

Penicillin Allergy: Why the Epidemic is Leading to Poor Clinical Outcomes


SHYAM JOSHI, MD
ASSISTANT PROFESSOR OF MEDICINE
SECTION OF ALLERGY AND IMMUNOLOGY

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Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.



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Objectives

- Characterize and stratify penicillin allergic reactions
- Review the clinical data on clinical decision making in patients with penicillin allergies
- Be able to identify which patients should have further evaluation after a drug-related adverse event



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Presentation Outline

- Case presentation
- Defining drug allergies
- Penicillin allergies
 - Prevalence
 - Importance of penicillin allergy label
 - Evaluation methods



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Case Presentation

RJ is an 18 yo male with newly diagnosed syphilis.

DK is a 32 yo female with AML s/p chemotherapy that presents with neutropenic fever.

RS is a 63 yo male with a history of diabetes and ESRD s/p DDKT on chronic immunosuppression that presents with pneumonia.

All have a distant history of penicillin allergy.



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How Common are Adverse Drug Events?

Allergy Label

- 36% of patients have a listed allergy in their EMR
 - 43% of these had multiple allergies
 - 4-7% have MDIS
- Risk factor: Drug exposure

Adverse Events

- Adverse drug events occur in up to 25% of prescriptions
 - 13% of these were serious
- Allergic reactions (immunologically mediated) account for only 5-10% of all ADEs



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Classifying Adverse Drug Events

Type A Reactions

- Predictable – Due to known pharmacodynamics of the drug (dose-dependent)
- Based more on drug than host
- >85% of ADEs
- Examples
 - Sedation with diphenhydramine
 - Diarrhea with amoxicillin
 - Bleeding due to warfarin

Type B Reactions

- Unpredictable
- Based more on host than drug
- ~15% of ADEs
- Examples
 - Hypersensitivity reactions
 - Pseudoallergies



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Variety of Drug Reactions

Examples of Drug Allergies		
IgE-mediated	Pneumonitis	Urticaria multiforme
Hemolytic anemia	AIN	Erythema multiforme
Thrombocytopenia	Drug-induced lupus	AGEP
Granulocytopenia	FDE	Infusion reactions
Serum sickness	Contact dermatitis	Atopic dermatitis
Serum sickness-like	Acne	Angioedema
Vasculitis	Photosensitivity	IgE-mediated anaphylaxis
Arthus reaction	SDRIFE	Non-IgE-mediated anaphylaxis
DRESS	Drug exanthema	IgG-mediated anaphylaxis
SJS	Drug fever	MRGPRX2-mediated
TEN	Bullous pemphigoid	Pemphigus vulgaris



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Penicillin Allergy Labels

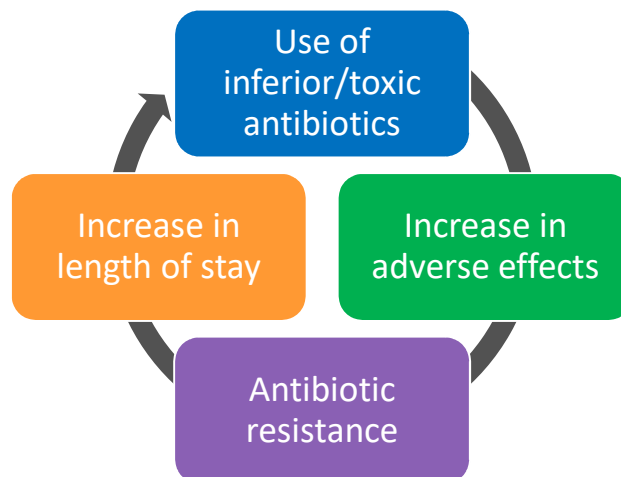
- 8-10% of the US population carries a history of penicillin allergy
 - >95% will tolerate penicillin use after evaluation
- Waning sensitivity to penicillin
 - 50% lose sensitivity by 5 years
 - 80% lose sensitivity by 10 years
- Subsequent penicillin use after negative testing does not increase risk of sensitization

Sogn DD, Evans R, Shepherd GM, et al. *Ann Intern Med.* 1992.
 Gadde J, Spence M, Wheeler B, et al. *JAMA.* 1993.
 Macy E, Contreras R. *J Allergy Clin Immunol.* 2014.
 Solensky R, Earl HS, Gruchalla, RS. *Arch Intern Med.* 2002.
 Dorman SM, Seth S, Khan DA. *J Allergy Clin Immunol Pract.* 2018.



