

Penicillin Allergy Evaluation and De-labeling

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Learning Objectives

- Understand the benefits of penicillin allergy de-labeling
- Compared evidence-based approaches to penicillin allergy de-labeling
- Discuss allergy de-labeling program successes and implementation challenges

Benefits of Penicillin Allergy De-labeling

Penicillin Allergy

- Over 10% of the US population reports having a penicillin allergy¹
- When tested, up to 95% of these patients could tolerate penicillin
 - Many non-allergic reactions are reported as allergy
 - Penicillin-targeting IgE antibodies wane over time
- Leads to use of broader-spectrum antibiotics, worsening several patient outcomes

1. Gonzalez-Estrada A, Radojicic C. Penicillin allergy: a practical guide for clinicians. Cleve Clin J Med. 2015 May;82(5):295-300.

Patient Outcomes

- Increased antibiotic resistance¹
 - 14.1% increase in methicillin-resistant *Staphylococcus aureus* (MRSA)
 - 30.1% increase in vancomycin-resistant *Enterococcus* (VRE)
- 23.4% increase in *Clostridioides difficile* infection¹
- 50% increase in surgical site infections²
 - Less cefazolin prophylaxis - more vancomycin, clindamycin, or gentamicin

1. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: A cohort study. *J Allergy Clin Immunol.* 2014;133(3):790-796.

2. Blumenthal K, Ryan E, Li Y, et al. The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk. *Clin Infect Dis.* 2018;66(3):329-336.

Additional Patient Outcomes

- 14% increase in all-cause mortality in a large cohort study¹
 - 63,960 patients with penicillin allergy to 237,167 without listed allergy
 - Followed over a 6-year period
- Increased cost²
 - Penicillin allergy removal results in ~\$1444 for an average U.S. inpatient
 - Direct antibiotic cost
 - Length of stay
 - Readmission rates

1. Blumenthal K, Lu N, Zhang Y, et al. Recorded Penicillin Allergy and Risk of Mortality: a Population-Based Matched Cohort Study. *J Gen Intern Med.* 2019;34(9):1685-1687.

2. Sousa-Pinto B, Blumenthal KG, Macy E, et al. Penicillin Allergy Testing Is Cost-Saving: An Economic Evaluation Study. *Clin Infect Dis.* 2021;72(6):924-38.

Penicillin Allergy De-labeling

- Important antimicrobial stewardship initiative
- American Academy of Allergy, Asthma, and Immunology (AAAAI) 2022 practice parameter update on drug allergy¹
 - “We recommend that a proactive effort should be made to de-label patients with reported penicillin allergy, if appropriate”
- Several strategies exist to remove inappropriate penicillin allergies

1. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. *J Allergy Clin Immunol.* 2022;150(6):1333-1393. doi:10.1016/j.jaci.2022.08.028

Methods of Penicillin Allergy De-labeling

Allergy Risk Assessment

- Patient interview is essential to all de-labeling efforts
- Components of a penicillin allergy assessment
 - Allergy risk determined through a validated risk assessment tool
 - What the reaction was
 - When the reaction occurred
 - If treatment was required for the reaction
 - Antibiotics tolerated in the past

Allergy Risk Assessment – PEN-FAST

Criteria	Points
Five years or less since reaction	2
Anaphylaxis/angioedema OR Severe cutaneous adverse reaction	2
Treatment required for reaction	1

- Score of 0 = very low risk (<1%)
- Score of 1-2 = low risk (5%)
- Score of 3 = moderate risk (20%)
- Score of 4+ = high risk (50%)
- Negative predictive value of 96.3% for low-risk allergy

Direct De-labeling

- Lowest risk patients can be de-labeled without further testing
- AAAAI 2022 practice parameter update:
 - “For patients with histories that are inconsistent with penicillin allergy (such as headache or family history of penicillin allergy), no testing is required and the patient may be de-labeled”
 - Consider oral amoxicillin challenge in patients reluctant to remove allergy without testing

