etc.)
  - **Intermediate risk**: immediate or delayed reaction (isolated cutaneous involvement, urticaria, angioedema)
  - **High risk**: immediate reaction (anaphylaxis) or penicillin allergy confirmed by allergist
  - **Contraindication**: severe reaction with organ dysfunction, severe cutaneous adverse reaction (DRESS, SJS/TEN, etc.), or serum sickness

Risk Stratification Using the 1-1-1 Criterion

Journal of Allergy and Clinical Immunology 2021 Urticaria: The 1-1-1 Criterion for Optimized Risk Stratification in β-Lactam Allergy De-labeling	
Objective	Determine the significance of the characteristics of urticaria in the risk stratification for de-labeling β-lactam allergies
Methods	• Characteristics of urticarial eruptions during β-lactam therapy (time interval between exposure and onset, dose after which urticaria appeared, duration of eruption) were correlated to systematic allergy workup (skin tests, IgE measurements, challenges) • 410 patients
Results	• Urticarial eruption appearing within 1 hour after 1st dose and had regressed within 1 day (1-1-1) was more frequently reported in the group with a positive allergy workup, with odds ratios of 17 (95% CI 9-31), 11 (95% CI 6-20), and 48 (95% CI 14-157), respectively (P < 0.005) • 1-1-1 criterion sensitivity and specificity of 85%, negative predictive value of 80%, and positive predictive value of 90%
Conclusion	Patients with urticaria meeting 1-1-1 criterion should be considered high risk and referred for an allergy workup (skin and IgE testing) prior to challenging

abato V, Gaeta F, et al. Urticaria: The 1-1-1 Criterion for Optimized Risk Stratification in β-Lactam Allergy Delabeling. J Allergy Clin Immunol Pract 2021;9(1):3697-3704

Low Risk Patients

Proposed algorithm by the Canadian Society of Allergy and Clinical Immunology 2020

Patient deemed low risk → Prescribe beta-lactam or proceed to oral challenge

eimy S, Ben-Shoshan M, et al. Practical guide for evaluation and management of beta-lactam allergy: position statement from the Canadian Society of Allergy and Clinical Immunology. Allergy, Asthma & linical Immunology 2020;16(95): https://doi.org/10.1186/s13223-020-00494-2

Oral Provocation or Challenge

- Considered "gold standard" diagnostic test for β-lactam allergy
- Two general approaches:
  - Single-step challenge
  - Graded oral challenge
    1. Administer 10% of therapeutic dose
    2. If asymptomatic after 30-60 minutes, give remaining 90% of therapeutic dose
    3. At least 60 minutes of observation
- Most reactions are mild, self-limited, cutaneous eruptions or subjective symptoms

eimy S, Ben-Shoshan M, et al. Practical guide for evaluation and management of beta-lactam allergy: position statement from the Canadian Society of Allergy and Clinical Immunology. Allergy, Asthma & linical Immunology 2020;16(95): https://doi.org/10.1186/s13223-020-00494-2

Systematic Review of Direct Oral Challenges

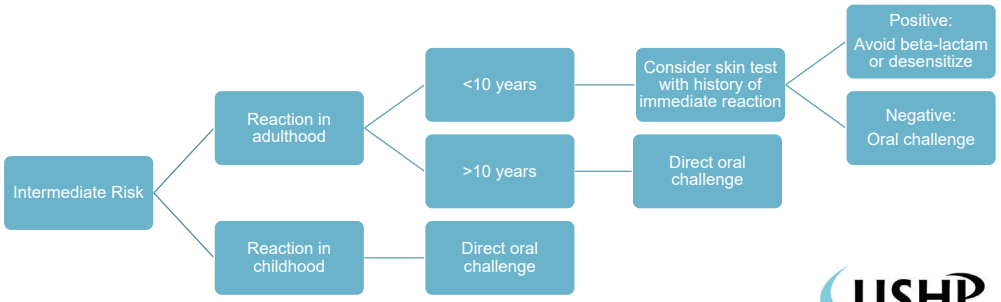
JAC-Antimicrobial Resistance 2021
Safety and efficacy of de-labeling penicillin allergy in adults using direct oral challenge: a systematic review