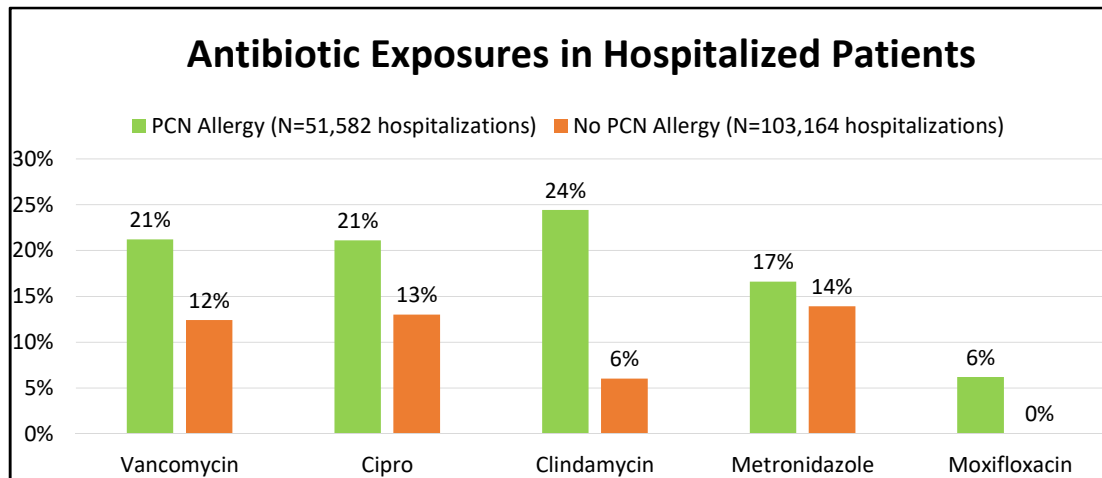
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Effects of Penicillin Allergy Label



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Antibiotic Exposure



Macy E, Contreras R. *J Allergy Clin Immunol*, 2014.

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Outcomes: PCN Allergy Label

1. Higher rate of treatment failures
2. Increased prevalence of *Clostridium difficile*, MRSA, and VRE
3. Increased future healthcare utilization
 - Longer hospital length of stay
 - Higher rate of readmission
4. Increased healthcare dollars
5. Higher rates of surgical site infections

Macy E, Contreras R. *J Allergy Clin Immunol*, 2014.
 Jeffres MD, et al. *J Allergy Clin Immunol*, 2016.
 Picard M, et al. *J Allergy Clin Immunol Pract*, 2013.
 Blumenthal KG, et al. *Clin Infectious Dis*, 2018.



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Treatment Failure with Alternative Antibiotics

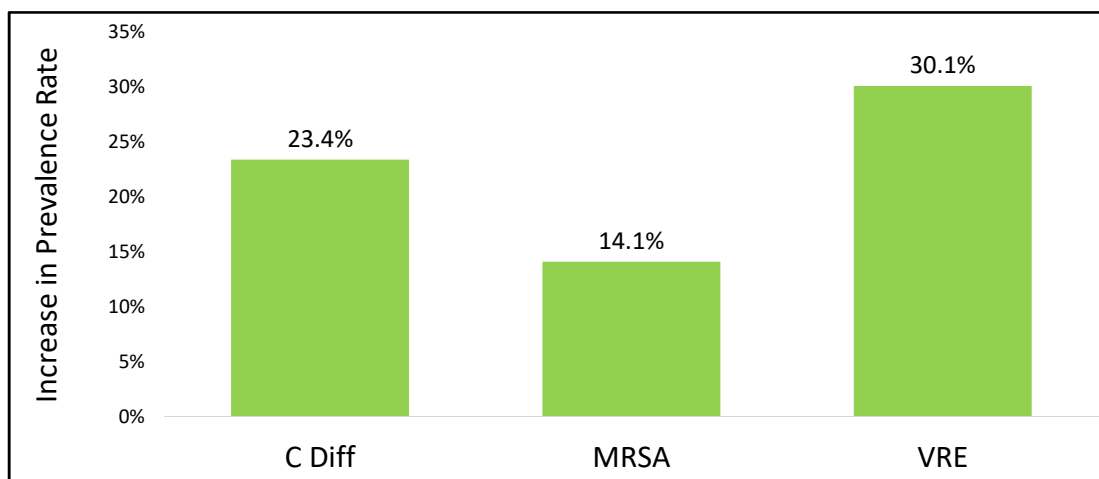
- GNB bacteremia (Jeffres et al.)
 - Non- β -lactam failure rate: 39%
 - β -lactam failure rate: 27%
- MSSA bloodstream infections (McDanel et al.)
 - β -lactams had a 35% lower mortality rate for definitive treatment compared to vancomycin