Penicillin Skin Testing

- Step 1: A small drop of penicillin is pricked into the skin
- Step 2: A small dose of penicillin is injected intradermally
- Step 3: If both tests are negative, may proceed to an oral amoxicillin challenge
- **Advantages**
 - Low risk of systemic reactions
 - Allows for testing of multiple specific antibiotics at once
- **Disadvantages**
 - Time consuming
 - Requires allergist training
 - Inconsistent interpretation of results

Amoxicillin Oral Challenge

- Step 1: Patient receives amoxicillin 250 mg dose x 1
- Step 2: Patient is monitored every 30 minutes for 60-120 minutes
- Step 3: If patient has no symptoms of IgE-mediated reaction, the penicillin allergy can be removed from their chart
- **Advantages**
 - Fast and cheap
 - Does not require allergist resources
- **Disadvantages**
 - Difficult to interpret results in patients on concurrent antihistamines/steroids
 - Best suited for low-risk allergy history

PALACE Trial¹

- Randomized clinical trial comparing oral challenge alone to oral challenge after skin testing
- Included 377 patients with a PEN-FAST score of 0-2
- Primary outcome: physician-verified immune-mediated reaction following oral challenge
- 1 reaction occurred in the direct challenge group, 1 reaction occurred in the skin testing group
- Conclusion: In low-risk patients, direct oral challenge is non-inferior to skin testing followed by oral challenge

1. Copaescu AM, Vogrin S, James F, et al. Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial. *JAMA Intern Med.* 2023;183(9):944-952. doi: 10.1001/jamainternmed.2023.2986

De-labeling Program Successes and Challenges

Allina Inpatient De-labeling Protocol

- Pharmacist or provider collects an accurate allergy history
- For intolerances reported as allergy, remove allergy label without testing
- For low-risk allergies (PEN-FAST 0-2), proceed to amoxicillin challenge
- For moderate-high risk allergies (PEN-FAST 3+), refer to allergist for skin testing
- 213 allergies de-labeled since protocol went live in September 2024:
 - 85 allergies de-labeled from interview alone
 - 134 amoxicillin challenges undertaken
 - 128 successful amoxicillin challenges (95.5%)
 - Estimated cost savings: \$307,572

International Network of Antibiotic Allergy Nations (iNAAN) Study

- Smartphone app developed to evaluate penicillin allergies
- Conducted in 40 hospitals in 8 countries over 2.5 years

- 5121 penicillin allergies assessed
- 1573 oral challenges, 1502 successful (95.5%)
- 913 direct de-labels

Challenge #1 – Scope

More than 20,000 patients with penicillin allergies are admitted to Allina hospitals each year

Who, What, When, and Where of Inpatient Direct Oral Penicillin Challenge¹

- Assessed 1104 low-risk penicillin allergies
 - 624 patients (56.5%) elected to proceed to oral challenge
 - Primary objective: determine which low-risk patients were most likely to proceed to challenge
 - Secondary objective: determine which patients received a beta-lactam antibiotic in the next 12 months after de-labeling
- Factors associated with proceeding to challenge
 - **Admitted with an infectious diagnosis**
 - In a surgical unit
 - Childhood exanthema as historical reaction
 - Assessment NOT on day 1 of admission
- Factors associated with receiving a beta-lactam
 - **Any infective diagnosis, especially bacterial infection**
 - Immunocompromised
 - Requiring surgical prophylaxis

Challenge #2 – Role Delineation

Who is best suited to do the work?

iNAAN Results by Specialty

Specialty	Number of Assessments	Number of Oral Challenges	Number of Positive Challenges
Allergist	434	171 (39.4%)	5 (2.9%)
Non-allergist Medical Practitioner	1205	434 (36%)	6 (1.4%)
Pharmacist	2768	829 (29.9%)	37 (4.5%)
Nurse / Nurse Practitioner	714	139 (19.5%)	4 (2.9%)

Challenge #3 – Re-labeling

More than 20,000 patients with penicillin allergies are admitted to Allina hospitals each year