- **Objective**: assess efficacy and safety of direct oral challenge without prior skin testing in adults with beta-lactam allergy label
- **Methods:** population weighted mean was used to calculate the proportion of patients who developed an immediate or delayed reaction to a direct oral challenge
- **Results**:
  - 13 studies included; sample size of 1202; inpatient and outpatient cohorts
  - 3.41% patients had mild immediate or delayed reactions to an oral challenge in pooled analysis; no reports of serious adverse reactions
  - 96.5% patients could be de-labeled

ooper L, Harbour J, Sneddon J, et al. Safety and efficacy of de-labelling penicillin allergy in adults using direct oral challenge: a systematic review. *JAC-Antimicrobial Resistance* 2021;3(1):dlaa123

Intermediate Risk Patients

Proposed algorithm by the Canadian Society of Allergy and Clinical Immunology 2020



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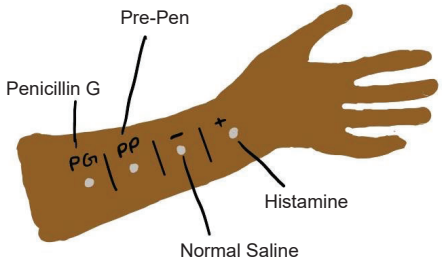
Penicillin Skin Testing

- Good tool for ambiguous allergy histories or history of potentially severe allergies
- Detects presence of penicillin-specific IgE to help predict type I allergic reactions
- Indicated in patients with a documented or suspected type I hypersensitivity
- Requires logistics: policies/protocols, staff training, storage/prep of materials
- Epicutaneous + intradermal skin testing using degradation products of penicillin (major and minor antigen determinants)



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Limitations of Penicillin Skin Testing

- Possibly not the best screening tool given available evidence
  - **High negative predictive value**: 93-99%
  - **Low positive predictive value**: 50-75%; as low as <10% in the pediatric population
  - **False-positive** test rate of up to 80%
- **Gadde et al. 1993**
  - Patients with a mixed history of penicillin allergy had rates of skin sensitization identical to that of patients without a penicillin allergy (1.7%)
- **Chiriac et al. 2019**
  - Some patients may have a positive penicillin skin test, but not be clinically allergic when followed by a negative oral challenge

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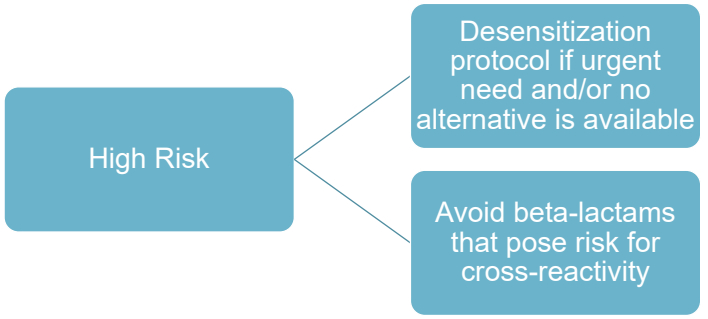
High Risk Patients

Proposed algorithm by the Canadian Society of Allergy and Clinical Immunology 2020



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What About HLA Typing?

- **Practical guide for evaluation and management of beta-lactam allergy: position statement from the Canadian Society of Allergy and Clinical Immunology 2020**
  - T-cell-mediated, delayed reactions may be associated with HLA markers
  - HLA risk alleles have shown to have a low positive predictive value (<1%)
  - High number needed to test (NNT) >10,000

Bottom line: HLA screening is impractical for the prevention of a beta-lactam allergic reaction

What About Serum Specific IgE Testing?

- Poor positive and negative predictive value
- May identify clinically irrelevant co-reactivity between beta-lactams
- Presence of measurable anti-beta-lactam IgE does not necessarily mean the exposure will result in a hypersensitivity reaction

Bottom Line: Serum specific IgE testing for beta-lactam allergies is a suboptimal screening measure

Poll Everywhere – Pharmacist Question

A patient reports that they are allergic to penicillin. Upon interviewing the patient about their symptoms, they reveal that they developed a headache and urticaria approximately 24 hours after a dose of amoxicillin. Which risk category do they fall in?

A. Low risk
B. Intermediate risk
C. High risk

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Poll Everywhere – Pharmacist Question

Your patient has been referred for penicillin skin testing. Your attending asks you to discuss the integrity of penicillin skin testing results. Which of the following may you include in your response?