Jeffres MD, et al. *J Allergy Clin Immunol*, 2016.
McDanel JS, et al. *Clin Infect Dis*, 2015.

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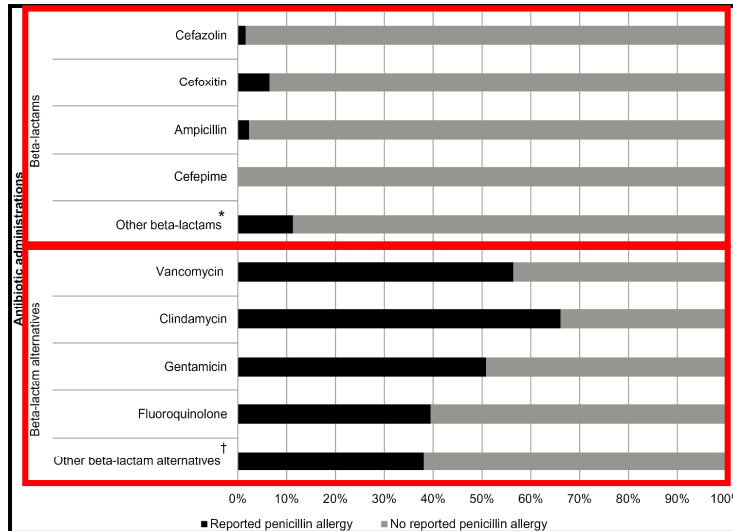
C difficile, MRSA, and VRE



Macy E, Contreras R. *J Allergy Clin Immunol*, 2014.
Reddy V, Baman NS, Whitener C, Ishmael FT, *J Allergy Clin Immunol*, 2013.
Blumenthal KG, et al. *BMJ*, 2018.

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Surgical Site Infections



When controlled for surgery type, age, sex, race, American Society of Anesthesiologists class, procedure duration, and wound class



51% increased risk
of a SSI in patients
that have a PCN
allergy label ($p < 0.04$)

Blumenthal KG, et al. *Clin Infectious Dis*, 2018.



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Anesthesiologist Perspective

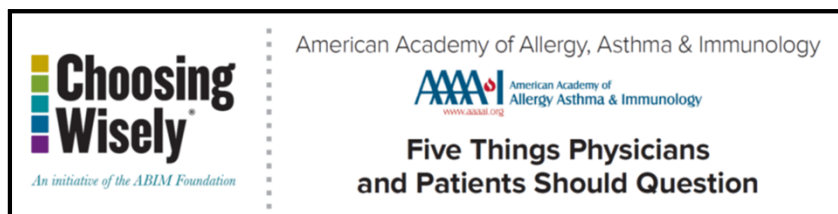
- Up to 60% of anesthesiologists will not give β -lactam antibiotics to penicillin-allergic patients
 - Medical-legal concerns
- Studies have supported:
 - Penicillin allergy evaluation prior to surgery
 - Cephalosporins without prior evaluation/testing (in penicillin allergic patients)

Savic LC, et al. *Br J Anes*, 2019.
Beltran RJ, et al. *J Pediatr Surg*, 2015.
Haslam S, et al. *Iowa Orthop J*, 2012.
Goodman EJ, et al. *J Clin Anaesth*, 2001.
Epstein RH, et al. *A A Case Rep*, 2016.