Re-labeling

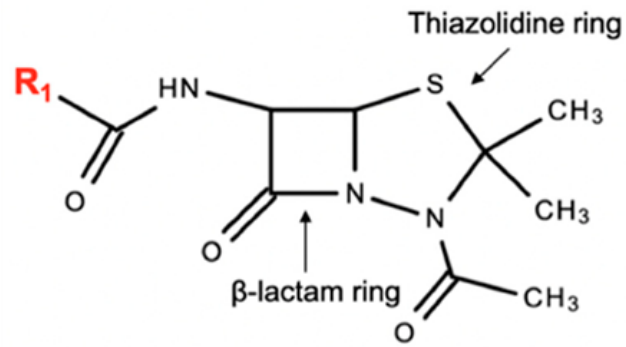
- iNAAN: 6% of patients had allergy label added back within 12 months¹
 - 70% due “inadvertent” re-labeling
 - 30% due to new penicillin reaction / intolerance
- De-labeling results do not carry over into other health systems
 - Patients should be thoroughly educated about the results of their penicillin de-labeling
 - They should also let their providers and pharmacy know about their updated allergies
- Inadequate documentation of allergy testing may also contribute

1. Metri EA, Fletcher LR, Trubiano JA, et al. Direct Oral Challenge for Penicillin Allergy: The International Network of Antibiotic Allergy Nations (iNAAN) Study. Clin Infect Dis. 2026. doi: 10.1093/cid/ciag082

