Penicillin Allergy Evaluation & De-labeling

MINNESOTA ONE HEALTH ANTIBIOTIC STEWARDSHIP COLLABORATIVE

Background

- 10% of the U.S. population reports having a history of penicillin allergy; however, less than 1% have a true type 1, IgE-mediated reaction. [1]
- Penicillin allergy mislabels are not benign. Penicillins are first-line antibiotics for many infections. Penicillin allergy labels are associated with: [1,2]
  - Increased health care cost and higher risk of MRSA, *C. difficile,* and surgical site infections.
  - Inappropriate prescribing, worse clinical outcomes and higher mortality.
- Penicillin allergy wanes over time with 80% of patients no longer allergic after 10 years. [3]
- Prior to the 1980s, cephalosporin products were often contaminated with penicillin. [1] This contributed to the erroneous assumption that all cephalosporins should be avoided in the setting of any penicillin allergy. [4]

Cross-Reactivity

- It is estimated < 1% of patients with a history of penicillin reaction may react to cephalosporins, but it's unclear if this is due to true beta-lactam (ß-lactam) cross-reactivity or an increased general risk of medication hypersensitivity in this patient population. [4,5]
- Cross reactivity between ß-lactams is mostly due to similarities with R-group side chains (not the ß-lactam ring) and therefore agents with dissimilar side chains may reduce risk of hypersensitivity. [1] Refer to the cross-reactivity chart below for more information.
- Although cross-reactivity between ß-lactams in IgE-mediated hypersensitivity reactions (e.g., anaphylaxis) is primarily based on the R-group side chains, there is uncertainty regarding severe non-IgE-mediated reactions, such as severe cutaneous adverse reactions (SCARs). It is generally recommended to avoid all ß-lactams in patients with a history of SCAR to a ß-lactam. [1] More studies are needed to determine the safety of using alternative ß-lactams in these patients. Allergist consultation would be beneficial in patients with a history of severe non-IgE mediated reaction to a ß-lactam.

PEN-FAST

- PEN-FAST is a scoring tool to identify low-risk penicillin allergies and has been validated by multiple studies with negative predictive value ranging from 93-100%. [6,7,8]

F: Five years or less since reaction *(2 points)*

A: Anaphylaxis or Angioedema
OR
S: Severe cutaneous reaction *(2 points)*

T: Treatment required for reaction *(1 point)*

PEN-FAST Score	Risk of Penicillin Allergy
0	<1% (very low risk)
1-2	5% (low risk)
3	20% (moderate risk)
4-5	50% (high risk)

- The PALACE Trial demonstrated non-inferiority of direct oral penicillin challenge in patients with a low-risk penicillin allergy (PEN-FAST score < 3) compared to standard of care skin testing followed by oral challenge. [9]

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[3] Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321(2):188–199.
[4] Macy E. Why Was There Ever a Warning Not to Use Cephalosporins in the Setting of a Penicillin "Allergy"? J Allergy Clin Immunol Pract. 2021 Nov;9(11):3929-3933.
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[6] Trubiano, Jason A et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. JAMA Internal Medicine vol. 180,5 (2020): 745-752.
[7] Piotin A, Godet J, Trubiano JA, et al. Predictive factors of amoxicillin immediate hypersensitivity and validation of PEN-FAST clinical decision rule. Ann Allergy Asthma Immunol. 2022;128(1):27-32.
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		Penicillins (PCN)				1st-generation cephalosporins (1st)			2nd-generation cephalosporins (2nd)			3rd-generation cephalosporins (3rd)						4th	5th-generation cephalosporins (5th)		
		Penicillin G/V	Amoxicillin	Ampicillin	Piperacillin	Cefadroxil	Cefazolin	Cephalexin	Cefoxitin	Cefuroxime	Cefprozil	Cefdinir	Cefixime	Cefotaxime	Cefpodoxime	Ceftriaxone	Ceftazidime	Cefepime	Ceftaroline	Ceftolozane	Cefiderocol
PCN	Penicillin G/V				*																
	Amoxicillin			*	*	x		*			x										
	Ampicillin		*		*	*		x			*										
	Piperacillin	*	*	*		*		*			*										
1st	Cefadroxil		x	*	*			x			x										
	Cefazolin																				
	Cephalexin		*	x	*	x					*										
2nd	Cefoxitin									x											
	Cefuroxime								x				*	*	*	*	*	*		*	
	Cefprozil		x	*	*	x		*													
3rd	Cefdinir												*								
	Cefixime									*		*		*	*	*	*	*		*	*
	Cefotaxime									*			*		x	x	*	x		*	*
	Cefpodoxime									*			*	x		x	*	x		*	*
	Ceftriaxone									*			*	x	x		*	x		*	*
	Ceftazidime									*			*	*	*	*		*		*	x
4th	Cefepime									*			*	x	x	x	*			*	*
5th	Ceftaroline																				
	Ceftolozane									*			*	*	*	*	*	*			*
	Cefiderocol												*	*	*	*	x	*		*	

x Identical side chain
highest risk of cross-reactivity

* Similar side chain
moderate risk of cross-reactivity

Lack of side chain similarity
no risk of cross-reactivity

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To obtain this information in a different format, call: 651-201-5414.

Learn more

- American Academy of Allergy, Asthma & Immunology: Penicillin Allergy Center (https://education.aaaai.org/penicillin-allergy-center/penicillin)
- CDC: Clinical Features of Penicillin Allergy (www.cdc.gov/antibiotic-use/hcp/clinical-signs/index.html)
- ContagionLive: Discussing the Legal Liability of Prescribing Beta-Lactams to Penicillin-Allergic Patients (www.contagionlive.com/view/discussing-the-legal-liability-of-prescribing-beta-lactams-to-penicillin-allergic-patients)
- MDH: Antibiotic Stewardship Resources for Public Education (www.health.state.mn.us/diseases/antibioticresistance/human/edpublic.html)

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