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Choosing Wisely Campaign



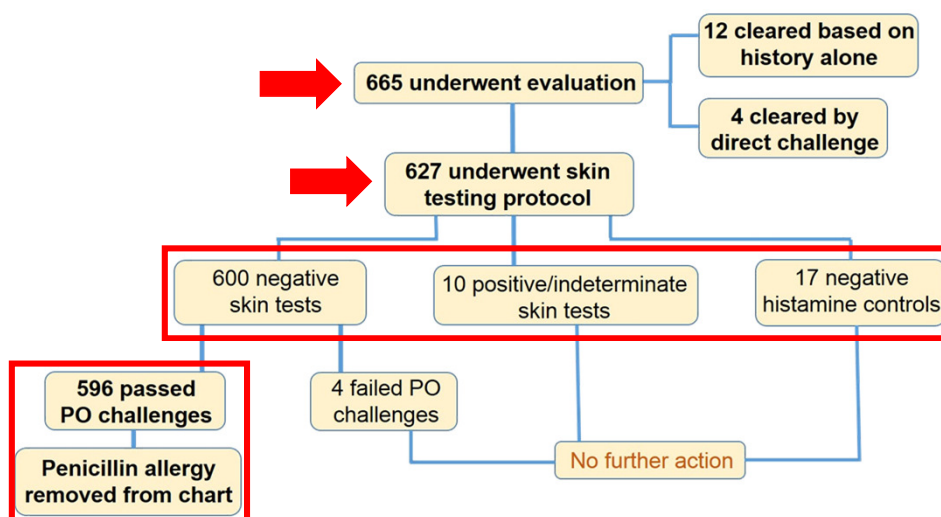
10 Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.

<https://www.choosingwisely.org>



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Penicillin Testing (Inpatient)



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Who Should We Be Evaluating?

- Everyone!
- High risk patients and high utilizers of the healthcare system
 - Chronic disease (CF, diabetes, COPD, asthma)
 - Immunosuppressed (chemotherapy, autoimmune, transplant)
 - Immunodeficient (HIV, primary immunodeficiency)
 - Malignancy



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How Should We Test Patients?

- Inpatient vs Outpatient?
- Skin testing vs Direct Provocation Challenge?
- Allergist vs Non-allergist?



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Inpatient Vs Outpatient Evaluation

- Traditionally, penicillin allergy evaluation has occurred in the outpatient setting
- Outpatient:
 - Allergist primary practice in the outpatient setting
 - Can perform multiple evaluations simultaneously
 - Difficult to schedule testing
- Hospitalized patients:
 - Incidence of penicillin allergy is higher (up to 15%)
 - Older, more ill and greater need for antibiotics
 - Testing could alter antibiotic therapy immediately



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Penicillin Skin Testing

- Modified protocol
 - Skin prick and intradermal testing
 - Penicilloyl-polylysine
 - Penicillin G
 - Observed (graded) oral amoxicillin challenge
- NPV of 97-100%
 - PPV not well established