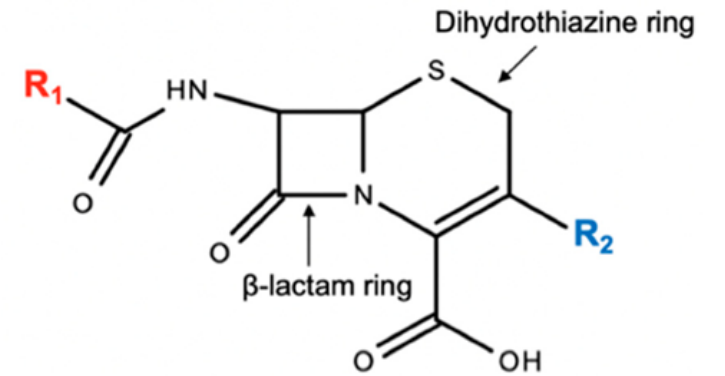
Challenge #4 – Cross Reactivity

Penicillin allergies affect more than just penicillin antibiotics

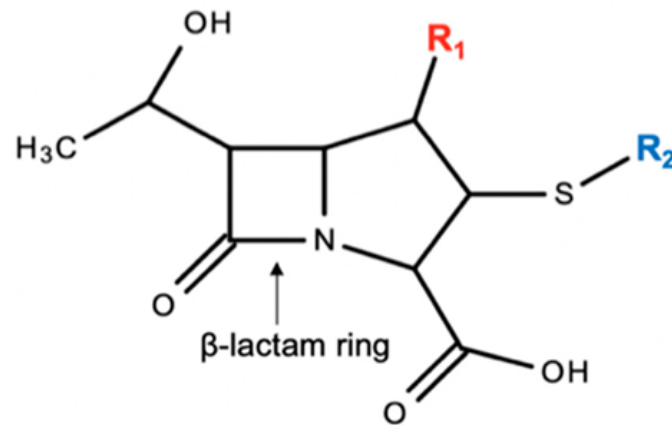
Penicillin Cross Reactivity



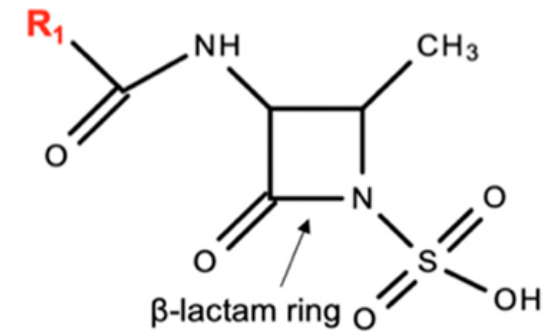
Penicillin Core Structure



Cephalosporin Core Structure



Carbapenem Core Structure



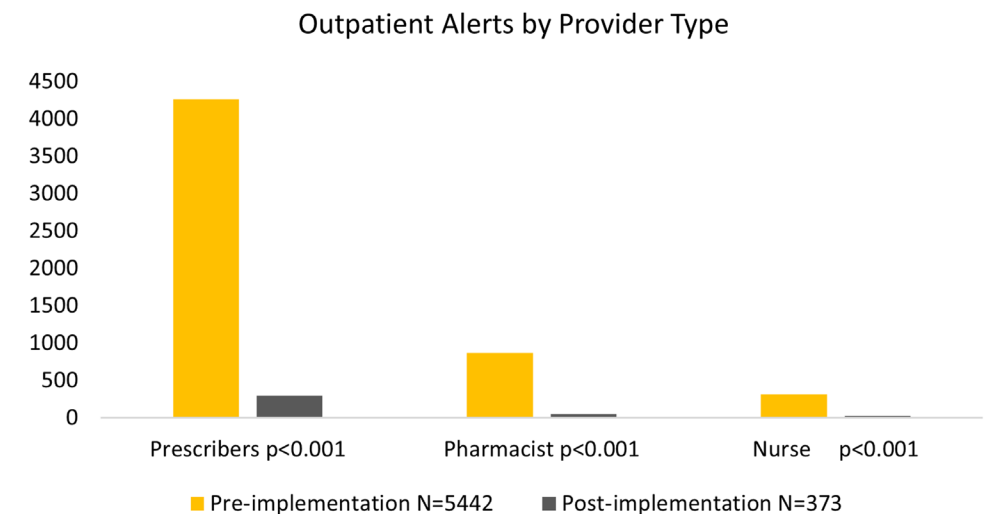
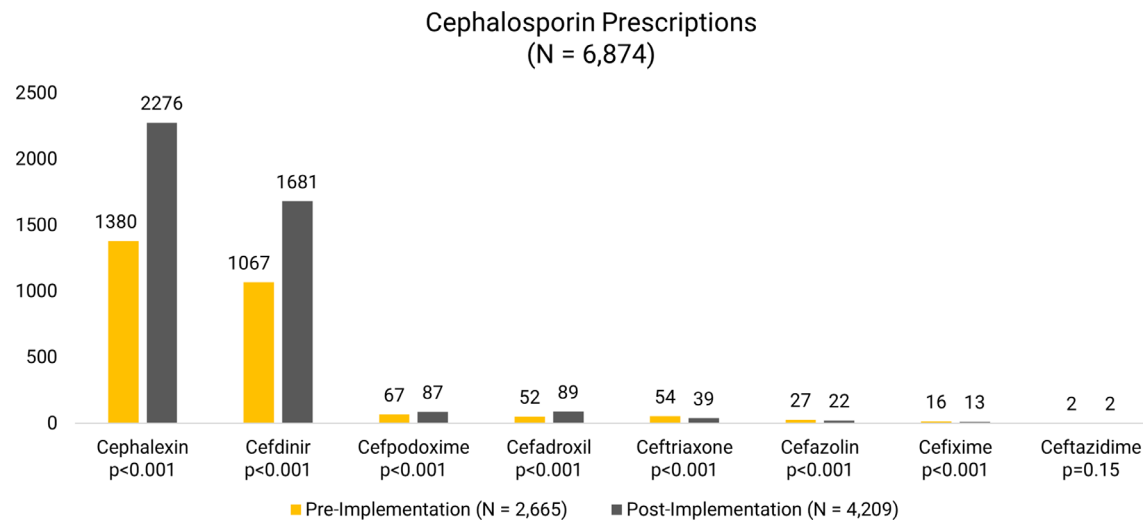
Monobactam Core Structure