A. High negative predictive value
B. Low negative predictive value
C. High positive predictive value
D. False-positive rate of up to 10%

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Poll Everywhere – Technician Question

Which of the following is not an assessment tool for evaluating beta-lactam allergies?

A. Patient clinical history
B. Penicillin skin test
C. Direct oral challenge
D. All of the above are potential assessment tools

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Management Strategies

THE ROLE OF PHARMACY

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The Role of Pharmacy

- Navigate choosing alternative antibiotic
- Gather beta-lactam allergy histories
- Acting on penicillin skin testing results
- Desensitization preparation
- Educate patients and providers and update EMR

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Beta-Lactam Desensitization

The process of introducing a specified antigen at incremental increasing amounts to slow or change a process of antigen recognition and reaction by the body

- Sometimes indicated in patients with systemic Type I reactions and/or a positive or indeterminate penicillin skin test who require beta-lactams
- Specialist administers incremental increases of beta-lactam doses
- Inpatient or ICU setting, requiring frequent monitoring
  - Signs/symptoms of reaction: itching/rash, breathing difficulties, chest tightness, tingling of lips, changes in blood pressure or heart rate, new onset of nausea/vomiting, elevated temperature
- Time frame of several hours to days to complete
- Numerous protocols exist

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Desensitization & The Pharmacy

- **Pharmacy Role**
  - Supply emergency medications at the bedside:
    - Epinephrine 1 mg vial for intramuscular injection
    - Diphenhydramine 50 mg vial
    - Hydrocortisone 100 mg vial
  - Prepare desensitization syringes and IV piggyback (7 total doses)
  - Can assist in assessing patient (at baseline, before each dose of antibiotic, at least every 15 minutes until after the 4th dose has been administered, and at least 30 minutes after all subsequent doses)
  - Order continuous infusion beta-lactam regimens to prevent lapses in therapy and subsequent reactions

Managing Reactions

- **Mild cutaneous reactions**: non-sedating, 2nd generation antihistamines preferred
- **Systemic reactions (generalized urticaria, anaphylaxis):** stop challenge, promptly initiate anaphylaxis management including epinephrine as needed
- Protocols/policies should exist to guide clinical assessment, monitoring strategies, and interventions in case of a beta-lactam allergic reaction
- **Bottom Line**: update EMR with appropriate allergy label and counsel patient

Evidence Supporting Pharmacy's Role

- ***Holmes et al. 2019***
  - Retrospective study of 418 patients
  - **Methods**: alert system notified pharmacy staff of any patient with a documented penicillin allergy receiving a non-penicillin antibiotic prompting an allergy assessment
  - **Results**: increased beta-lactam prescribing by 12.9%, decrease in days of therapy of non-penicillin antibiotic use by 123 days of therapy per 1000 patient days
- ***Campbell et al. 2020***
  - 380 patients in community hospital
  - **Methods**: chart review, patient interview, recommendations to provider, updating EMR
  - **Results**: improved use of guideline-preferred antibiotics by 13% and reduced fluoroquinolone use by 11%

Poll Everywhere – Pharmacist Question

Once a beta-lactam desensitization protocol is complete, what is a strategy to help prevent lapses in therapy and the development of a reaction?

A. Order continuous infusion regimens
B. Decrease the dosing interval by 1-2 hours
C. It doesn't matter; the risk of reactions is eliminated after desensitization.

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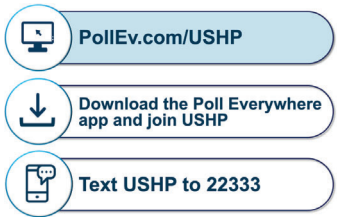
Poll Everywhere – Technician Question

Which of the following tasks regarding management of beta-lactam allergies can pharmacy technicians NOT participate in?

A. Interviewing patients to gather allergy histories
B. Updating the EMR with current allergy information
C. Recommending alternative antibiotics for patients who are truly allergic to beta-lactams



Looking Forward

Final Considerations

- Understanding beta-lactam allergies is critical to making changes
- Train staff to complete beta-lactam allergy assessments and make recommendations
  - When to refer to an allergist
  - De-labeling beta-lactam allergies if appropriate and updating patient medical records accordingly
- Develop institution-specific protocols if not done already and follow them

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