<https://www.medscape.com/viewarticle/871833>



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Direct Provocation Testing

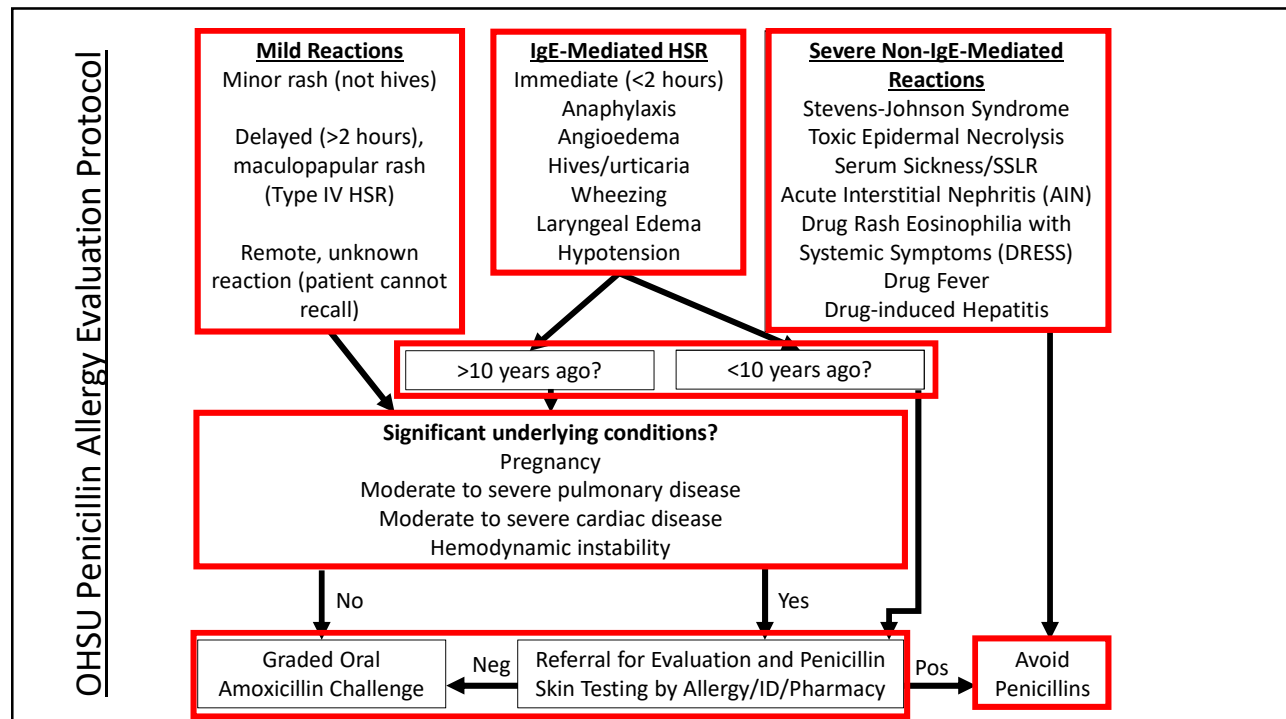
Outcome	Penicillin SPT	DC	Difference
Patients	80	79	
PST Positive/DC fail, n (%)	10 (12.5)	3 (3.8)	8.7% ($P = .079$)
PST Negative/DC pass	70 (87.5)	76 (96.2)	
Time (min)			
Mean \pm SD	72.7 \pm 5.3	66.7 \pm 4.8	6.0 ($P < .001$)
Median (IQR)	73.5 (68.8-75.3)	66.0 (62-70)	7.5 ($P < .001$)
Cost			
Each	\$393.66	\$53.66	\$340.00
Total	\$29,092.80	\$4,239.14	\$24,853.66

- DC reactions were all minor cutaneous reactions
- False positive results from SPT

Mustafa SS, et al. *J Allergy Clin Immunol Pract*, 2019.
Mill C, et al. *JAMA Pediatr*, 2016.



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Risk Stratifying PCN Allergy Patients

- No consensus with high variability between studies
 - Time since reaction
 - Symptoms (cutaneous only)
 - Severity of reaction
- UK Tertiary Center Study – Multivariate regression analysis
 - Self reported history of anaphylaxis
 - Patients' recall of index penicillin
 - Time of less than 1 year since index reaction

Siew LQC, et al. *J Allergy Clin Immunol Pract*, 2019.



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Allergist or Non-Allergist?

- Both should be involved!
- Lower risk patients -> Non-Allergist
 - Penicillin Allergy Toolbox
 - Evaluation and Management of Penicillin Allergy: A Review
 - Shenoy ES, Macy E, and Rowe T.
 - *JAMA*. 2019;321(2):188-199.
- Higher risk patients -> Allergist



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Take Home Points

- Always question drug allergies
 - Especially penicillin
- Penicillin allergy labels can drastically alter clinical outcomes and lead to more expensive care
- Performing inpatient and/or outpatient penicillin evaluations (history, testing) is safe and reliable in removing penicillin allergy labels



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Questions?