Cross Reactivity Chart

	Nafcillin	Oxacillin	Dicloxacillin	Penicillin G/V	Piperacillin	Ampicillin	Amoxicillin	Cefadroxil	Cephalexin	Cefazolin	Cefoxitin	Cefuroxime	Cefotetan	Cefprozil	Cefaclor	Ceftibuten	Cefdinir	Cefixime	Ceftriaxone	Cefditoren	Cefotaxime	Cefpodoxime	Ceftazidime	Cefepime	Ceftaroline	Ceftolozane
Nafcillin	■																									
Oxacillin		■	X																							
Dicloxacillin		X	■																							
Penicillin G/V				■	X	X	X	X	X					X	X											
Piperacillin				X	■	X	X	X	X					X	X											
Ampicillin				X	X	■	X	X	X					X	X											
Amoxicillin				X	X	X	■	X	X					X	X											
Cefadroxil				X	X	X	X	■	X					X	X											
Cephalexin				X	X	X	X	X	■					X	X											
Cefazolin										■																
Cefoxitin											■	X								X						
Cefuroxime											X	■						X	X	X	X	X			X	X
Cefotetan													■													
Cefprozil				X	X	X	X	X	X					■	X											
Cefaclor				X	X	X	X	X	X					X	■											
Ceftibuten																■	X	X	X	X	X	X	X	X	X	X
Cefdinir																X	■	X	X	X	X	X	X	X	X	X
Cefixime												X			X	X	■	X	X	X	X	X	X	X	X	X
Ceftriaxone												X		X	X	X	X	■	X	X	X	X	X	X	X	X
Cefditoren												X		X	X	X	X	X	■	X	X	X	X	X	X	X
Cefotaxime											X		X	X	X	X	X	X	X	■	X	X	X	X	X	X
Cefpodoxime												X		X	X	X	X	X	X	X	■	X	X	X	X	X
Ceftazidime													X	X	X	X	X	X	X	X	X	■	X	X	X	X
Cefepime													X	X	X	X	X	X	X	X	X	X	■	X	X	X
Ceftaroline														X	X	X	X	X	X	X	X	X	X	■	X	X
Ceftolozane																X	X	X	X	X	X	X	X	X	■	X

Removal of Cephalosporin Cross Reactivity Alerts¹

- Prescribing a cephalosporin in patients with a penicillin allergy will often generate an allergy interaction alert in the electronic health record
- These alerts do not represent current understanding of cross-reactivity
- Removal of cross-reactivity alerts has been shown to be safe and effective



1. Schneider B, Percival KM, Rhinehart AM, et al. Assessing the safety of increased outpatient cephalosporin use following the modification of penicillin allergy cross-reactivity alerts. *Infection Control & Hospital Epidemiology*. 2025;46(4):416-421. doi: 10.1017/ice.2025.9

Conclusion

- Penicillin allergies are overreported, and cause significantly worse patient outcomes
- Identification and removal of low-risk penicillin allergies are important stewardship initiatives
- Multiple strategies exist to de-label penicillin allergies
- There are significant (but not insurmountable) challenges with establishment of a penicillin allergy de-labeling protocol

Resources

- Chaudhry SB, Veve MP, Wagner JL. Cephalosporins: A Focus on Side Chains and β -Lactam Cross-Reactivity. *Pharmacy* 2019, 7, 103.
- Copaescu AM, Vogrin S, James F, et al. Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial. *JAMA Intern Med.* 2023;183(9):944-952. doi: 10.1001/jamainternmed.2023.2986
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- Schneider B, Percival KM, Rhinehart AM, et al. Assessing the safety of increased outpatient cephalosporin use following the modification of penicillin allergy cross-reactivity alerts. *Infection Control & Hospital Epidemiology.* 2025;46(4):416-421. doi: 10.1017/ice.2025.9
- Trubiano JA, Vogrin S, Mitri E, et al. The Who, What, When, and Where of Inpatient Direct Oral Penicillin Challenge – Implications for Health Services Implementation. *Clin Infect Dis.* 2023;77(1):19-22. Doi: 10.1093/cid/ciad156
- 2. Sousa-Pinto B, Blumenthal KG, Macy E, et al. Penicillin Allergy Testing Is Cost-Saving: An Economic Evaluation Study. *Clin Infect Dis.* 2021;72(6):924-38.
- Zagursky R, Pichichero M. Cross-Reactivity in β -Lactam Allergy. *J Allergy Clin Immunol Pract.* 2018;6(1):72-81.

Questions / Discussion