Clinic for

Asthma & Allergic Diseases

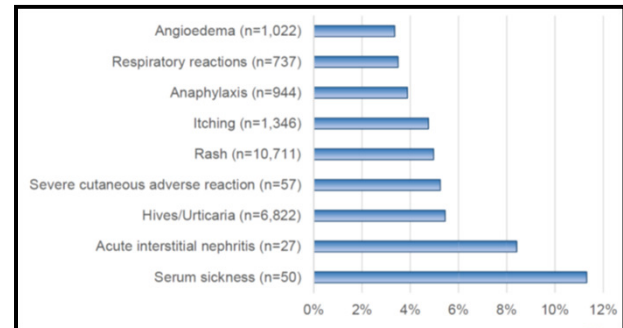
**Combined Clinic for
Severe Sinus Disease**
ENT & Allergy



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Updates on Cephalosporin Allergies

- Most commonly used antibiotic in US hospitals
- 1.3-1.7% of patients report ADRs to cephalosporins
- Can cause all types of HSRs
 - SSLR (11% of cases)
 - AIN (9% of cases)
 - SCAR (5% of cases)
 - Anaphylaxis (4% of cases)
- 60% of patients lose cephalosporin sensitivity after 5 years



Khan DA, et al. *J Allergy Clin Immunol Pract*, 2019.
 Wong A, et al. *J Allergy Clin Immunol Pract*, 2019.
 Blumenthal KG, et al. *J Allergy Clin Immunol Pract*, 2015.
 Romano A, et al. *Allergy*, 2014.



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Cephalosporin Testing

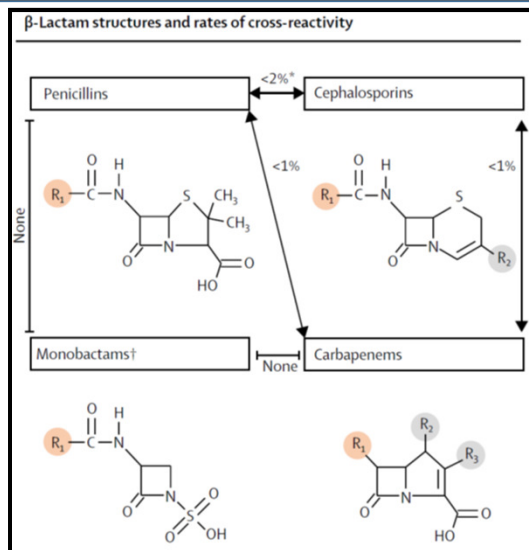
- Skin testing (prick and ID)
 - Limited data on sensitivity and specificity
 - False positive rate in healthy population (1421 patients): 5.2%
 - Perioperative anaphylaxis: Skin testing has high PPV
 - Danish study showed 7 of 7 patients had a positive DPT after positive skin test
 - Wide range of concentrations used
- Skin testing (delayed ID and patch)
- *In vitro* sIgE testing
 - Limited commercially availability and limited data
- Direct provocation testing

Yoon SY, et al. *Allergy*, 2013.
 Christiansen IS, et al. *Clin Exp Allergy*, 2015.



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PCN Cross-Reactivity



- Historically, cross-reactivity has been overestimated
- Recent meta-analysis (PCN Allergic)
 - Aminocephalosporins: 16.5%
 - Intermediate-similarity-score: 5.6%
 - Low-similarity-score: 2.11%
- R1 and R2 side chains

Blumenthal KG, et al. *Lancet*, 2019.

Picard M, et al. *J Allergy Clin Immunol Pract*, 2019.



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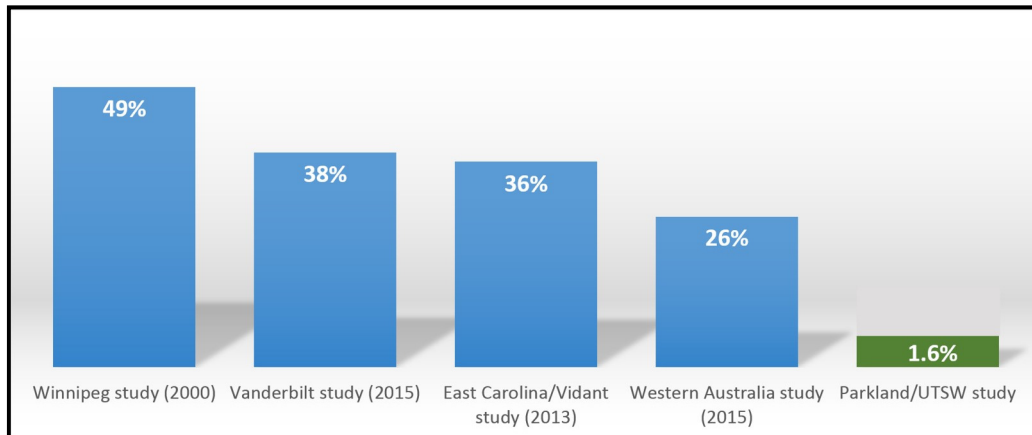
PCN Cross-Reactivity

Cephalosporin		Type of penicillin allergy			
Generation	Name	n/N	AR in % (95% CI)	IgE	
				n/N	AR in % (95% CI)
First	Cephalexin	40/310	12.9 (9.6-17.1)	57/383	14.9 (11.7-18.8)
	Cefadroxil	75/287	26.1 (21.4-31.5)	20/270	7.4 (4.8-11.2)
	Cephalexin	8/128	6.3 (2.7-11.9)	1/56	1.8 (0.3-11.6)
	Cefazolin	0/47	0.0 (0.0-7.5)	1/26	3.8 (0.0-19.6)
	Cefatrizine	NA	NA	1/56	1.8 (0.3-11.6)
Second	Cephalexin	0/17	0.0 (0.0-19.5)	NA	NA
	Cefamandole	22/418	5.3 (3.5-7.9)	1/56	1.8 (0.3-11.6)
	Cefaclor	41/282	14.5 (10.9-19.2)	49/397	12.3 (9.5-16.0)
	Cefuroxime	7/490	1.1 (0.2-5.8)	7/423	0.5 (0.0-8.0)
	Cefprozil	NA	NA	3/39	7.7 (1.6-20.9)
Third	Cefpodoxime	NA	NA	1/71	1.4 (0.0-7.6)
	Ceftazidime	2/433	0.3 (0.0-4.7)	NA	NA
	Cefotaxime	5/380	1.3 (0.6-3.1)	0/56	0.0 (0.0-6.4)
	Cefixime	0/39	0.0 (0.0-9.0)	2/285	0.7 (0.2-2.8)
	Ceftriaxone	12/474	2.5 (1.4-4.4)	1/367	0.2 (0.0-9.5)
Fourth	Ceftibuten	NA	NA	0/153	0.0 (0.0-2.4)
	Cefepime	1/285	0.3 (0.0-10.3)	NA	NA

Picard M, et al. *J Allergy Clin Immunol Pract*, 2019.

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Penicillin Relabel



Warrington RJ, Lee KR, McPhillips S. *Allergy Asthma Proc.* 2000;21(5):297-9.
 Gerace KS, Phillips E. *J Allergy Clin Immunol Pract.* 2015;3(5):815-816.
 Rimawi RH, Shah KB, Cook PP. *Journal of Hospital Medicine.* 2013;8:615-618.
 Bourke J, Pavlos R, James I, et. al. *J Allergy Clin Immunol Pract.* 2015;3:365-74.



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Interventions to Maintain Penicillin Allergy Label Removal

1. Pharmacist counseling at the time of negative test
 - Active removal of allergy, procedure note documentation
2. Pharmacist counseling at post-discharge visit
 - Telephone call or face to face visit
3. Best practice advisory in the electronic medical record
 - Alerting providers to the negative penicillin allergy test result on attempt to add back allergy
4. Wallet card given to patient documenting negative testing
 - Given at time of negative test documentation



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Wallet Card for Patient

ALLERGY INFORMATION

Name: _____

Date of Birth: _____

Allergies:

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

I am NOT Allergic to Penicillin

Penicillin Skin Testing (Prick and Intradermal) followed by an oral graded Amoxicillin Challenge was performed at Oregon Health and Science University (OHSU) on:

_____.

RESULTS: Negative (No Reaction)

Test performed by _____.

